Washington Marriott
Wardman Park

Washington, DC

April 1-6, 2017

North American Neuro-Ophthalmology Society

1975-2017

North American Neuro-Ophthalmology Society
43rd Annual Meeting

April 1 – April 6, 2017

Washington Marriott Wardman Park • Washington, DC

SCHEDULE AT A GLANCE

SATURDAY, APRIL 1		**LOCATION**
2:00 pm - 8:00 pm	Registration/Help Desk	Thurgood Marshall Foyer
8:00 am - 12:00 pm	NANOS Board Meeting	Hoover
6:00 pm - 7:30 pm	Opening Reception (All are welcome!)	Marriott Foyer
SUNDAY, APRIL 2		
6:00 am - 6:45 am	Yoga Class	Washington Room 1
6:30 am - 5:30 pm	Registration/Help Desk	Thurgood Marshall Foyer
6:30 am - 7:45 am	Breakfast	Exhibit Hall C
6:30 am - 3:00 pm	Exhibits	Exhibit Hall C
7:45 am - 5:00 pm	FRANK B. WALSH SESSION [6 CME]	Thurgood Marshall Ballroom
10:00 am - 10:30 am	Coffee Break	Exhibit Hall C
12:30 pm - 1:00 pm	Lunch	Exhibit Hall C
1:00 pm - 2:45 pm	Poster Session I: Clinical Highlights in Neuro-Ophthalmology	Exhibit Hall C
5:15 pm - 5:45 pm	Frank B. Walsh Committee Meeting	Harding
5:15 pm - 5:45 pm	Fellowship Director's Meeting	Coolidge
5:30 pm - 6:30 pm	Members-in-Training Program and Reception	Marriott Foyer
5:45 pm - 6:15 pm	Fellowship Committee Meeting	Coolidge
MONDAY, APRIL 3		
6:00 am - 6:45 am	Yoga Class	Washington Room 1
6:30 am - 5:30 pm	Registration/Help Desk	Thurgood Marshall Foyer
6:30 am - 7:30 am	Breakfast	Exhibit Hall C
6:30 am - 12:15 pm	Exhibits	Exhibit Hall C
7:00 am - 7:30 am	NOVEL Editorial Board/Curriculum Committee Meeting	Washington 2
7:30 am - 9:30 am	Journal Club [2 CME]	Thurgood Marshall Ballroom
9:30 am - 10:00 am	Coffee Break	Exhibit Hall C
10:00 am - 12:00 pm	Hot Topics in OCT [2 CME]	Thurgood Marshall Ballroom
1:30 pm - 3:00 pm	Applications of Advanced Retinal Vascular Imaging in Neuro-Ophthalmology [1.5 CME]	Thurgood Marshall Ballroom
2:30 pm - 4:30 pm	Forum for New and Future Neuro-Ophthalmologists	Washington Rooms 3-6
3:15 pm - 4:45 pm	Radiation Oncology for the Neuro-Ophthalmologist [1.5 CME}	Thurgood Marshall Ballroom
4:45 pm - 5:00 pm	Overview of the NANOS Practice & Compensation Survey	Thurgood Marshall Ballroom
5:00 pm - 7:00 pm	SCIENTIFIC PLATFORM PRESENTATIONS: SESSION I [2 CME]	Thurgood Marshall Ballroom
8:30 pm - 9:30 pm	Medicare Reviews and Audits with Dr. Cheryl Ray	Thurgood Marshall Ballroom
TUESDAY, APRIL 4		
6:00 am - 6:45 am	Yoga Class	Washington Room 1
6:30 am - 12:30 pm	Registration/Help Desk	Thurgood Marshall Foyer
6:30 am - 7:30 am	Breakfast	Exhibit Hall C
6:30 am - 10:30 am	Exhibits	Exhibit Hall C
6:30 am - 7:30 am	JNO Editorial Board Meeting	Hoover
7:30 am - 12:00 pm	SCIENTIFIC PLATFORM PRESENTATIONS: SESSION II [3.75 CME}	Thurgood Marshall Ballroom
9:15 am - 9:30 am	Update: The Journal of Neuro-Ophthalmology	Thurgood Marshall Ballroom
9:30 am - 10:00 am	Coffee Break	Exhibit Hall C
12:00 pm - 6:00 pm	Free Afternoon	
12:30 pm – 4:30 pm	Optional Excursions	Depart- 24th Street Entrance
6:00 pm - 9:30 pm	Poster Session II: Scientific Advancements in Neuro-Ophthalmology	Exhibit Hall C
9:00 pm – 10:00 pm	Abstract Committee Meeting	Hoover
WEDNESDAY, APRIL 5		
6:30 am - 5:30 pm	Registration/Help Desk	Thurgood Marshall Foyer
6:30 am - 7:30 am	Breakfast	Exhibit Hall C
7:00 am - 7:30 am	Annual NANOS Business Meeting (All are encouraged to attend.)	Thurgood Marshall Ballroom
7:30 am - 11:15 am	Afferent and Efferent Rehabilitative Strategies in Neuro-Ophthalmology [3.5 CME]	Thurgood Marshall Ballroom
9:00 am - 9:15 am	Coffee Break	Thurgood Marshall Foyer
11:15 am - 11:20 am	NOVEL Update	Thurgood Marshall Ballroom
11:20 am - 12:00 pm	Jacobson Lecture: Going with the Flow [.75 CME]	Thurgood Marshall Ballroom
12:15 pm - 1:30 pm	Research Committee Meeting Luncheon	Stone's Throw Restaurant
1:30 pm - 2:30 pm	Women in Neuro-Ophthalmology (WIN) Forum: Gender Pay	Exhibit Hall C
1:30 pm - 3:00 pm	My baby can't see! [1.5 CME]	Thurgood Marshall Ballroom
3:00 pm - 3:30 pm	Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO)	Thurgood Marshall Ballroom
3:15 pm - 5:15 pm	Coding: A Day in the Life of a Neuro-Ophthalmologist	Washington Room 3-6
4:00 pm – 5:00 pm	International Relations Committee Meeting	Hoover
6:30 pm - 11:30 pm	Annual NANOS Reception and Banquet	Thurgood Marshall Ballroom
THURSDAY, APRIL 6		
6:30 am - 12:00 pm	Registration/Help Desk	Thurgood Marshall Foyer
6:30 am - 7:30 am	Breakfast	Exhibit Hall C
7:30 am - 9:30 am	Neuro-Ophthalmologic Side Effects of More Recently Used Medications in Treating Cancer, Rheumatologic Disorders, and Multiple Sclerosis [2 CME]	Thurgood Marshall Ballroom
9:30 am - 10:00 am	Coffee Break	Thurgood Marshall Foyer
10:00 am - 12:00 pm	Eye Movement Challenge: The Advanced Level [2 CME]	Thurgood Marshall Ballroom

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MISSION STATEMENT
The North American Neuro-Ophthalmology Society (NANOS) is dedicated to the achievement of excellence in patient care through the support and promotion of education, communication, research, and the practice of Neuro-Ophthalmology.

TARGET AUDIENCE
Neurologists, Ophthalmologists, Neuro-Ophthalmologists, physicians and other health care professionals who have a special interest in Neuro-Ophthalmology, or have fellowship training in Neuro-Ophthalmology and are members of the North American Neuro-Ophthalmology Society.

POLICY ON COMMERICAL SUPPORT AND FACULTY DISCLOSURE
The North American Neuro-Ophthalmology Society maintains a policy on the use of commercial support which ensures that all educational activities sponsored by NANOS provide in-depth presentations that are fair, independent, and scientifically rigorous. To this end, all speakers and planners are required to complete a "Disclosure Form." This information is included in this syllabus and/or may be supplemented by announcements by moderators.

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ACCREDITATION
The North American Neuro-Ophthalmology Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION
NANOS designates this live activity for a maximum of 28.5 AMA PR Category 1 Credits. Physicians should claim only the credit commensurate with the extent of their participation.

NANOS CME MISSION STATEMENT

The North American Neuro-Ophthalmology Society (NANOS) is dedicated to achieving excellence in care of patients with neuro-ophthalmic diseases by the support and promotion of education, research, and the practice of Neuro-Ophthalmology.

The Society's main CME activity is its annual scientific meeting. The educational meeting includes seminars, workshops, hands-on training, platform presentations, and discussion of cases and best practices in neuro-ophthalmic research, basic science, and patient care.

The CME goal of the meeting is to improve the attendees' knowledge of Neuro-Ophthalmology basic science and practice. More specifically, the goals of the meeting are:

1) To achieve competence in neuro-ophthalmic diagnosis, treatment, and teaching; 2) To improve performance as physicians, teachers, and researchers by using information presented at the meeting to change clinical practice and instruction; and 3) To review research projects to investigate questions raised by the meeting's scientific sessions.

The expected results of our CME program, and of our annual meeting as its main CME activity, is that our members will increase their knowledge of Neuro-Ophthalmology and improve their skill in its practice, so that they can apply that knowledge and skill to enhance their performance and competence as clinical Neuro-Ophthalmologists, research Neuro-Ophthalmologists, and teachers of Neuro-Ophthalmology.

NANOS uses multiple data sources to measure the impact of its educational activities on learners and on the discipline of Neuro-Ophthalmology. These sources translate professionals' need into current practices to improve competence in knowledge, diagnosis, performance, and treatment of neuro-ophthalmic diseases.

Approved by the NANOS CME Subcommittee and NANOS Board of Directors as of 2017

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NANOS 2017 SPEAKERS AND MODERATORS

Ore-ofe O. Adesina, MD
McGovern Medical School
Houston, TX

Laura J. Balcer, MD, MSCE
New York University
School of Medicine
New York, NY

Jason J. S. Barton, MD, PhD, FRCPC
University of British Columbia
Vancouver, Canada

M. Tariq Bhatti, MD
Duke Eye Center
Duke University Medical Center
Durham, NC

Michael C. Brodsky, MD
Mayo Clinic
Rochester, MN

Mark Borchert, MD
Children's Hospital Los Angeles
Los Angeles, LA

Yanjun (Judy) Chen, MD, PhD
University of Wisconsin
School of Medicine and Public Health
Madison, WI

John Jing-Wei Chen, MD, PhD
Mayo Clinic
Rochester, MN

Sophia M. Chung, MD
Saint Louis University
St. Louis, MO

Fiona Costello, MD, FRCP
University of Calgary
Calgary, Canada

Susan Cotter, OD, MS
Southern California College of Optometry
Marshall B Ketchum University
Fullerton, CA

Jenny Edgar, CPC, CPCO, OCS
AAO
Columbus, OH

Eric R. Eggenberger, DO, MSEpi
Michigan State University
East Lansing, MI

William A. Fletcher, MD, FRCPC
University of Calgary
Calgary, Canada

Rod Foroozan, MD
Baylor College of Medicine
Houston, TX

Steven L. Galetta, MD
NYU Langone Medical Center
NYU School of Medicine
New York, NY

James A. Garrity, MD
Mayo Clinic
Rochester, MN

Caterina Giannini, MD, PhD
Mayo Clinic
Rochester, MN

David B. Glasser, MD
Johns Hopkins University
School of Medicine
Columbia, MD

Judith E. Goldstein, OD
Johns Hopkins University
School of Medicine
Baltimore, MD

Gena Heidary, MD, PhD
Boston Children's Hospital
Boston, MA

Ruth Huna-Baron, MD
Sheba Medical Center
Israel

Krystel Huxlin, PhD
Flaum Eye Institute
University of Rochester
Rochester, NY

Hong Jiang, MD, PhD
Bascom Palmer Eye Institute
University of Miami
Miami, FL

Guy V. Jirawuthiworavong, MD, MA
Southern California Permanente Medical Group
La Palma, CA

Randy Kardon, MD, PhD
VA Center for the Prevention and Treatment of Vision Loss
University of Iowa and Iowa City
Iowa City, IA

Jacqueline A. Leavitt, MD
Mayo Clinic
Rochester, MN

Y. Joyce Liao, MD, PhD
Stanford University
Stanford, CA

Grant T. Liu, MD
University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA

Collin McClelland, MD
University of Minnesota
Minneapolis, MN

Neil R. Miller, MD
Johns Hopkins University
School of Medicine
Baltimore, MD

Jonathan Morris, MD
Mayo Clinic
Rochester, MN

Heather E. Moss, MD, PhD
Stanford University
School of Medicine
Palo Alto, CA

Mark Moster, MD
Wills Eye Institute
Thomas Jefferson University
Philadelphia, PA

Steven A. Newman, MD
University of Virginia
Charlottesville, VA

Victoria S. Pelak, MD
University of Colorado
School of Medicine
Aurora, CO

Eli Peli, MSc, OD
Schepens, Mass Eye & Ear
Harvard Medical School
Boston, MA

Paul H. Phillips, MD
Jones Eye Institute
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, AR

Stacy Pineles, MD
Jules Stein Eye Institute
Los Angeles, CA

Sashank Prasad, MD
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

John Pula, MD
NorthShore University HealthSystem
Glenview, IL

Cheryl Ray, DO, MBA
WPS-Government Health Administrators
Madison, WI

Marie-Benedicte Rougier, MD, PhD
University of Bordeaux
France

Robert C. Sergott, MD
Wills Eye Hospital Neuro-Ophthalmology Service
Thomas Jefferson University
Philadelphia, PA

Scott L. Stafford, MD
Mayo Clinic
Rochester, MN

Matthew J. Thurtell, MBBS, MSc, FRACP
University of Iowa
Iowa City, IA

Caroline Tilikete, MD, PhD
Hospices Civils de Lyon
University Lyon I
Lyon Est Medical School
France

Michael S. Vaphiades, DO
Callahan Eye Hospital
University of Alabama
Birmingham, AL

Jianhua Wang, MD, PhD
Bascom Palmer Eye Institute
University of Miami
Miami, FL

Judith E. A. Warner, MD
John A. Moran Eye Center
University of Utah
Salt Lake City, UT

David S. Zee, MD
Johns Hopkins University
School of Medicine
Baltimore, MD

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Sponsored by: The North American Neuro-Ophthalmology Society

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It is the policy of the North American Neuro-Ophthalmology Society (NANOS) in accordance with the Accreditation Council for Continuing Medical Education (ACCME) to ensure independence, balanced view of therapeutic options, objectivity, scientific rigor, and integrity in all of its continuing education activities.

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Please note that platform presenter disclosure information is listed in the syllabus at the end of each abstract.

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Eric	Eggenberger	DO, MSEpi (F)	Genzyme	Financial Support	Consultant,Research, Speaker
Rod	Foroozan	MD (F)	Lundbeck	Consulting Fees	Consultant
Steven	Galetta	MD (F)	Biogen	Consulting Fees	Consultant
Neil	Miller	MD (F)	Quark Pharmaceuticals	Remuneration	Principal Investigator in Clinical Trial
Eli	Peli	MSc, OD (F)	Chadwick Optical	Future patent royalty share through Schepens in expected	Patent assigned to Schepens and licensed to Chadwick
Marie-Benedicte	Rougier	MD, PhD (F)	Carl Zeiss	Honorarium	Speaker
Robert	Sergott	MD (F)	Heidelberg Engineering	Consulting Fees, Grant Support	Consultant, Research
Jianhua	Wang	MD, PhD (F)	Optical Imaging Ltd	Honorarium	Scientific Advisory Panel Member

Key: P = Planner; F = Faculty
All other faculty and planners have declared that they have no relevant financial disclosures.

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Program Schedule

SATURDAY, APRIL 1

2:00 pm - 8:00 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
8:00 am - 12:00 pm	**NANOS Board Meeting**	**Hoover**
6:00 pm - 7:30 pm	**Opening Reception (All are welcome!)**	**Marriott Foyer**

SUNDAY, APRIL 2

6:00 am - 6:45 am	**Yoga Class**	**Washington Room 1**
6:30 am - 5:30 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
6:30 am - 7:45 am	**Breakfast**	**Exhibit Hall C**
6:30 am - 3:00 pm	**Exhibits**	**Exhibit Hall C**
7:45 am - 5:00 pm	**FRANK B. WALSH SESSION [6 CME]** *Co-Chairs: John Jing-Wei Chen, MD, PhD and Jacqueline A. Leavitt, MD* *Neuroradiologist*: *Jonathan Morris, MD* *Neuropathologist: Caterina Giannini, MD, PhD*	**Thurgood Marshall Ballroom**

This symposium is designed to present a wide variety of Neuro-Ophthalmic cases to an audience of physicians with varying neuroscience backgrounds who have a common intellectual interest in the broad range of conditions that impact the human visual pathways and ocular motor systems.

The format is a clinicopathologic conference. Clinical cases will be presented by Neuro-Ophthalmologists with comments by a neuroradiologist, neuropathologist and other selected experts. Necropsy, surgical pathology, and neuroimaging will help illuminate clinical points. Cases will be discussed from clinical, anatomic, radiologic and pathologic aspects with emphasis on diagnosis, pathophysiology and management.

Upon completion of this course, participants should be able to: 1) Recognize the varied presentations of Neuro-Ophthalmic disease; 2) Correlate the anatomic localization and histopathologic appearance with the clinical presentations; 3) Effectively use radiologic procedures in diagnosis; 4) Recognize both the value and limitations of neuropathology; and 5) Discuss newly described diseases and their connection to Neuro-Ophthalmology.

7:45 am - 8:00 am	**Introduction**	**Thurgood Marshall Ballroom**
8:00 am - 10:00 am	**Frank B. Walsh Session I** *Moderators: Sophia M. Chung, MD & Collin McClelland, MD*	**Thurgood Marshall Ballroom**
10:00 am - 10:30 am	**Coffee Break**	**Exhibit Hall C**
10:30 am - 12:30 pm	**Frank B. Walsh Session II** *Moderators: Michael C. Brodsky, MD & Yanjun (Judy) Chen, MD, PhD*	**Thurgood Marshall Ballroom**
12:30 pm - 1:00 pm	**Lunch**	**Exhibit Hall C**

1:00 pm - 2:45 pm	**Poster Session I: Clinical Highlights in Neuro-Ophthalmology**	**Exhibit Hall C**
3:00 pm - 5:00 pm	**Frank B. Walsh Session III** *Moderators: James A. Garrity, MD & Heather E. Moss, MD, PhD*	**Thurgood Marshall Ballroom**
5:15 pm - 5:45 pm	**Frank B. Walsh Committee Meeting**	**Harding**
5:15 pm - 5:45 pm	**Fellowship Director's Meeting**	**Coolidge**
5:30 pm - 6:30 pm	**Members-in-Training Program and Reception** (All students, residents and fellows-in-training are encouraged to attend.)	**Marriott Foyer**
5:45 pm - 6:15 pm	**Fellowship Committee Meeting**	**Coolidge**

Frank B. Walsh Session I

Moderators: Sophia M. Chung, MD & Collin McClelland, MD

Frank B. Walsh Session II

Moderators: Michael C. Brodsky, MD & Yanjun (Judy) Chen, MD, PhD

Frank B. Walsh Session III

Moderators: James A. Garrity, MD & Heather E. Moss, MD, PhD

"Pseudo-Pseudotumor Cerebri"

Valerie Biousse[1], Jose Velázquez Vega[2], Amit Saindane[3], Nancy Newman[4]

[1]Emory University School of Medicine. Emory Eye Center, Atlanta, Georgia, USA, [2]Emory University School of Medicine. Department of Pathology, Atlanta, Georgia, USA, [3]Emory University School of Medicine. Department of Radiology, Atlanta, Georgia, USA, [4]Emory University School of Medicine, Atlanta, Georgia, USA

History & Exam

A 54-yo man presented with a 10-month history of daily headaches and bilateral disc edema. PMHx was remarkable for uncomplicated type-2 diabetes mellitus, and hypothyroidism. He developed headaches in 07/2014 after being stung by wasps. He also had fluctuating blurry vision. An ophthalmologist found normal VA and disc edema OU. MRI brain/orbits with contrast (12/19/2014) was normal except for some "volume loss". RPR, Lyme, TSH, ANA, ESR were normal/negative. A neurologist (03/03/2015) found normal neurologic and general examinations (BMI 30kg/m2). Brain MRI with contrast (03/11/2015) showed no abnormal enhancement and normal parenchyma. The subarachnoid spaces along the bilateral perirolandic and posterior frontal parenchyma were prominent. Repeat ophthalmologic evaluation (April 23, 2015) showed normal VA and persistent bilateral disc edema. HVF showed enlarged blind spots and nasal steps OU. Headaches and visual changes persisted with pulsatile tinnitus. Brain MRV/MRA with contrast (04/28/2015) showed a large left arachnoid granulation in distal left transverse sinus. LP (04/29/2015) was traumatic and painful and showed CSF-OP 12cm, pink hazy CSF, 124/ul nucleated cells (32% neutrophils, 66% lymphocytes), 22599 RBC/ul, glucose 104mg/dl, protein >300mg/dl, CSF cytology negative; there were a few plasmacytoid/plasmablasts felt to result from blood contamination. SPEP showed moderate hypogammaglobulinemia. Headaches and tinnitus improved dramatically after the LP. The diagnosis of pseudotumor cerebri was made and he was given acetazolamide 500 mg bid, which was not tolerated and was stopped. Ophthalmologic examination (05/22/2015) was unchanged with persistent bilateral disc edema and improved VF. Neurologic evaluation (06/02/2015) continued to be unremarkable. LP under fluoroscopy (06/03/2015) was again difficult and painful and showed CSF-OP 25.8cm, clear CSF with xanthochromia, 90/ul nucleated cells (90% lymphocytes), 288 RBC/ul, glucose 100mg/dl, protein <6mg/dl, CSF cytology negative. His symptoms improved for 10 days. Ophthalmologic examination (06/25/2015) was unchanged with persistent bilateral disc edema and stable VF. Another test was recommended.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Pseudo-Pseudotumor Cerebri"

Answer

Final Diagnosis
Isolated raised intracranial pressure for one year revealing a primary spinal leptomeningeal malignant melanoma.

Summary of Case
Imaging of the spine was recommended. The abnormal CSF suggested a meningeal process, and we had no explanation for what seemed to be bilateral papilledema. The two LPs were technically difficult and painful and we were concerned about a spinal cord/spinal meningeal neoplasm. Spinal imaging was not done and instead, his evaluation focused on looking for evidence of lymphoma (because of the few plasmacytoid/plasmablasts seen on first LP). A repeat LP under fluoroscopy (07/31/2015), which was again difficult and painful, showed CSF-OP 24cm, only 1cc of CSF was obtained and sent to pathology; cytology was negative. His symptoms did not improve. Repeat SPEP was unchanged. CBC showed mildly elevated WBC. He had normal chest/abdomen/pelvis CT (05/26/2015), hematology evaluation (08/12/2015) followed by a bone marrow biopsy (09/03/2015), bone survey, chest X-Ray, whole body PET-CT (09/02/2015). Ophthalmologic examination (09/10/2015) was unchanged with persistent bilateral disc edema and stable VF. He still complained of severe headaches and fluctuating vision. He mentioned episodic unusual feeling in his legs with episodes during which he was not able to walk normally. MRI of the entire spine with contrast showed diffuse leptomeningeal enhancement involving the entire spine, worse at the lumbar and sacral levels, where there was circumferential thickened leptomeningeal enhancing soft tissue occupying the thecal sac. Repeat brain MRI with contrast showed mild leptomeningeal enhancement at the skullbase. The patient was admitted to the hospital and a biopsy of the mass at the L2 level was performed via posterior laminectomy. Pathology showed a leptomeningeal melanocytic neoplasm, consistent with a malignant melanoma.1 He had no prior skin melanoma and repeat CT of chest/abdomen/pelvis was normal. Molecular studies were negative for BRAF, GNAQ and GNA11 mutations,2 but showed alteration in the RIPK1 gene which has been recently described as a driver in melanoma.3

Struggle/Dilemma of the Clinical Presentation Description
Our patient had clinical evidence of increased intracranial pressure with headaches and papilledema. The diagnosis of idiopathic intracranial hypertension had been suggested despite abnormal CSF, and his CSF changes were felt to be secondary to traumatic LPs. The absence of elevated CSF protein on the second LP and the lack of neurologic symptoms resulted in delayed spine imaging. Chronic papilledema in spinal cord neoplasm remains difficult to explain and will be discussed at the meeting.4,5,6

Keywords: Papilledema, headaches, Malignant melanoma, Spinal cord neoplasm

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"A "Frosty" Altered Level of Consciousness"

Alaa Bou Ghannam[1], Emily McCourt[1], Victoria Pelak[1], Jeffrey Bennett[1], Prem Subramanian[1], David Smits[1]

[1]*University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA*

History & Exam

15-year-old previously healthy male, transferred because of 9-day history of headache, difficulty walking, diplopia, blurry vision and new onset altered level of consciousness. Neurologic examination was remarkable for delirium with semi-coherent speech, VA of CF 2ft and 20/400, no APD, and bilateral abduction deficits. He had bilateral hip flexor weakness(3/5), 2+ DTR, flexor plantar responses, bilateral upper extremity dysmetria, and ataxic gait requiring two-person assist. Prior MRI imaging showed bilateral optic sheaths' complex enlargement and leptomeningeal enhancement. Lumbar puncture revealed opening pressure of 46 cmH2O with 298WBCs (46% PMN, 36% L, 14% Mono), protein 266, and glucose 20. Cytology was negative for atypical cells. Patient was started on vancomycin, ceftriaxone and levofloxacin. Extensive workup for infections was negative (Quant gold, EBV, Bartonella, RPR, HIV, Coxiella, Brucella, VZV, Enterovirus, HSV, WNV and Lyme). CSF cultures were negative for bacterial and fungal growth. ESR(47) and CRP(7.7) were both elevated. ANA, c-ANCA, p-ANCA, ACE, C3, C4 were all negative. The patient's mental status declined and he developed bilateral lower extremity weakness; after 10 days, he became difficult to arouse with moaning verbal responses, 3+ DTR, and extensor plantar responses. Serial LPs showed rising WBC. Repeat MRI brain and spine showed increased diffuse leptomeningeal enhancement, T2 hyperintensity extending from lower cervical spine to conus involving ventral gray matter ; bilateral optic nerve, chiasm and optic tract enhancement, and irregularities in posterior globes on T2 weighted images. Ophthalmologic exam revealed visual acuity of CF at 1ft in right and BTL in left eye with normal intraocular pressures. Pupils were small and minimally reactive with no APD; EOM assessment was difficult due to impaired mental status. Dilated fundus exam showed bilateral disc edema with diffuse, perivascular sheathing of the major retinal veins, and scattered intraretinal hemorrhages. Several studies were performed and a diagnostic test was completed.

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"A “Frosty” Altered Level of Consciousness"

Answer

Final Diagnosis

The final diagnosis was primary angiitis of the central nervous system (PACNS) with frosted branch angiitis (FBA) PACNS is a rare condition (2.4 per one million), defined as vasculitis limited to the CNS with no identifiable cause. The clinical features of PACNS are highly variable. The most common symptoms are headache (50–60%) and altered cognition (50–70%). Most patients can have hemiparesis, ataxia, cranial neuropathy, visual symptoms, extrapyramidal signs, seizures and/or myelopathy. PACNS usually arises in the fourth or fifth decade of life, with half of cases beginning between ages 37–59 years. MRI brain can be as variable as the clinical presentation and can show T2 hyperintensities involving the cortex, subcortical white matter and/or deep grey matter. Brain biopsy is needed for definitive diagnosis and typically shows transmural inflammation with injury to the vessel wall. There is typcially an angiocentric inflammatory infiltrate as seen in this case. There are different subtypes and in the granulomatous subtype, extensive beta amyloid deposition in vessel walls with associated inflammation can be present Acute frosted branch angiitis in children is a very rare presentation that has been reported mostly in Japan. The condition is bilateral and characterized by extensive perivascular exudates with a “frostlike” quality. The reported age range is between 2 and 42 years. Although the etiology of frosted branch angiitis can be unknown, other causes of retinal vasculitis should be excluded, especially viral retinitis (CMV, EBV…) sarcoidosis, multiple sclerosis, toxoplasmosis, syphilis, and Behçet's disease. Infiltrative causes such as lymphoma and leukemia may occasionally mimic FBA. These conditions were excluded in our patient, and to our knowledge, there is no other reported cases in the literature of frosted branch angiitis associated with primary CNS vasculitis

Summary of Case

This is a case of a 15-year-old male with altered level of consciousness, visual changes and CSF studies showing neotrophilic pleocytosis with low glucose and high protein. His retinal exam was consistent with frosted branch angiitis and MRI brain and spine showed diffuse leptomeningeal enhancement. Patient was getting worse on broad spectrum antibiotics, so the team proceeded with a right frontal craniotomy for leptomeningeal and cortical biopsy. Pathology revealed small vessel necrotizing vasculitis, predominantly affecting the white matter with mixed lymphocytic, histiocytic and neutrophilic infiltrates consistent with primary angiitis of the central nervous system (PACNS). Patient was started on IV steroids 40mg BID for 6 days and then shifted to oral steroids (1mg/kg) with slow taper. Cyclophosphamide infusions monthly was initiated for a total of 6 months. The patient improved clinically and radiologically. His vision improved to 20/150 and CF 3ft and there was resolution of the frosted branch angiitis with residual macular edema and optic nerve swelling. To our knowledge, there is no other reported cases in the literature of frosted branch angiitis associated with primary angiitis of the central nervous system

Struggle/Dilemma of the Clinical Presentation Description

This clinical presentation and CSF studies were consistent with bacterial meningitis. However all CSF infectious studies, including gram stains and cultures were negative and the patient was getting worse on broad-spectrum antibiotics. Retinal exam was consistent with frosted branch angiitis. Although rare, FBA is a non-specific finding associated with long differential diagnosis including infectious, inflammatory and infiltrative causes. In this case, retinal findings supported consideration of non-infectious processes, and diagnosis was made after brain biopsy.

Keywords: CNS vasculitidies, bilateral vision loss

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"Uncertainty with a Twist of Lyme"

Amrita-Amanda Lakraj[1], Sang Hong[2], Jennifer Connelly[3], Elizabeth Cochran[4]

[1]Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, Milwaukee, Wisconsin, USA, [2]Froedtert Eye Institute and Medical College of Wisconsin, Milwaukee, Wisconsin, USA, [3]Froedtert Hospital and Medical College of Wisconsin, Dept. of Neuro Oncology, Milwaukee, Wisconsin, USA, [4]Froedtert Hospital and Medical College of Wisconsin, Dept. of Pathology, Milwaukee, Wisconsin, USA

History & Exam

The patient is a 59-year-old woman who presented with vision loss. Her ophthalmologic history is significant for myopic astigmatism and presbyopia. Her past medical history is notable for left breast cancer (T2N0 invasive lobular carcinoma, ER/PR positive, HER2/neu negative) s/p left mastectomy, chemotherapy, and radiation (2006); Celiac disease; Grave's disease s/p partial thyroidectomy (1977) and radioactive iodine (2000); Lyme disease (2013); and progressive neuropathy of unclear etiology (onset 1998). Extensive testing for her neuropathy from 1998-2014 was significant for positive serum Lyme IgM Western Blot 10/2013 (treated with IV antibiotics). In January 2015, the patient developed blurred vision. By April 2015 she presented to her optometrist with double vision and was found to have mild fullness of bilateral optic discs. MRI brain was reportedly unremarkable. Recent MRI of the C/T spine demonstrated abnormal leptomeningeal enhancement extending along the conus medullaris and lumbar nerve roots as well as mild cord edema. Lumbar puncture revealed elevated white count (12), elevated protein (>600), normal glucose, positive Lyme IgM western blot, and negative culture and cytology. She was referred for Neuro-ophthalmologic evaluation. Her initial neuro-ophthalmologic exam 5/2015 was notable for visual acuities with correction of 20/50 OD (ph 20/50+2) and count fingers at 6 inches OS; 1+ APD OS; 11/11 Ishihara color plates OD and 4/11 OS; superotemporal constriction OD on confrontation visual fields, and generalized constriction OS; mild limitation of upgaze OU, mild limitation of adduction and abduction OD and mild limitation of abduction OS. On fundus exam she had mild optic disc swelling OU. The presence of bilateral optic neuropathy with multifocal cranial nerve involvement on exam raised concern for a leptomeningeal process, particularly given recent leptomeningeal enhancement on spinal MRI. The patient was admitted for further workup and management.

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Grant Support: None.

"Uncertainty with a twist of Lyme"

Answer

Final Diagnosis
Metastatic leptomeningeal carcinomatosis

Summary of Case
The patient was admitted and started on Ceftriaxone for possible CNS Lyme disease. ID consultation suggested CNS Lyme to be unlikely; antibiotics were stopped. The patient insisted that she had "chronic Lyme disease". MRI orbits demonstrated diffuse enlargement and hyperenhancement of bilateral cranial nerves 3, 5, 7/8 and right cranial nerves 9 /10; mild abnormal enhancement of the superior and inferior colliculus, bilateral optic canals, and right optic nerve. Repeat lumbar puncture again showed elevated WBC count and protein; flow cytometry was negative. CT chest/abdomen/pelvis was negative for occult malignancy. A PET scan showed increased uptake (likely physiologic) in the right breast, with subsequent normal breast MRI. IVIG was initiated for possible autoimmune/inflammatory process. The patient's visual acuity worsened to 20/150 OD and hand motion OS. Leptomeningeal biopsy was recommended, however neurosurgery felt the risks of a biopsy outweighed the benefits and declined. IV methylprednisolone was then initiated (1g /day x 5 days). Subsequent ophthalmologic exam demonstrated improved visual acuity (20/40-2) OD and stable vision OS. PLEX with oral steroid taper was initiated; subsequent exam demonstrated improved visual acuities of 20/25-3 OD and 20/400 eccentrically OS (niph); the bilateral optic disc swelling had resolved. The etiology of her leptomeningeal disease remained unclear. The optic nerve sheath was considered for potential biopsy target and the patient was referred to oculoplastics, however repeat MRI orbits demonstrated resolution of the previously seen abnormal enhancement of the right optic nerve. We again advocated for biopsy of an involved lumbosacral nerve root. Neurosurgery acquiesced and carried out a biopsy of the leptomeninges (L5 rootlet). Pathology demonstrated metastatic carcinoma consistent with invasive lobular carcinoma of breast origin (ER/PR positive; HER2Neu negative). The patient was started on high dose systemic methotrexate x 5 cycles and subsequently letrozole/palbociclib for treatment of metastatic leptomeningeal breast cancer.

Struggle/Dilemma of the Clinical Presentation Description
Leptomeningeal carcinomatosis was felt unlikely based on the biology/low grade of her original breast cancer, and the fact that PET, MRI breast, CT chest/abdomen/pelvis, and multiple CSF evaluations (with repeated cytology) failed to demonstrate any evidence for metastatic breast cancer. Suspicion for an inflammatory process was heightened by the clinical and radiographic improvement (albeit transient) to IVIG, PLEX, and high dose steroids. The positive Lyme IgM result in the CSF was misleading.

Keywords: Optic Neuropathy, Optic disc edema, Metastatic Breast Carcinoma, Cranial nerve palsies, Complications of cancers

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"Papilledema Gone Wrong"

Ahmara Ross[1], Payal Patel[2], Jessica Panzer[3], Grant Liu[4]

[1]University of Pennsylvania Scheie Eye, Philadelphia, Pennsylvania, USA, [2]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [3]The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [4]Perelman School of Medicine at the University of Pennsylvania., Philadelphia, Pennsylvania, USA

History & Exam

A 12 year old obese female with a history of enterovirus meningitis presented with throbbing, constant, 10/10, occipital and positional headaches, associated with diplopia, photophobia, nausea, and vomiting for one week in the setting of a recent 20 lb. weight gain. Her vision, pupils, fields, and color vision were all unremarkable. Her fundus exam was significant for bilateral papilledema, and her neurologic exam was otherwise normal. MRI with and without contrast and MRV were unremarkable. Her lumbar puncture opening pressure was 60 cmH2O with a normal CSF cell count, protein and glucose. She was started on Diamox with a presumptive diagnosis of IIH and discharged home. Two weeks later she re-presented with similar symptoms and a change in mental status. Neurologic exam was remarkable for posturing, mutism, poor food intake, and regressive behaviors such as urinary incontinence. Her fundus exam showed improved papilledema but her neurologic exam was significant for delirium and slowed reaction time. Routine EEG, MRI brain, MRA head and CSF studies were obtained and all were unremarkable, except for a repeat but bland lumbar puncture with an elevated opening pressure of 48 mmHg. Six weeks later her exam was significant for obtundation, extensive bulbar dysfunction requiring intubation for airway protection, and flaccid quadriparesis resulting in admission to the Neuro-NICU. Extensive tests showed abnormal laboratory findings that were non-specific including a persistently elevated ESR, normocytic anemia, mild transaminitis. Repeat MRI showed diffuse white matter changes involving the periventricular regions extending into the centrum semiovale, corpus callosum, brainstem and cerebral peduncles. MR spectroscopy showed non-specific findings of diffuse elevation of lactate throughout the brain parenchyma, especially in the CSF. N-acetylasparate was decreased diffusely with a pronounced decrease of N-acetylasparate in the right basal ganglia compared to the left basal ganglia. Choline and myoinositol was diffusely elevated.

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"Papilledema Gone Wrong"

Answer

Final Diagnosis

Paradichlorobenzene (PDCB) toxicity

Summary of Case

She underwent brain biopsy of the frontal lobe, which revealed non-specific reactive astrocytosis. Dermatology was consulted for areas of skin thickening and discoloration, which were felt to be non-specific thin hyperpigmented, lichenified plaques on her ankles, knees and elbows bilaterally suggestive of retention hyperkeratosis. She was treated with IVIg, steroids, and plasmapheresis for a presumed autoimmune process, but she did not demonstrate improvement.. With directed questioning, the neurology team elicited a history of significant chronic mothball inhalation exposure describing use of multiple mothballs as air fresheners. Serum paradicholorobenzene level was 2800 ug/L with the asymptomatic mean reported to be 2.1 ug/L. Urine dichlorophenol levels were 200,000ug/L with asymptomatic mean reported at 200ug/L. The progressive neurologic decline associated with periventricular white matter hyperintensities on MRI, is consistent with paradichlorobenzene (PDCB) toxicity2. Fifteen cases have been reported in the literature. Additionally, as with our patient, it is not uncommon to have an ichthyosis-like dermatosis early in the presentation.1,2 In retrospect, normocytic anemia and mildly elevated transaminases were also present since admission, findings consistent with systemic effects of PDCB toxicity.3 Her elevated serum paradicholorobenzene and urine dichlorophenol (DCP) levels confirmed the diagnosis. This rare presentation of PDCB toxicity consistent initially with pseudotumor cerebri syndrome/IIH but later characterized by encephalopathy and white matter changes has been reported only once before. This is the first pediatric case presented.

Struggle/Dilemma of the Clinical Presentation Description

This presentation of paradichlorobenzene (PDCB) toxicity presented a dilemma given his initial presentation of pseudotumor cerebri in an obese female. Additionally, this patient had a slowly progressive followed by an acute neurological decline. Finally, given the storage properties of PDCB in fat, as the patient weight loss significantly effected her clinical course

Keywords: Papilledema, Idiopathic intracranial hypertension., Disc edema

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"Occam Rings True"

Reid Longmuir[1] Michael Bradshaw[1], Taylor Davis[1], Woon Chow[1], Laura Craig-Owens[1], Kim Ely[1], Katherine McDonell[1]

[1]Vanderbilt University Medical Center, Nashville, Tennessee, USA

History & Exam

A 57-year-old, previously healthy man was referred for vision loss in both eyes. Six weeks before our evaluation, he presented to an outside ophthalmologist with "greying" of the central vision in his right eye that progressed to blindness over a week. After another week, the same symptoms affected his left eye and likewise progressed over two weeks, although he remained able to see hand motion with the left eye. There was a new holocephalic headache that was worse in the mornings and evenings but was not positional. He also reported burning, electric pain over the left shoulder that radiated down the spine with neck movements. Review of systems was otherwise unremarkable. His ophthalmologist noted severe bilateral papilledema and a brain MRI reportedly revealed a 2-3 cm presumed olfactory groove meningioma. An outside neurosurgeon felt there was no indication for intervention on the olfactory groove lesion and the patient was referred to neuro-ophthalmology 2 weeks later. He was a prison guard but never had positive purified protein derivative testing. He neither drank alcohol nor smoked and was current on preventative cancer screening. His mother died of a brain tumor in her 70s but there was otherwise no significant family history. He was transferred to the emergency department and admitted to the neurology service the day of presentation to clinic, based on poor vision and need for further diagnostic testing. He had normal vital signs, left-sided anosmia, a relative afferent pupillary defect on the right, and severe bilateral papilledema. Visual acuity was counting fingers at 1 foot OD and at 4 feet OS. He had a large central scotoma in each eye with confrontation visual field testing. He had normal ocular motility. He reported Lhermitte's phenomenon and had subtle nuchal rigidity. The remaining general and neurologic examinations were normal.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Occam Rings True"

Answer

Final Diagnosis
Intestinal type sinonasal adenocarcinoma with diffuse meningeal metastases

Summary of Case
Brain and orbit MRI with fat suppression demonstrated a left olfactory groove contrast-enhancing mass, bilateral papilledema with enhancing right optic nerve head, longitudinally extensive perineural enhancement of the meninges surrounding both optic nerves, sparing the optic nerve fascicles and chiasm, as well as meningeal enhancement along the ventral pons and surrounding the cervical spinal cord. No intraparenchymal lesions were identified. Computed tomography of the chest, abdomen and pelvis was normal. Sedimentation rate and C-reactive protein, complete blood count and complete metabolic panels were normal other than a mild elevation in ALT to 71 units/L. Lumbar puncture demonstrated elevated opening pressure at 31 cm H_2O, 28 nucleated cells/uL (79% lymphocytes), 0 erythrocytes/uL, hypoglycorrhachia with glucose 27 mg/dL, elevated protein at 162 mg/dL. Infectious studies, including syphilis, tuberculosis and fungal testing as well as serum and CSF angiotensin converting enzyme levels were normal. CSF cytology and flow cytometry was nondiagnostic. After infectious studies returned negative, he was treated empirically with 1000 mg intravenous methylprednisolone every 24 hours. After the first dose, his visual acuity remained 2/400 OD but improved to 20/40 -2 OS. However, after the second dose his funicular pain and his vision worsened to admission baseline. Biopsy of the olfactory groove lesion revealed an adenocarcinoma with signet ring cell features. The CSF cytology was re-evaluated after the tissue diagnosis was established and felt to be consistent with metastatic adenocarcinoma with signet ring features. As body positron emission tomography did not reveal another source of his cancer, the tumor is consistent with an intestinal type sinonasal adenocarcinoma with diffuse meningeal metastases. The patient was evaluated by oncology and radiation oncology and given a very poor prognosis. Palliative whole-brain irradiation was given and he was discharged with home hospice.

Struggle/Dilemma of the Clinical Presentation Description
The presentation suggested bilateral optic neuritis versus raised intracranial pressure with papilledema, and the clinical, laboratory and imaging findings supported carcinomatous meningitis, neurosarcoidosis or fungal meningitis. The key to unraveling this case was Occam's "lex parsimoniae": all of his neurologic manifestations must be related, including the anosmia/olfactory groove mass. Although initially dismissed as a benign meningioma, biopsy of the oflactory groove mass proved the diagnosis of carcinomatous meningitis from sinonasal adenocarcinoma in the end.

Keywords: Papilledema, metastatic carcinoma, Optic neuritis, Meningitis, headaches

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"A Prolonged Path To The Final Diagnosis"

Cindy Lam[1], Edward Marglin[1]

[1]*Department of Ophthalmology & Vision Sciences, University of Toronto, Toronto, Canada*

History & Exam

Previously healthy 25-year-old male presented with a 3-week history of frontal headache, right 3rd nerve palsy with ptosis, and areflexia of the left leg. MRI brain was normal. Two days later new symptoms developed: lower back pain, paresthesias, left leg weakness, right facial weakness. On neuro-ophthalmic exam pertinent findings included bilateral upper lid ptosis, right adduction deficit, pupil-sparing left 3rd nerve palsy, and right 7th nerve palsy. MRI brain and spine demonstrated enhancement and thickening of the cauda equina nerve roots, enhancement within the right internal auditory canal with a nodularity of the right facial nerve, and enhancement in left Meckel's cave. Two LPs demonstrated very elevated protein (3.3-5.5 g/L), oligoclonal banding, and pleocytosis (100 cells/um, 98% lymphocytes). Extensive infectious and inflammatory work-up of the serum and CSF was negative. CSF flow cytometry, lymphoma panel, and SPEP were negative. A provisional diagnosis of atypical GBS (Miller Fischer variant) was made and IVIG was administered without symptom improvement. Methylprednisolone was administered intravenously (1 g x 5 days), leading to improvement in lower back pain, paresthesias and left leg weakness. Two months later all symptoms had resolved. However, eleven months after initial presentation, new progressive right sided weakness developed. MRI of the brain and spine demonstrated a large enhancing lesion in the left centrum semiovale with a surrounding halo of restricted diffusion. No cauda equina enhancement was seen. Four expert neuroradiologists debated whether diagnosis was Balo's concentric sclerosis or CNS lymphoma. Three LPs were performed: cytology was negative for malignancy and flow cytometry was inconclusive. CT thorax, abdomen, and pelvis was negative. A new left facial palsy developed. Repeat MRI showed increase in the left frontal mass, enhancement of left facial nerve and internal auditory canal and resolution of enhancement in right IAC and left Meckel's cave. A diagnostic procedure was performed.

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"A Prolonged Path To The Final Diagnosis"

Answer

Final Diagnosis
Burkitt's CNS lymphoma.

Summary of Case
Brain biopsy was performed which established the final pathological diagnosis of Burkitt's CNS lymphoma. This 25-year-old patient presented with asymmetric weakness predominantly of the lower limb, areflexia, and cranial neuropathies that fluctuated over 11 months. He was initially suspected to have Miller Fisher variant of GBS based on CSF findings of increased protein, MRI demonstrating cauda equina enhancement, and a negative extensive infectious, inflammatory, and malignant work-up [1,2]. However, a high index of suspicion for masquerade was maintained. Several features of the presentation were atypical for GBS: extremely high protein level in CSF, moderate CSF pleocytosis, marked asymmetrical weakness and areflexia, lack of ataxia, lack of response to IVIG, and marked steroid responsiveness [2]. Onset of new neurological symptoms and new brain lesions prompted a brain biopsy that ultimately diagnosed Burkitt's CNS lymphoma. Burkitt's CNS lymphoma is extremely rare, with only a handful of described cases. Patients mainly present with intraparenchymal involvement, usually of the cerebral hemispheres, and rarely of the pituitary, cerebellum, or brainstem [3]. Three cases with primary spinal or epidural involvement have been described with one case also demonstrating spinal nerve root enhancement [4-6]. Our case is unique in that it demonstrated widespread extraparenchymal manifestations of Burkitt's lymphoma: enhancing lesions of the facial nerves, within the internal auditory canal, Meckel's cave, and spinal nerve roots. Another striking feature was steroid responsiveness with complete resolution of symptoms for nine months following treatment with steroids before relapsing and re-presenting with a large frontal mass. A total of five LPs performed before the diagnosis was made were negative for malignancy demonstrating how difficult it can be to diagnose CNS lymphoma by CSF analysis alone.

Struggle/Dilemma of the Clinical Presentation Description
The patient presented with atypical features of GBS, with MRI brain and spine demonstrating extraparenchymal enhancement. Though masquerade was suspected, an extensive work-up including numerous LPs failed to provide an alternate diagnosis. Treatment with steroids led to dramatic resolution of all symptoms masking further manifestations of malignancy for a very long time. Despite three more LPs, it was only after developing a lesion amenable for brain biopsy that the final diagnosis was made.

Keywords: Complications of cancers, Cranial nerve palsies, Guillain-Barré, Miller Fisher variant, Spinal cord neoplasm

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"Keep Your Eye On the Ball"

Danielle Rudich[1], Eugenia Vining[2], Kenneth Allen[3], Joel Geffin[1], Mena Mansour[2], Robert Lesser[1]

[1]The Eye Care Group, Waterbury, Connecticut, USA, [2]Yale University School of Medicine, New Haven, Connecticut, USA, [3]Waterbury Hospital, Waterbury, Connecticut, USA

History & Exam

In March 2014, an 82-year-old male developed left sided facial pain and numbness over his left temple and periorbital region. He was treated for a presumed dental infection with no response. MRI brain in July 2014 showed only microvascular white matter changes. Because his symptoms persisted, MRI brain was repeated in February 2015, and the left sided muscles of mastication were relatively hyperintense on FLAIR/T1 post contrast weighted images and there was abnormal enhancement of the third branch of the left fifth cranial nerve, just beyond Meckel's cave. MRI orbits showed questionable asymmetric enhancement of the second branch of the left trigeminal nerve within the left infraorbital foramen. Neuro-oncology work up including spinal tap and laboratory workup were negative. A neurologist diagnosed Tolosa Hunt syndrome but there was no response to Prednisone. The patient gradually developed binocular horizontal diplopia, blurred vision and redness of the left eye, and was referred for neuro-ophthalmology consultation in May 2015. Visual acuity was 20/20 OD and 5/200 OS with left fifth and sixth cranial nerve palsies. The left eye was injected with a central corneal ulcer and small hypopyon. MRI from June 2015 showed subtle enhancement of the left fifth and sixth cranial nerves at the brainstem exit, atrophic left pterygoid and temporalis muscles and thinning of the left lateral rectus muscle. Prior dermatology records/pathology slides showed no malignancy. ENT felt there was no lesion to biopsy for diagnosis. Perineural tumor spread was suspected but there were no available biopsy sites. MRA/V brain was normal and PET scan showed no evidence of malignancy or metastases. The corneal ulcer grew Candida albicans and worsened, leading to a corneal perforation, requiring penetrating keratoplasty. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Keep Your Eye On the Ball"

Answer

Final Diagnosis
Desmoplastic Melanoma with perineural tumor spread along the left fifth and sixth cranial nerves.

Summary of Case
In August 2015, the patient complained that a firm area developed along the left side of his nose. MRI showed a new soft tissue mass along the left lateral nose and anterior to the left maxillary sinus, tracking posteriorly along the inferior orbital groove towards the left foramen rotundum and left cavernous sinus. There was progressive enhancement of the proximal left fifth and sixth cranial nerves. Transnasal biopsy demonstrated high-grade spindle cell neoplasm, positive for SOX-10, S-100 immunostains and rare tumors cells were Melan-A positive, consistent with desmoplastic melanoma (DM). DM, a spindle cell neoplasm, is a rare cause (less than 4% of cases) of cutaneous melanomas. DM most commonly presents as a painless non-pigmented plaque of the head or neck (1) and is most commonly positive for S-100 and rarely HMB-45 and Melan-A (2,3). In the literature, there are only seven reported cases of perineural invasion of the intracranial trigeminal nerve secondary to DM (3). Treatment with immunotherapy and radiation has been described (3,4). The patient was treated with Pembrolizumab, but the mass grew and he was switched to hypofractionated radiation therapy and ipilimumab/nivolumab in November 2015. MRI in July 2016 showed decreased enhancement and reduction in tumor size.

Struggle/Dilemma of the Clinical Presentation Description
The clinical findings suggested perineural tumor spread. There were no skin lesions or prior history of malignancy. Multiple imaging studies, blood work and spinal tap were inconclusive for over one year. The patient was followed closely and underwent biopsy as soon as there was accessible tissue. He developed a perforating corneal ulcer due to cranial nerve dysfunction, highlighting the importance of close monitoring of corneal status in patients with perineural spread along the trigeminal nerve.

Keywords: 6th nerve palsy, trigeminal, Tumor, Diplopia

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"Alcohol is Never the Answer, but it Does Make you Forget the Question"

Ali Saber Tehrani[1], Diana Londono[2], Thomas Rashid[3], Manuel Doria[4], Julia Biernot[2], Jorge Kattah[2]

[1]University of Illinois, Peoria, Illinois, USA, [2]Department of Neurology, University of Illinois College of Medicine in Peoria, Peoria, Illinois, USA, [3]University of Illinois College of Medicine in Peoria, Peoria, Illinois, USA, [4]Department of Pathology, University of Illinois College of Medicine in Peoria, Peoria, Illinois, USA

History & Exam
A 63-year old male with a history of alcohol abuse presented with two weeks of confusion and imbalance. On exam, he had left beating nystagmus on left gaze, and right beating and torsional nystagmus on right gaze. Head impulse test was abnormal in all canals bilaterally with video head impulse test showing left horizontal vestibulo-ocular reflex gain: 0.3, right: 0.4. Finger to nose and heel to shin were abnormal bilaterally. Gait was abnormal and he was falling towards his right side. Neuropsychiatric evaluation revealed impairment in the following domains; intellectual skills, attention/visual sequencing and memory. MRI did not show any acute abnormalities. Infusion of 500 mg of thiamine did not improve head impulse test gain.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Alcohol is never the answer, but it does make you forget the question"

Answer

Final Diagnosis
A pelvic CT scan showed adenopathy in the right pelvis, suspicious for metastatic disease. An MRI pelvis demonstrated stage T3b N1 M0 prostate carcinoma on the right, with possible involvement of the seminal vesicle. Pathologic analysis of biopsy results from the radical prostatectomy and lymph node dissection revealed mixed neuroendocrine carcinoma (75%) and adenocarcinoma (25%). The patient underwent chemotherapy with Etoposide and Cisplatin. T2 MRI signal changes improved transiently. Repeated anti-Hu level was negative three weeks after surgery. The patient did not improve neurologically, and unfortunately passed away about four months after presentation. Final diagnosis: Anti-Hu paraneoplastic process associated with neuro-endocrine tumor of the prostate.

Summary of Case
A 63-year old male presented with confusion, ataxia, nystagmus, and bilateral abnormal head impulse test in the context of alcohol abuse. A brain MRI on day of admission did not reveal any acute abnormalities. A diagnosis of Wernicke's encephalopathy was entertained. Of note, the patient's head impulse test gain did not improve after thiamine infusion. Two days later, the patient developed right inter-nuclear ophthalmoplegia, left facial palsy, and dysphagia. CSF studies revealed 52 nucleated cells, 94% lymphocytes, normal protein and glucose. Repeat MRI revealed a T2 signal hyper-intensity in the left anterior inferior lateral frontal lobe, left hippocampus, left para-hippocampal gyrus, left amygdala, bilateral thalamic pulvinar nuclei, and the medial right frontal lobe. There was also subtle inferior extension to the mesencephalon/left paramedian pons. Thiamine levels came back normal. A paraneoplastic panel showed presence of anti-Hu paraneoplastic antibodies. The patient received 5 days of high dose steroids, followed by IVIG, and was continued on 60 mg daily of prednisone. An evaluation to establish the primary neoplastic etiology was initiated.

Struggle/Dilemma of the Clinical Presentation Description
The initial presentation of this patient with ataxia, nystagmus, bilaterally abnormal head impulse test, confusion, and history of alcohol abuse was concerning for Wernicke's encephalopathy. However, daily thorough examination revealed changes that prompted further investigation, including repeat MRI and CSF studies, to reach the underlying diagnosis.

Keywords: Autoimmune diseases, Nystagmus, 7th Nerve palsy, Paraneoplastic syndromes, Internuclear ophthalmoplegia

References
None.

"Nonchalant Midterm-taker Develops Altered Mental Status"

Shira Simon[1], Bruno Policeni[2], Matthew Thurtell[3]

[1]University of Iowa, Department of Ophthalmology, Iowa City, Iowa, USA, [2]University of Iowa, Department of Radiology, Iowa City, Iowa, USA, [3]University of Iowa, Department of Ophthalmology, Department of Neurology, Iowa City, Iowa, USA

History & Exam

A 19 year-old female presented in April 2016 with two weeks of worsening headaches, malaise, left-hand weakness, and confusion. Symptoms started during a trip to Cancun and one week after visiting a friend with mumps. Although she was becoming increasingly lethargic, she refused to seek medical attention during midterm exams. En route to an exam, she bent over to tie her shoelaces and collapsed, prompting her hospital presentation. Past medical history included optic neuritis of the right eye in 2013 with good response following ONTT protocol steroid therapy and headaches since junior high, which responded to NSAIDs. During her examination, she became increasingly confused, paranoid, and combative. She required sedation and sitters to obtain further investigations. Due to concern for meningoencephalitis, she was empirically started on IV vancomycin, ceftriaxone, and acyclovir. MRI brain and spine with contrast demonstrated enhancement of both optic nerves as well as a 6 mm focus of enhancement in the anterior aspect of the C4 vertebral body. CSF gram stain was negative, but there was an elevated protein concentration (132 mg/dL) and white cell count (195 cells per milliliter) with lymphocytic predominance. EEG demonstrated generalized slowing. Visual acuity was 20/40 in each eye, with no RAPD. Ocular motility was full without pain, internuclear ophthalmoplegia, or nystagmus. The anterior segment examination was normal; posterior segment showed optic disc pallor in the right eye and mild diffuse optic disc edema with no associated pallor in the left eye. Formal perimetry could not be obtained secondary to her confusion. Serologic and CSF testing demonstrated no infectious etiology (negative HSV, VZV, EBV, HHV5, West Nile, enterovirus, Lyme, mycoplasma, syphilis, HIV, TB, histoplasmosis, cryptococcus, bartonella, Q fever, and mumps). She was started on IVIG (400 mg/kg/day) for presumed aseptic meningitis. Her mental status continued to worsen. A diagnostic test was performed.

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Grant Support: None.

"Nonchalant Midterm-taker Develops Altered Mental Status"

Answer

Final Diagnosis
Tumor-negative anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis with bilateral optic neuritis

Summary of Case
Repeat MRI and LP were performed, along with a complete autoimmune and paraneoplastic panel. MRI demonstrated persistent mild patchy bilateral optic nerve enhancement as well as subtle leptomeningeal enhancement. ANA titer was positive; ESR, CRP, and anti-thyroid peroxidase antibody were elevated. CSF testing revealed negative aquaporin-4, with positive oligoclonal bands, elevated IgG index, and positive NMDA receptor antibody. NMDA receptor antibody was positive in serum, consistent with anti-NMDA receptor encephalitis with optic neuritis. Repeat PET and ultrasound examinations showed no teratoma or other malignancy. Anti-NMDA receptor encephalitis was first described in 2007, in association with ovarian teratoma. The classic presentation is with a prodromal illness, psychiatric symptoms, and decreased responsiveness. Since its description, it has become the second most common immune-mediated cause of encephalitis after acute disseminated encephalomyelitis. 80% of patients are women, 60% of whom have an associated tumor (5% of men). 75% of patients with anti-NMDA receptor encephalitis have a good recovery with treatment. Brain MRI is normal in up to 67% of patients, and EEG is abnormal in 90% of patients. Brain biopsy is unhelpful in diagnosis. Tumor-negative anti-NMDA receptor encephalitis with optic neuritis is very rare. There have been two adult cases reported since 2007: a 29 year-old male with history of presumed lymphocytic meningitis and a 32 year-old female with chronic depression. No standard of care exists, but case studies report promising results with concurrent IVIG (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) as first line therapy, and then second-line therapy of rituximab and cyclophosphamide. Our patient continued to deteriorate despite receiving IVIG with methylprednisolone. She was subsequently treated with rituximab and methylprednisolone with taper, and has returned to her baseline, with no recurrences to date.

Struggle/Dilemma of the Clinical Presentation Description
The differential diagnosis was originally infectious given her history of recent travel and exposures. However, clinical evaluation was challenging due to suboptimal patient cooperation with the precipitous decline in mental status necessitating quick action. Diagnostic and management dilemmas arose given a largely unrevealing infectious and inflammatory work-up and lack of clinical response to IVIG therapy.

Keywords: Optic neuritis, Meningo-encephalitis

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"It must be Voodoo... and he was Far from Spineless"

Norah Sydney Lincoff[1], Charles Chung[2], Lucia Balos[3]

[1]Jacobs School of Medicine and Biomedical Sciences, SUNY at Buffalo, Buffalo, New York, USA, [2]Jacobs School of Medicine, Department of Radiology, SUNY at Buffalo, Buffalo, New York, USA, [3]Jacobs School of Medicine, Department of Pathology, SUNY at Buffalo, Buffalo, New York, USA

History & Exam

A 35 yo legally blind gentleman was referred for evaluation because of neck and new lower back pain. His visual loss began 4 years prior, following a trip to "N'Orleans". He had been on a "Boys Trip" for 10 days, and had been cursed with Voodoo for not paying a cemetery tour guide as promised. He also was cursed with hearing loss and imbalance. He reported that no trial of medicine saved his sight, but that he was now at least less off balance, and felt his hearing loss was 50% improved. He was diagnosed with aseptic meningitis. He had been treated with antibiotics, steroids, IVIG, Methotrexate, and Cyclophosphamide. To further convince himself of the curse, he found himself in Tower One on 9/11, barely making it out alive. Neuro-ophthalmologic exam revealed vision of HM right eye and CF left eye. His pupils were poorly reactive. Motility exam was normal. Slit lamp examination was normal. Applanation Tonometry was normal. Funduscopic examination revealed bilateral severe optic atrophy,cupping, and vascular narrowing. He had markedly constricted visual fields of less than 20 degrees both eyes. An MRI of his brain revealed bilateral optic atrophy. An MRI of his spine revealed a diffuse "moth eaten" appearance to his vertebrae. A biopsy was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"It must be Voodoo... and he was Far from Spineless"

Answer

Final Diagnosis

Late involvement of the axial skeleton and pelvis with CNS sarcoid. Sarcoidosis of the axial skeleton is uncommon, but when it does occur, it fortunately can have this classic picture radiologically. CNS involvement is also rare (<16% of cases) and bilateral blinding optic neuropathy even less common (<5%). After the thorax, the skin and uvea of the eye are the most commonly affected, followed by the liver and heart. Only 10-30% of cases will have a chronic progressive pattern of disease. Gold standard for diagnosis is of course histological by biopsy.

Summary of Case

Maybe it is Voodoo. Patient is a 31 year old male with bilateral optic neuropathy, hearing loss which began following a bout of "aseptic meningitis", presented with the new symptom of low back pain. Past skin, bone marrow, liver and a brain biopsy had been unrevealing. A past imaging study revealed bilateral optic nerve enhancement. A past lumbar puncture showed 270 white cells and a protein of 140. The rest of his work up had been unrevealing including a negative Gallium Scan, Pet Scan, ACE level and Lysozyme titer. An updated study of his axial skeleton radiologically finally clinched the diagnosis. Biopsy of the patient's L1 pedicle confirmed the radiologic diagnosis of non caseating granulomatous disease, that some may equate with Voodoo. Though sarcoidosis involving the axial skeleton is unusual, it is radiologically a classic finding and very important to recognize.

Struggle/Dilemma of the Clinical Presentation Description

Imaging, laboratory testing, gallium scan testing and multiple biopsies were non diagnostic leaving the patient convinced for years that he was under a Voodoo spell. His LP suggested an inflammatory condition, so he carried the dx of probable AARON, and aseptic meningitis for 4 years. It is difficult to aggressively treat or convince other physicians to treat on suspicion alone, but one SHOULD, until further symptoms occur that clarify/confirm the diagnosis.

Keywords: Optic neuritis, Optic Neuropathy, Hearing Loss, Sarcoidosis

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"M.I.A."

Julie DeBacker[1], Janet Rucker[1], Josef Gutman[1], Heather Lau[1], Laura Balcer[1], Steven Galetta[1]

[1]NYU Langone Medical Center, New York, New York, USA

History & Exam

A 69-year-old man presented with a several year history of vertical double vision. At age 46, he presented with a two year history of imbalance, four year history of urinary urgency/frequency, and a six-month history of leg numbness and tingling. His history was significant for tuberculosis, treated (age 12). He took a multivitamin. He had no known toxic exposures. Family history revealed two brothers, ages 45 and 39 with dysuria. Prior exams revealed gynecomastia and high feet arches with hammertoe deformity, decreased right hearing, normal strength, lower extremity hyperreflexia, and progressive impaired pinprick and vibration sensation and tandem gait. Brain MRI was initially unremarkable, though two years later showed cerebellar vermian atrophy and 4 years later atrophy and T2 hyperintensities in the periventricular, deep, and subcortical white matter of both cerebral hemispheres. MR spectroscopy showed decreased parieto-occipital NAA. C-T spine MRI showed thoracic cord atrophy without abnormal signal. EMGs showed severe axonal polyneuropathy. Serum and CSF were unremarkable for vitamins B12 and E, ANA, heavy metals, Lyme, leukocyte Arylsulfatase A, CPK, Anti-glycolipid antibodies, very long chain fatty acids, phytanic acid, HTLV-1 and 2, peripheral blood smear for monocyte/lymphocyte vacuoles, and a peroxisomal panel. A debranching enzyme assay was inconclusive twice. Urine porphyrins were unremarkable. Skin punch biopsy electron microscopy demonstrated a demyelinating neuropathy. On our exam, mental status was normal. Visual acuities were 20/30 OU. Visual fields were intact to confrontation. He perceived Ishihara control plate only OU. There was no APD. He had a right 4th palsy, saccadic pursuits. Optic discs were atrophic OU. OCT showed RNFL thinning. Muscle bulk in his legs was reduced with 0/5 lower and normal upper extremity strength. Sensation was diminished to knees B/L. Patient was in a wheelchair with trunk support. Reflexes were absent.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"M.I.A."

Answer

Final Diagnosis
Bilateral chronic optic neuropathy and a 4th cranial nerve palsy secondary to Adult Polyglucosan Body Disease

Summary of Case
This patient had an adult-onset chronic neurological condition marked by both central and peripheral nervous system dysfunction, and it took nearly a decade to make the correct diagnosis. The diagnosis of adult polyglucosan body disease was made by nerve biopsy, and subsequent results for glycogen branching enzyme activity in leukocytes showed marked reduction, as has been reported for Ashkenazi Jewish patients with adult polyglucosan body disease. This was confirmed by DNA analysis of his glycogen branching enzyme gene showing homozygosity for the Tyr 329 Ser mutation. DNA testing of the glycogen branching enzyme gene was performed on the family, and his brothers who were at that time age 49 and 54 had no issues with walking but did have bladder problems, and they were also found to be homozygous for Tyr 329 Ser while their parents were both carriers. The patient's visual dysfunction was most likely due to nerve infiltration of polyglucosan bodies and cerebral degeneration.

Struggle/Dilemma of the Clinical Presentation Description
This patient's condition was very slowly progressive for years, and it affected both the central and peripheral nervous system. His visual symptoms were mild and could have been attributed to many other entities. Optic neuropathy in Adult Polyglucosan Body Disease has been described in few cases with pathology demonstrating optic nerve atrophy and polyglucosan bodies within the optic nerves and the afferent pathways. Cranial nerve palsies including fourth nerve palsies appear to be extremely uncommon.

Keywords: Optic Neuropathy, 4th Nerve palsy

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"The Sound of Hoofbeats"

Lilangi Ediriwickrema[1], Neil Miller[1], Thomas Bosley[1]

[1]Johns Hopkins University, Wilmer Eye Institute, Baltimore, Maryland, USA

History & Exam

A 42-year-old woman with a recurrent cerebral malignant glioma in the left frontal lobe on clinical trial presented with blurry vision in her right eye 6 days after undergoing sinus surgery for paranasal inflammatory changes. She presented approximately 1 month after the sixth cycle of systemic steroids, Durvalumab (PD-L1 inhibitor), and Bevacizumab. Her initial examination revealed best-corrected visual acuity of 20/25 OU, a right relative afferent pupillary defect, and an unremarkable anterior segment exam. Fundus exam was notable for mild right optic disc swelling. Automated static perimetry showed no deficits in either eye. Magnetic resonance imaging (MRI) of the brain showed parenchymal disease progression. In addition, the orbital portion of right optic nerve was enlarged, hyperintense on T2-weighted imaging, and enhanced after intravenous injection of paramagnetic contrast material. Ten days later, the patient developed sudden, complete vision loss in her right eye. Examination revealed no light perception vision OD and 20/20 OS. The anterior segment was unchanged; however, she now had marked optic disc swelling, a peripapillary retinal hemorrhage, and a superior branch artery occlusion. The patient underwent a lumbar puncture that showed no abnormalities. Examination two days later showed interval development of a central retinal artery and vein occlusion, as well as a new collection of layered, whitish material suspended anterior to the internal limiting membrane, forming a pocket in the posterior vitreous just inferior to the optic disc. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"The Sound of Hoofbeats"

Answer

Final Diagnosis
Infiltrative optic neuropathy with vitreous seeding due to secondary glioblastoma multiforme.

Summary of Case
The procedure was a biopsy of the whitish material in the vitreous. The hypercellular vitreous sample demonstrated an astrocytic neoplasm within a necrotic background, consisting of small-to-medium sized cells with scant cytoplasm and oval, pleomorphic, hyperchromatic nuclei. Immunohistochemistry showed diffuse cytoplasmic glial fibrillary acid protein (GFAP) and nuclear oligodendrocyte transcription factor (Olig2) expression. The Ki67 proliferation labeling index was approximately 10%, and a subset of cells were also positive for mutant IDH-1 protein, revealed strong positivity for p53, and exhibited loss of ATRX. The histological and immunohistochemical findings were identical with those of the brain tumor. Cerebral high grade astrocytomas typically harbor poor outcomes as their invasive nature makes resection difficult and their resistance to chemoradiation usually leads to local recurrence. Furthermore, our patient's glioblastoma exhibited expression of the mutant IDH-1 protein, which has been shown to correlate with increased tumor size, presence of satellite lesions, and evidence of diffuse spread on MRI.

Struggle/Dilemma of the Clinical Presentation Description
A patient with a known recurrent glioblastoma multiforme undergoing clinical trial presented with rapid vision loss in the setting of disc edema, mixed central retinal artery-vein occlusion, and a vitreous collection, after undergoing sinus surgery. The differential diagnosis included endophthalmitis (progression from 20/20 to NLP over 10 days), drug-induced uveitis, an autoimmune process (several patients on Durvalumab had previously developed autoimmune optic neuropathy), a new primary tumor (eg, lymphoma), or infiltration by the known malignancy.

Keywords: Complications of cancers, Vision loss, Branch retinal artery occlusions, Central Retina Vein Occlusion, Disc edema

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"A Wrong Turn at the Angle"

Erica Archer[1], Jonathan Trobe[2], Hemant Parmar[3], Mohannad Ibrahim[3], Paul McKeever[4], Thomas Giordano[4]

[1]Kellogg Eye Center, University of Michigan Department of Ophthalmology, Ann Arbor, Michigan, USA, [2]University of Michigan Medical Center, Department of Ophthalmology and Neurology, Ann Arbor, Michigan, USA, [3]University of Michigan Medical Center, Department of Radiology, Ann Arbor, Michigan, USA, [4]University of Michigan Medical Center, Department of Pathology, Ann Arbor, Michigan, USA

History & Exam

A 54-year-old woman developed numbness of the right jaw and right side of the tongue. She attributed her symptomatology to recent dental work, but when dental examination, including dental x-rays, failed to reveal an answer, she underwent brain MRI. Imaging disclosed an enhancing right cerebellopontine angle (CPA) mass that appeared to originate in the tentorial dura (Slides 1,3). There was also a small mass on the right medullary surface (Slides 2,3). Neurosurgical examination found decreased sensation in the right V2 and V3 distributions and diminished hearing in the right ear. The lesion was interpreted as a meningioma. Over the next few weeks, she developed vertical diplopia. Our neuro-ophthalmologic examination diagnosed a small comitant right hypertropia interpreted as skew deviation, together with mild right appendicular and gait ataxia. The diplopia was palliated with a Fresnel prism. Because of increasing symptoms, the patient underwent right retrosigmoid craniotomy with "90% resection of the tumor" (Slide 4). Post-operatively, the ataxia worsened and right hearing loss became complete. Neuro-ophthalmologic evaluation disclosed no change in the skew deviation, but now development of sidebeat nystagmus to both sides and saccadic pursuit, as well as profound ataxia. The pathology report on the brain lesion came next…

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"A Wrong Turn at the Angle"

Answer

Final Diagnosis
Systemic sarcoidosis with symptomatic intracranial (leptomeningeal, pachymeningeal and parenchymal) involvement.

Summary of Case
The surgical specimen revealed numerous giant cells scattered within abundant chronic inflammation and fibrosis (Slides 5-11). Stains for organisms were negative. The original brain MRI was reinterpreted as showing that the medullary mass arose from the pia. Subtle FLAIR signal abnormalities were identified in the adjacent medulla and pons (Slide 12). These abnormalities were, in retrospect, considered more consistent with inflammation than meningioma. Total spine imaging revealed cervical, thoracic, and lumbosacral intradural/extramedullary lesions (Slide 13). Imaging of the chest/abdomen/pelvis showed mediastinal and hilar lymphadenopathy (Slides 14, 15). Bronchoscopic biopsies of mediastinal lymph nodes showed pathologic abnormalities similar to those of the brain lesion, consistent with sarcoidosis (Slides 16, 17). Treatment with corticosteroids, mycophenolate, and infliximab resolved the spine abnormalities but did not improve the patient's neurologic status, which has remained stable for 2 years (Slide 18). She cannot walk unassisted. The imaging diagnosis of meningioma was reasonable for the CPA mass, and metastasis could also be considered (1,2,3). The T2 hypointensity of the mass made meningioma less likely in hindsight. When the pial and parenchymal signal abnormalities are considered along with the CPA mass, though, the diagnosis is much more likely to be inflammation, such as sarcoidosis. That diagnosis would trigger an imaging evaluation of the chest/abdomen/pelvis and spine, which in our case disclosed the lesions of sarcoidosis. In retrospect, the imaging characteristics of the large CPA mass (T1 isointensity, T2 hypointensity, and intense enhancement) were entirely consistent with sarcoidosis (1,2). Symptomatic intracranial involvement in sarcoidosis occurs in about 5 percent of cases, but imaging and post-mortem involvement is higher (1,2,4). Leptomeningeal disease is more common than dural or parenchymal disease (1,4,5).

Struggle/Dilemma of the Clinical Presentation Description
Was it appropriate to assume that the large brain lesion was a meningioma? What else could mimic meningioma? Would a more detailed interpretation of the MRI scan have led to more widespread scanning?

Keywords: Sarcoidosis, Skew deviation

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"Strike a Chord"

Anastasia Neufeld[1], Kathleen Digre[1], Cheryl Palmer[1], H. Christian Davidson[1], Alison Crum[1], Bradley Katz[1], Judith Warner[1]

[1]University of Utah, Salt Lake City, Utah, USA

History & Exam

A 26 year old woman presented in August 2016 with migraine over the last 4 years, getting worse over the last 2 weeks. She reported occasional "glittering" in her vision in both eyes. She had no constitutional symptoms. Her past medical history included migraine, idiopathic leukocytosis, and nephrolithiasis. There was no family history of neurocutaneous disease. Due to worsening of her headache, her primary care provider ordered an MRI Brain, which showed an enhancing solid mass, measuring 2.3 cm in the suprasellar region, thought to be originating from the optic chiasm with involvement of both pre-chiasmatic optic nerves as well as the optic tracts. There was no hydrocephalus or any other lesions in the brain parenchyma. Primary diagnosis of concern based on imaging characteristics was optic pathway glioma. Endocrine work up was normal. Best-corrected visual acuity was 20/20 OD and 20/30 OS. There were no pupillary abnormalities. Intraocular pressure was normal in both eyes. Optic nerve function tests were normal, including color, critical flicker fusion frequency, red desaturation, and Humphrey visual field. Dilated fundus examination showed mild temporal pallor of the optic nerves. OCT of the retinal nerve fiber layer showed superior and inferior elevation and mild temporal atrophy on the right, and superior elevation and mild temporal atrophy on the left. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Strike a Chord"

Answer

Final Diagnosis
Chordoid Glioma

Summary of Case
Optic pathway gliomas are traditionally observed until clinical signs indicate visual compromise. The patient's general and neuro-ophthalmic examinations did not support surgical intervention for this suspected optic pathway glioma. Upon insistence of the patient, she was taken to the operating room, and an excisional biopsy was performed using a right fronto-temporal craniotomy approach. Surgical biopsy specimen showed a chordoid glioma of the third ventricle, WHO Grade II. Post-operative visual examination was stable, with no visual field deficits. Chordoid glioma is a term used to describe a low-grade neoplasm that arises from the anterior third ventricle in the central nervous system. It was first described in 1998 (1). There are fewer than 100 pathology-confirmed cases of chordoid glioma published in the literature. Clinically, the mean age of diagnosis is 48 years of age, with the most common symptoms being headache, visual symptoms, mental status changes and memory deficits (2). A small number present with obstructive hydrocephalus, and about 10% have endocrine dysfunction (2). Although radiological characteristics of the tumor are variable, computed tomography imaging most often shows a hyperdense homogenously enhancing lesion (2). MRI shows a well-circumscribed ovoid mass, iso-intense on T1-weighted sequences, with uniform and intense enhancement (2, 3). Pathologically, the origin of chordoid glioma is controversial, but histopathologic evidence suggests that the tumor originates from the area of lamina terminalis (4). Histopathology shows cords and clusters of epithelioid cells with eosinophilic cytoplasm and uniform nuclei. The underlying background is basophilic and myxoid in nature, with lymphoplasmacytic infiltrates. The tumor traditionally does not infiltrate surrounding tissues (4).

Struggle/Dilemma of the Clinical Presentation Description
Although the patient's general and neuro-ophthalmic examination did not support surgical intervention for this suspected optic pathway glioma, upon insistence of the patient, the tumor was excised. This case illustrates the need for close attention to radiologic findings in this location to differentiate between optic pathway gliomas, which are observed in absence of visual compromise, and chordoid gliomas, which must be excised, as incomplete excision carries a poor prognosis.

Keywords: Optic chiasm, Tumor

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"Island Fever"

Laura Hanson[1], Judith Warner[1], Alison Crum[1], Bradley Katz[1], Kathleen Digre[1]

[1]John A Moran Eye Center, University of Utah, Salt Lake City, Utah, USA

History & Exam

A 22 year-old male paralegal in the military presented with double and blurred vision. One month ago, he had traveled to Hawai'i for a wedding. Two weeks ago, he had been evaluated for an acute onset of fever, headache, emesis, light sensitivity and neck stiffness. He was diagnosed with viral meningitis after a lumbar puncture revealed 270 WBC with 85% mononuclear cells, 12% eosinophils and 3% PMNs, and sent home on convalescent leave to recuperate with his family. Shortly after arriving home, his headache, neck stiffness and malaise had improved, but he developed new horizontal, binocular diplopia and blurred vision in both eyes. Ophthalmologic examination revealed bilateral 6th nerve palsies and Frisen stage 3-4 optic disc edema. Humphrey visual field testing showed enlarged blind spots. A second lumbar puncture was performed, which revealed 588 WBC with an eosinophilic predominance of 61%, protein 343 mg/dL, and glucose 36 mg/dL. The opening pressure was 28 cm of water. A contrasted CT of the chest revealed multiple pulmonary nodules with surrounding ground-glass appearance. A gadolinium-enhanced MRI of the brain revealed scattered cortical-based nodular foci of enhancement with areas of T2 signal abnormality and sheet-like enhancement. An MRV showed no venous sinus thrombosis. A diagnostic procedure was performed.

Financial Disclosures: The authors had no disclosures.

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"Island Fever"

Answer

Final Diagnosis

Eosinophilic Meningitis secondary to Angiostrongylus cantonensis. Angiostrongylus cantonensis is also known as the "Rat Lungworm" and was first found in the lungs of rats in South China. The nematode larvae live in the pulmonary veins of their definitive host, the rat, and are perpetuated by snails, which serve as a secondary host. It is endemic in Southeast Asia, the Pacific Basin, the Caribbean, and Hawai'i. Humans become infected by eating undercooked snails, freshwater shrimp, frogs, or unwashed produce contaminated by one of these hosts. The larvae migrate to the central nervous system and the induced inflammatory response creates the manifestations typically seen in humans, including meningitis, cranial nerve abnormalities, ataxia, encephalitis, and increased intracranial pressure. The larvae are presumed to die before reaching the lungs. Treatment generally includes high-dose systemic corticosteroids. Albendazole can be used in combination with steroids, but there is some concern that the rapid death of the larvae from the anthelmintic can worsen the inflammatory response.

Summary of Case

The infectious workup for this patient included testing stool for ova and parasites, CSF PCR for VZV, HSV, and EBV, and CSF evaluation for Syphilis, Rickettsia, Cryptococcus and Bartonella, all of which were normal. Evaluation for coccidioides and HIV was also normal. Cytology of the CSF revealed the absence of abnormal cells, but did show an abundance of eosinophils. CSF and serum were sent to the CDC for ELISA testing of parasites, which confirmed the presence of Angiostrongylus cantonensis. Repeat lumbar punctures revealed persistently elevated intracranial pressures. The patient was treated with oral corticosteroids for three weeks, as well as acetazolamide.

Struggle/Dilemma of the Clinical Presentation Description

Appropriate treatment for this condition was delayed, as it was initially misdiagnosed as a viral meningitis. Increased intracranial pressure is common in Angiostrongylus Eosinophilic Meningitis, and may have been detected earlier, if appropriate clinical suspicion was maintained. The imaging was another clue to the diagnosis, but was not obtained during his initial hospitalization.

Keywords: Meningitis, Increased intracranial pressure, 6th nerve palsy

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"Lions and Tigers and Bears, Oh My!"

Larissa Ghadiali[1], Danlin Mao[2], Gul Moonis[1], Adam Sonabend[1], Catherine Shu[1], Terri Kreisl[1], Esther Coronel[1], Jeffrey Odel[1]

[1]Columbia University Medical Center, New York, New York, USA, [2]Augusta University, Augusta, Georgia, USA

History & Exam

A 79 year-old female s/p resection of a right CPA meningioma in 1998 noted sudden painless visual loss OD on 6-12-2016. Two days later examination revealed 20/150 vision OD, a right RAPD, and an otherwise normal ophthalmic exam. Her vision had been 20/40 OD on 5-31-2016. An MRI of the brain and orbits was interpreted as an intracranial meningioma of the right optic nerve. She was started on prednisone with subjective improvement and referred for radiation. Prior to radiation, she presented to us for a second opinion. Seen on 6-21-2016, she reported one month of generalized fatigue, a 10 pound weight loss and having a tick removed from her right upper lid in May 2016. Her visual acuity was 20/300 OD and 20/25 OS. She had a right RAPD and mild right temporal disc pallor. Visual fields on the right revealed a large cecocentral scotoma and were full on the left. The MRI was reviewed and revealed a thickened right prechiasmal optic nerve and chiasm with heterogeneous areas of both solid and peripheral enhancement, a previously unrecognized left temporal lobe infiltrating cortical T2 FLAIR hyperintensity, and a right frontal contrast-enhancing dural-based lesion. Postsurgical gliosis was noted in the right temporal lobe and pons secondary to prior meningioma resection. Bloodwork and lumbar puncture were unremarkable. She was tapered off prednisone and referred to neuro-oncology. Full body PET CT revealed a subpleural ground glass opacity in the left lower lobe with low-grade FDG uptake measuring 2.4 x 1.3 cm. A trial of azithromycin was initiated for the lung lesion with no change. What would you do next?

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"Lions and Tigers and Bears, Oh My!"

Answer

Final Diagnosis

1) Adenocarcinoma of lung 2) Right optic nerve anaplastic astrocytoma (WHO grade III)

Summary of Case

Lung biopsy revealed adenocarcinoma. Metastatic carcinoma to the intracranial optic nerve is very rare and we doubted that the optic nerve mass was a metastasis, especially with the lack of any mediastinal adenopathy. Over the next month, her vision deteriorated to no light perception in the right eye and a new superotemporal visual field defect developed in the left eye. MRI revealed an increase in size of the right optic nerve lesion. Repeat lab work and lumbar puncture were unrevealing. A pterional craniotomy and right optic nerve biopsy were performed revealing a diffusely infiltrating glial neoplasm of high cellularity with atypical, pleomorphic, hyperchromatic nuclei with irregular contours and occasional prominent nucleoli. A subset of cells with abundant eosinophilic cytoplasm and multinucleated bizarre tumor cells were also identified. Findings were consistent with anaplastic astrocytoma (WHO grade III). The patient recovered from surgery without additional neurological deficits. She was treated with partial brain radiation, lung radiation, and adjuvant temozolomide. Malignant optic glioma of adulthood (MOGA) was first described by Hoyt in 1973(1), and is an extremely rare, invasive entity, with only 66 cases reported in the literature. Visual loss with or without pain is usually the initial symptom and often leads to a misdiagnosis of optic neuritis or NAION. Neuroradiologic findings are non-specific, and diagnosis is biopsy dependent. Recommended treatment is radiotherapy and chemotherapy. Prognosis is poor with a lifespan of 1-2 years(2).

Struggle/Dilemma of the Clinical Presentation Description

What to biopsy and when? Should the nerve have been biopsied on discovery or should the usual suspects have been rounded up, respecting the history of weight loss and fatigue? Would the steroids have confounded the CSF results and/or biopsy if sarcoid, lymphoma or optic neuritis was the diagnosis(3)? Would the discovery of adenocarcinoma have stopped your investigation or would the rarity of adenocarcinoma metastasis to the nerve and the possibility of glioma forced biopsy?

Keywords: optic pathway glioma, Optic atrophy, Optic chiasm, Afferent pupillary defect, Optic nerve tumors

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"not surprised surprise"

Yu Zhao[1], Joshua Pasol[1], Sander Dubovy[1], Byron Lam[1]

[1]Bascom Palmer Eye Institute/Department of Ophthalmology, University of Miami, Miami, Florida, USA

History & Exam

A 68-year-old Hispanic woman presented to our emergency department with significant vision loss OS for 1 week. A month ago, she was evaluated locally for mild blurry vision OS, and corrected acuity was 20/30 OD, 20/40 OS. She was diagnosed with cataracts and epiretinal membrane OD. Medical history included smoking, hypertension, hypothyroidism, hyperlipidemia, transient ischemic attack, and aortic/mitral valve placement. Family history was positive for lymphoma and prostate cancer in father. Best-corrected visual acuity was 20/30 OD and 3/800 OS with RAPD OS and mild bilateral cataracts. Extraocular movements were normal. The right optic disc was small and crowded, and the left disc had diffuse edema. There were no other cranial nerve dysfunction. She had no headaches and no giant cell arteritis symptoms. ESR was 20, CRP was 1.3 (normal <1.0), and CBC was normal. Non-arteritic anterior ischemic optic neuropathy OS was suspected given the risk factors and crowded disc on the right, and the patient was placed on prednisone 60 mg daily. Three days later, her corrected acuity OS had improved to 20/150. The left disc edema persisted with a peirpapillary hemorrhage nasally to the disc. Humphrey visual field showed temporal and inferior defects OS. Prednisone was continued at 60mg. Two days later, the patient presented with difficulty falling asleep, fatigue, severe stabbing left eye pain, scalp tenderness and neck pain. The corrected vision OS dropped to light perception with projection with an amaurotic pupil OS. A procedure was performed.

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"not surprised surprise"

Answer

Final Diagnosis
Sphenoid sinus diffuse large B cell lymphoma causing optic neuropathy

Summary of Case
Orbital MRI showed hyperintense T1 and isointense to hypertense T2 signals in the bilateral sphenoid sinuses with enhancement mainly of the right sphenoid sinus. There was a 25 x 27 mm markedly expanded left sphenoid sinus lesion and/or Onodi air cell extending into an opacified left anterior clinoid process with bony erosion and involvement of the left optic canal and orbital apex with resultant compression and enhancement of the left intracanalicular and prechiasmatic optic nerve. Mild perioptic nerve sheath enhancement was present. Paranasal sinus CT showed near to complete opacification of the sphenoid sinuses with an ill-defined erosive lesion. The patient underwent left maxillary antrostomy, left total ethmoidectomy, left sphenoidoctomy and biopsy/debulking of left sphenoid mass. Frozen section analysis was interpreted as a malignant neoplasm and possible esthesioneuroblastoma; however there were abundant apoptosis. Final pathology showed small blue cell tumor positive for CD20, BCL 2 (week, subset), CD30 (subset, 20%) and negative for CD3, CD5, CD10, BCL 6, CD4, CD8. By immunohistochemistry, the tumor cells were negative for keratin, synaptophysin and negative for S100. EBER was negative by in situ hybridization. K167 proliferation index in viable foci was 90%. The final diagnosis was diffuse large B-cell lymphoma (DLBCL). DLBCL is a common non-Hogkins lymphoma, but paranasal sinus DLBCL is very rare with more cases affecting the maxillary and ethmoid sinuses than sphenoid and frontal sinuses. Sphenoid DLBCL usually has very subtle presentation due to its deep location. Headache is the most common presentation, but ophthalmic signs and symptoms such as visual disturbance and diplopia may occur due to the close proximity of orbit to paranasal sinuses and can be very aggressive. The main treatment is chemotherapy. Our patient remained NLP after the decompression with no further response to steroid and was treated with chemotherapy.

Struggle/Dilemma of the Clinical Presentation Description
1) This case highlights the difficulty in identifying a rare disease that mimics NAION initially. The mild brief response to steroid suggests a possible inflammatory cause. In a patient with atypical clinical course, Imaging and biopsy are critical for diagnosis and management. 2) Existing data suggests 2-5 fold increase risk of non-Hodgkins lymphoma with first-degree family history and a greater proportion of aggressive tumors for those with any family history.

Keywords: Vision loss, Disc edema, Orbital decompression

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"A diagnostic potpourri"

Padmaja Sudhakar[1], Robert Lightfoot[1], Douglas Lukins[1], Dianne Wilson[1]

[1]University of Kentucky, Lexington, Kentucky, USA

History & Exam

A 63 yr. old incarcerated man with history of diabetes, hypertension, rheumatoid arthritis (RA) (on hydroxychloroquine, sulfasalazine and prednisone 7 mg), cutaneous lupus and Hepatitis C presented with sudden painless vision loss of the left eye without headache or symptoms of temporal arteritis. Visual acuity was 20/40 OD and count finger OS. He had left RAPD, quiet anterior segment OU, normal fundus on the right and optic disc edema on the left. Contrast enhanced brain and orbital MRI revealed an abnormal enhancing soft tissue involving left> right retrobulbar space, facial soft tissues, right temporal fossa, and bilateral infratemporal fossae. Differentials included lymphoma, lupus panniculitis and idiopathic orbital inflammatory syndrome. His labs showed ESR of 102 mm/hr, CRP 3 mg/dl, ACE 32, normal CBC and BMP, negative serology for HIV and syphilis. Lumbar puncture revealed opening pressure of 18 cm H2O, normal CSF contents except mild elevation of protein (53). CSF and serum IgG levels were also increased without CSF oligoclonal bands. CT chest suggested interstitial lung disease involving bilateral apices. CT abdomen and pelvis was normal. Left orbital biopsy showed sclerosing fibro-proliferative process. Oral prednisone was increased to 60 mg daily. Six weeks later his visual acuity improved to 20/30 OD and 20/50 OS. Fundus exam remained normal on the right and showed disc pallor on the left. Prednisone was slowly tapered with a plan to add another immunosuppressive agent (Rituximab). A follow-up MR orbit was recommended. While waiting for initiating treatment with Rituximab, he presented 8 weeks later with painful complete vision loss in the left eye concerning for ophthalmic artery occlusion. Did he have another disease?

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

"A diagnostic potpourri"

Answer

Final Diagnosis
Atypical ANCA + vasculitis, variant of Wegner's Bilateral orbital inflammation Ophthalmic artery occlusion

Summary of Case
The presence of sclerosing fibro-proliferative orbital pathology involving both orbits raised the suspicion that it was associated with a systemic inflammation since patient was known to have RA, cutaneous lupus and Hepatitis C. An extensive autoimmune work-up revealed elevated c-ANCA (1:20 titer- not known previously), negative p-ANCA staining, negative anti-protease 3 and anti-myeloperoxidase and negative ANA. He also had elevated anti-CCP 91 units/mL, and rheumatoid factor 110 IU/mL . This profile suggested a new diagnosis of an atypical c-ANCA positive autoimmune vasculitis such as atypical granulomatosis polyangitis. We believe this resulted in orbital inflammation with occlusive vasculitis leading to ophthalmic artery occlusion and ocular ischemia. Repeat MRI orbit continued to show abnormal enhancing soft tissue signal within bilateral orbits. He was treated with 60 mg prednisone mg and started on rituximab infusions subsequently. A month later he developed neovascular glaucoma for which he underwent pan retinal laser photocoagulation and placed on intraocular pressure lowering eye drops. His right eye remains asymptomatic with a visual acuity of 20/30 and left eye has no light perception. His history of hepatitis C and his incarcerated status led to administrative delays in initiating Rituximab for the current ANCA positive vasculitis. Low dose prednisone failed to control the orbital inflammation adequately and led to occlusive vasculitis causing his left eye vision loss.

Struggle/Dilemma of the Clinical Presentation Description
The left eye vision loss with bilateral orbital inflammation was initially attributed to Rheumatoid vasculitis or lupus panniculitis. A third disease ANCA+ve vasculitis was only later discovered. Despite this Rituximab treatment was delayed due to his Hepatitis C and incarceration. While waiting Rituximab, he only received steroids which was also subsequently tapered when visual acuity improved suggesting improved orbital inflammation. Devastating complication of ophthalmic artery occlusion could have been prevented with timely treatment with rituximab.

Keywords: Optic disc edema, Vasculitides, Afferent pupillary defect, Orbital inflammation, Vision loss

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Poster Session I: Clinical Highlights in Neuro-Ophthalmology

Sunday, April 2, 2017 • 1:00 pm – 2:45 pm

Authors will be standing by their posters during the following hours:
Odd-Numbered Posters: 1:15 pm - 2:00 pm
Even-Numbered Posters: 2:00 pm - 2:45 pm

**Please note that all abstracts are published as submitted.*

Poster #		Presenting Author
Category: Disorders of the Anterior Visual Pathway (Retina, Optic Nerve, and Chiasm)		
1	Brain Tumor Induced Narrow Angle Glaucoma	Nagham Al-Zubidi
2	Bilateral Option Neuropathy With Central Diabetes Inspidus In a Child	Selvakumar Ambika
3	Gradual Painless 10 Year Visual Loss then Sudden Painful Loss in 80 Year Old Man	Susan C. Benes
4	Case Report: A Unique Presentation of Birdshot Chorioretinopathy	Shagun K. Bhatia
5	Macular OCT Involvement In Ethambutol Toxicity: A Case Report	Maria L. Braccia Gancedo
6	Optic Neuropathy in Chronic Intracranial Hypotension with Bony Remodeling	Jessica R. Chang
7	A Case Report o Malignant Pleomorphic Adenoma metastasis affecting eye motility and visual acuity.	Macarena Clementi
8	VZV-induced optic neuropathy	Monica K. Ertel
9	Radiation-induced Optic Neuropathy following Whole-Brain Radiotherapy	Ian Ferguson
10	Non-arteritic Ischemic Optic Neuropathy – A Triple Threat?	Aubrey L. Gilbert
11	Compressive optic neuropathy caused by metastases to skull bones from non-small cell lung cancer.	Anna M. Gruener
12	Bilateral vision loss with p-ANCA associated lymphocytic vasculitis	Bokkwan Jun
13	Optic Nerve Compression Secondary to a Posterior Ethmoid Pyomucocele	Terri Key
15	Acute zonal occult outer retinopathy presenting as retrobulbar optic neuritis	Sungeun E. Kyung
16	Bilateral concentric visual field defect as an initial manifestation of multiple sclerosis	Sungeun E. Kyung
17	CRMP-5 positive Paraneoplastic Optic Neuropathy as Initial Presentation of Small Cell Lung Cancer	Jennifer Lee
18	Reversible Bilateral Optic Neuritis after Influenza Vaccination: A Case Report and Literature Review	Emily Li
19	Sphenoid Sinus Mucocele: A Case Series and Review of Literature	Emily Li
20	Tacrolimus associated Ischemic Optic Neuropathy	Shuai-Chun Lin
21	Idebenona off label- Visual improvement continuing 2 years after surgery of Meningioma with Idebenona.	Haydee Martinez
22	OCT and Ultrasound in a Myopic Patient with Spontaneous Trilaminar Papillary Hemorrhage Without Vitreopapillary Traction	Priya M. Mathews

23	Infiltrative Tubercular Optic Neuropathy in a Child	Preeti Patil Chhablani
24	Two Cases of Wolfram-Related Optic Atrophy: A New Mutation and A Misdiagnosis of Normal-tension Glaucoma	Victoria S. Pelak
25	Radiation-Induced Optic Neuropathy: Complication Of The Treatment Of Intracraneal Folicular Thyroid Carcinoma Metastases	Simón Quijada Angeli
26	Atypical Auto-Immune Bilateral Optic Neuritis- Post Multiple Flavivirus Infections.	Carolina F. Ramos
27	Optic Disc Edema and Retinal Abnormality Secondary to Dasatinib Treatment in a CML Patient	Reut Singer
28	Variable presentation of Leber's hereditary optic neuropathy in a family harbouring a rare mtDNA mutation.	Vasily M. Smirnov
29	Juxtapapillary retinal hemangioma masquerading as optic disc edema as the first manifestation of Von Hippel-Lindau	Kenneth J. Taubenslag
30	Bilateral Sequential Central Vision Loss in a Young Man	Samuel Thomsen
31	Nyctalopia as the presenting symptom of new onset alcoholic liver failure	Astrid Werner
32	Infantile presentation of Leber's hereditary optic neuropathy 'plus' disease.	Helena Zakrzewski
Category: Disorders of the Posterior Visual Pathway and Visual Processing		
33	Can occipital lesions produce pre-geniculate changes in humans?	Kimberly K. Gokoffski
34	JC Virus: An Uncommon Infection More Common with Immunosuppression	Ehtesham Khalid
35	Metastatic Hepatocellular Carcinoma Presenting as Left Homonymous Hemianopia	Hye Jin Lee
36	Bilateral Progressive Visual Loss Related to Toxic Leukoencephalopathy Due to Chronic Ingestion of Para-Dichlorobenzene (mothballs)	Abdallah Mahrous
37	Lateral Geniculate Bodies: Partners In Crime	Smita Praveen
38	Is it Glaucoma?	Sarwat Rahman
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39	Idiopathic Intracranial Hypertension in Addison´s Disease: A Case Report	Mirta Arana
40	Castleman disease with follicular dendritic cell sarcoma presenting with pseudotumor cerebri and myasthenia gravis	Alexander S. Fein
41	Recurrent Idiopathic Intracranial Hypertension in All-Trans Retinoic Acid and Arsenic-Treated Promyelocytic Leukemia	Gerard Hershewe
42	Unilateral adduction deficit in idiopathic intracranial Hypertension from tortuous optic nerve sheath.	Susiani Intan
43	Meningeal carcinomatosis mimicking pseudotumor cerebri	Hanqiu Jiang
44	A Case with a TWIST: Not so Benign Type 1 Dural Arteriovenous Fistula	Hang Pham

45	Intracranial Hypotension or Intracranial Hypertension?: A Case Caught in Transition	Sara N. Reggie
46	Bartonella Neuroretinitis Associated With Elevated Intracranial Pressure	Meagan Seay
47	Transverse Sinus Dural Arteriovenous Fistula Producing Intracranial Hypertension and Choroidal Folds	Stacy V. Smith
48	Iatrogenic pseudotumor cerebri from treatment of metastatic mixed-spindle-cell endometrial sarcoma with leuprolide acetate	Harris C. Sultan
49	Unilateral Papilledema in Idiopathic Intracranial Hypertension: A Report of Two Cases and Literature Review	Arun N. Sundaram
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50	A case of Vogt-Koyanagi-Harada	Juan Maya
51	Deficiency of Adenosine Deaminase 2: A Recently Described Autoinflammatory Disease with Neuro-Opthalmic Manifestations	Sean M. Gratton
52	Homonymous Visual Field Deficit Selected Ischemic Stroke as The Etiology of Transient Amnesia.	Editha D. Johnson
53	Seronegative progressive encephalomyelitis with rigidity and myoclonus (PERM)	Ehtesham Khalid
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54	Down, out, and blown- not always from an aneurysm	Michelle Abou-Jaoude
56	Gradenigo syndrome – maybe not	Ira A. Perszyk
57	Spontaneous Tectal Glioma Regression in an Adult	Evan R. Schloss
58	Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive To Steroids With Lung And Liver Involvement	Islam M. Zaydan
59	Parry Romberg Syndrome Presenting Initially With Extensive Unilateral Hemorrhagic Brain Lesions	Tarek A. Shazly
60	Bilateral Vision Loss Due to Sphenoidal Rhabdomyosarcoma	Swarup S. Swaminathan
61	Myelinated retinal nerve fibers of the optic nerve mimicking elevated ICP on MRI.	Michael S. Vaphiades
Category: Neuro-Ophthalmic Disorders of Neurologic and Systemic Diseases		
62	A Rip on One Side Causes a Lopsided Eye	Mohamed Al-Ameri
63	Homozygous A467T mutation in a patient with gastrointestinal symptoms, Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoplegia	Cesar A. Alfaro Cruz
64	Ophthalmic findings in a Hunter Syndrome patient on Idursulfase enzyme replacement therapy	Jarstad Allison
65	A Complex Arteriovenous Malformation Presenting with Bilateral Abducens Nerve Palsy	Laura Andrews
66	A Case of a Fatal Acute Disseminated Encephalomyelitis with Extensive Optic Pathways Involvement	Tatiana Bakaeva
67	Unusual ocular manifestation of granulomatosis with polyangiitis	Stuart R. Ball

68	Susac syndrome: clinical characteristics, radiological features and treatment	Ruchika Batra
69	An unusual cavernous mass	Shauna E. Berry
70	Characterization of Optic Neuropathy in Charcot-Marie-Tooth Disease	Benjamin Botsford
71	Episodic Unilateral Mydriasis – Malignancy Or Lyme Induced?	Mayur Chalia
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Poster 1
Brain Tumor Induced Narrow Angle Glaucoma

Nagham Al-Zubidi[1], Mohamed Al-Ameri[2], Jorge Mendoza-Valencia[2], Shaan Raza[3], Amanda Huynh[2], Rosa A. Tang[1], Jade Schiffman[4]
[1]Neuro-Ophthalmology of Texas, PLLC, Blanton Eye Clinic HMH, Houston, Texas, USA, [2]Neuro-Ophthalmology of Texas, PLLC, Houston, Texas, USA, [3]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [4]Neuro-Ophthalmology of Texas, PLLC, UHC of optometry, Houston, Texas, USA

Introduction:
Hemangioblastomas (HBLs) are tumors of indeterminate clinicopathologic or immunohistochemical features that may be sporadic or associated with von Hippel-Lindau (VHL) disease. Suprasellar HBLs without VHL are extremely rare, with and only 5 cases have been reported to date. The most common presenting symptoms are visual disturbance, headache, and endocrine disturbances. This is the first case where a suprasellar HBL presents with narrow angle glaucoma due to intratumoral AV shunting. The narrow angle glaucoma reversed after tumor resection.

Methods:
Case Report

Results:
A 57 year- old female who presented with decreasing vision OS for 2 weeks, who was sent to us regarding glaucoma management of her left eye which showed optic nerve cupping, nerve fiber loss and high intraocular pressure with a narrow angle. An MRI was prompted due to the presence of optic pallor in addition to the cupping. A 2.5-cm solid mass in the left suprasellar region superior to the left optic nerve with intense homogeneous contrast enhancement and aneurysmal distention of vessels posteriorly was found. The orbit was unremarkable, eg no obvious superior ophthalmic vein enlargement.. Angiogram showed a highly vascular tumor with AV shunting; multiple arterial feeders and venous drainage into the cavernous sinus with reflux into a large superior ophthalmic vein. Resection disclosed a very vascular tumor arising from the superomedial left optic nerve surrounded by hypertrophied arterial feeders from the internal carotid artery and arterialized venous drainage. Histopathologic examination confirmed hemangioblastoma and work up did not reveal the presence of VHL. Preoperative UBM showed angle closure of the left eye in 3 quadrants which opened after the surgery. The IOP post-op has remained normal without meds.

Conclusions:
This is the first case report where a patient presents with narrow angle glaucoma as a result of AV fistulas within a vascular suprasellar hemangioblastoma in a lady without VHL disease.

References: None.

Keywords: Orbit/ocular pathology, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Vascular disorders, Miscellaneous, Neuroimaging

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Poster 2

BILATERAL OPTIC NEUROPATHY WITH CENTRAL DIABETES INSIPIDUS IN A CHILD

selvakumar ambika[1], veena noronha[1], durga priyadarshini[1]

[1]*sankara nethralaya, chennai, India*

Introduction:

Bilateral sudden vision loss in children with optic neuritis like features are usually a diagnostic challenge.

Methods:

An eleven year old girl presented with complaints of bilateral sudden drop in vision with mild ocular discomfort of 6 weeks duration. On examination her best corrected visual acuity was 1/60 in right eye and 6/18 in left eye. Both eyes pupils were sluggishly reacting to light with relative afferent pupillary defect in right eye.She had pale discs in both eyes. MRI brain revealed bulky right optic nerve and chiasm with post contrast enhancement suspected to be ? Demyelination ? inflammatory. CSF analysis and serological work up for infectious, autoimmune and granulomatous diseases and NMO antibody were negative. She was diagnosed as bilateral optic neuritis and was treated with intravenous pulse steroids for three days followed by tapering oral steroids .Simaltaneously she developed skin lesions due to Varicella zoster was treated there with IV immunoglobulin and acyclovir. 2 months later, she presented with further drop in vision to light perception in right eye and 1/60 in left eye. She was again administered pulse steroids followed by intravenous rituximab 500 mg .But her vision further dropped to no perception of light in both eyes within 4 days . By then she complained of polyuria and polydipsia , which improved after oral desmopressin. She was advised for repeat MRI Brain and orbit which revealed diffuse irregular thickening of bilateral optic nerves , chiasm and infundibulum and pituitary stalk which was enhancing on contrast .

Results:

She had reduced pituitary hormones. Optic nerve and pituitary stalk biopsy revealed poorly differentiated malignant tumor probably germinoma. She was advised for radiotherapy and the patient lost to follow up .

Conclusions:

Progressive vision loss due to optic neuropathy in a child does require a biopsy to rule out infiltrative pathology .

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Keywords: Demeylinating disease, Pediatric neuro-ophthalmology, Neuroimaging, Optic neuropathy, Chemotherapy and radiation injury

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Poster 3
Gradual Painless 10 Year Visual Loss then Sudden Painful Loss in 80 Year Old Man

Susan Benes[1], Nour Tlimat[2], Deb Fredley[2], Patrick Brennan[3]

[1]The Eye Center of Columbus and The Ohio State University, Buena Vista, Colorado, USA, [2]The Eye Center of Columbus, Columbus, Ohio, USA, [3]The Ohio State University and The Eye Center of Columbus, Columbus, Ohio, USA

Introduction:
An 80 year old man experienced gradual painless visual loss starting at age 70, was diagnosed with "retinitis pigmentosa sine pigmentosa" based on normal-appearing anatomy, 20/20 acuity, enlarging ring scotomas, reduced amplitudes on ERG. He was not treated. He continued working and driving. At 80 years of age he was awakened at 5AM one morning with a sudden bilateral decline in his vision accompanied by headache, retrobulbar pain and pressure. He was taken to the emergency room, then referred to a neuro-ophthalmologist.

Methods:
Acuities were 20/50 OU. He had indistinct disc margins, subretinal fluid, tinier central islands. Ocular ultrasound: thickened choroid, dilated optic nerve sheaths. OCT: retinal edema, subretinal fluid. Retina consult with fluorescein angiography: perimacular RPE abnormalities, late perineural staining. MRI of the brain and orbits: no acute posterior brain pathology. Lumbar puncture: opening pressure of 170mm H20, normal cytology, protein 45. Stat blood work showed a normal sed rate, CBC, chemistries, pending auto-immune markers and anti-retinal antibodies (Oregon).

Results:
The team decided this was inflammatory. IV steroids failed to help. The subretinal fluid worsened. Blood work returned: borderline ANA of 1:40, 7 bands of positive anti-retinal antibodies. The presumptive diagnosis: auto-immune outer retinopathy with bilateral retinal and optic nerve effusions. IVIG helped the acuity for 6 weeks. Second infusion: too ill. Maintenance immune therapies which failed: azathioprine, dapsone. Improved acuity, field and reduced fluid on OCT were achieved for 18 months with both topical and oral carbonic anhydrase inhibitors and oral colchicine.

Conclusions:
Chest x-rays showed bilateral parenchymal changes and pleural plaques consistent with asbestosis. PMH: many years of exposure to the Libby Amphobile Asbestos (LAA) and its derivatives. Pulmonary and environmental experts confirmed a 3-fold increase in auto-immune disorders in LAA exposed persons. LAA-induced lung and pleural asbestosis: common. LAA-induced auto-immune retinopathy: not yet reported.

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Keywords: Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 4
Case Report: A Unique Presentation of Birdshot Chorioretinopathy

Shagun Bhatia[1], Thomas Berenberg[2], Danielle Rudich[2], Jeffrey Odell[3], Donald Hood[3], Nauman Chaudhry[4], Robert Lesser[1]

[1]Yale University, Department of Ophthalmology, New Haven, Connecticut, USA, [2]Eye Care Group, New Haven, Connecticut, USA, [3]Columbia University, New York, New York, USA, [4]Retina Group of New England, New London, Connecticut, USA

Introduction:
Here we share a unique presentation of birdshot chorioretinopathy (BCR) in a patient seen in neuro-ophthalmology clinic.

Methods:
A 74-year-old woman with history of colon cancer presented with flickering lights in both eyes. She had a history of bilateral optic nerve pits, glaucoma, cataracts, and amblyopia OS. On neuro-ophthalmic examination VA was 20/40 OD and 20/60 OS, pupils reacted 1+ with no relative afferent pupillary defect, and color vision testing revealed 80% red desaturation OS. Examination demonstrated cataracts OU, 1+ anterior vitreous cells (OS>OD), optic nerve pits and ERM OU. Visual fields showed a temporal defect OD and superior defect OS, which were both stable compared to prior. Given the concern for paraneoplastic disease, she underwent electroretinogram (ERG), antibody testing for cancer-associated retinopathy (CAR), and MRI brain and orbits, which were all normal. Three weeks later she returned with increased vitreous cells and multiple new yellow-white retinal lesions suspicious for BCR. FA revealed several hypo- and hyperflourescent lesions, optic disc, and perivascular leakage. Indocyanine green (ICG) angiography revealed hypofluorescent choroidal lesions. Serum HLA-A29 was positive.

Results:
There are several etiologies of photopsas, including infectious, inflammatory, ischemic, paraneoplastic and medication-induced. In patients with an oncologic history, paraneoplastic retinopathy must be considered and worked up. BCR often presents with vague symptoms and fundoscopic examination may be unrevealing early on. ICG can expose lesions not seen with FA or DFE. ERG is abnormal in ~90% of patients and HLA-A29 is positive in over 90% of patients. Currently there are no well-defined treatment guidelines.

Conclusions:
In this unique presentation of BCR, it initially appeared as though the patient had paraneoplastic disease; but initial retinal exam, antibodies for CAR, and ERG were all normal. Because presentation of BCR can be vague, the physician should maintain a high clinical suspicion, examine carefully, and obtain an FA, ICG, and ERG.

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Keywords: Vascular disorders, Paraneoplastic syndromes, Pupils Retina, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Poster 5
Macular OCT Involvement In Ethambutol Toxicity: A Case Report

Maria Braccia Gancedo[1], Haydée Martinez[2], Mariana de Virgiliis[1], Luciana Iacono[1], Pablo Perez Vega[1], Gabriel Patane[3], Dolores Ribero Ayerza[4], Lidia Sarotto[2]

[1]Hospital Oftalmológico Dr. Pedro Lagleyze, Buenos Aires, Argentina, Lomas de Zamora. Buenos Aires, Argentina, [2]Hospital de Clínicas José de San Martín, Buenos Aires, Buenos Aires, Argentina, [3]Centro de Ojos Quilmes, Hudson, Argentina, [4]Hospital Británico de Buenos Aires, Olivos, Argentina

Introduction:
Ethambutol, in combination with others drugs, are indicated in Mycobacterium infections. About 10% of patients develop visual disturbance during treatment. The toxic optic neuropathy (TON) is the most severe and frecuent complication althought there´s some evidence of retinal involvement. Other toxics, nutritional and Leber optic neuropathies share similar clinical manifestations. The purpose of this report is to present a case of macular involvement in Ethambutol Toxicity.

Methods:
Twenty-one years old female with medical history of pulmonary tuberculosis treated with ethambutol and Rifampicin for thirteen months, experience bilateral painless progressive visual loss within four months after treatment onset. Ophthalmology evaluation: Visual Acuity Right Eye: 20/200 Left Eye: 20/100, Ishihara plates: 1/6 Both Eyes. Right Relative Afferent Pupillary Defect. Bilateral optic disc pallor, with marked papilo-macular bundle atrophy and alteration of macular reflex. Bilateral centrocecal scotoma in visual field . OCT showed anular Macular thinning, marked vacuolization of inner nuclear layer and decreased retinal nerve fiber layer with preserved nasal fibers.

Results:
Ethambutol TON was diagnosed, with a concomitant macular involvement. Vitamin B complex, Lutein with vitamin E and Omega 3 and Idebenone 45 mg was prescribed. Only improvement of color vision was reported.

Conclusions:
The retinal involvement in the physiopathology of ethambutol ocular toxicity has been reported: studies shows abnormal multifocal electroretinogram (mfERG) and vacuolization of the retinal ganglion cell layer in mouse. There is a report of choroidal involvement in OCT in patients with Leber Optic Neuropathy, but the vacuolization of the inner nuclear layer in the OCT was not linked with ethambutol TON. We emphasize the importance of visual screening in all patients under ethambutol treatment, and the study of the macular architecture in the presence of ethambutol TON in order to detect this compromise and help understand the process that leads to the damage and the visual impairment

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Keywords: Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields, Neuro-ophth & infectious disease (eg, AIDS, prion)

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Poster 6
Optic Neuropathy in Chronic Intracranial Hypotension with Bony Remodeling

Jessica Chang[1], Timothy McCulley[1]

[1]Wilmer Eye Institute, Baltimore, Maryland, USA

Introduction:
Bony remodeling of the orbit and sphenoid sinus with chronic intracranial hypotension has been described. The sphenoid sinus has been observed to enlarge with intracranial hypotension, sometimes leaving the optic canal completely surrounded by air. This radiographic finding also occurs in a condition called sphenoid pneumosinus dilatans (SPD). While many cases of idiopathic SPD come to attention because of optic neuropathy, the presence or development of optic neuropathy in severe intracranial hypotension has not been closely examined.

Methods:
Case report and review of the literature: A 31-year-old man presented with severe progressive enophthalmos related to chronic intracranial hypotension from cerebrospinal fluid (CSF) overshunting. In 2003 he was struck by a car, suffering closed-head injury resulting in placement of a CSF shunt. On examination in 2016, vision measured 20/200 in the right eye and 20/25 in the left, pupils were sluggish with no relative afferent defect, and fundus exam revealed mild pallor of the optic nerves with cup to disc ratio 0.5 in both eyes. Computed tomography demonstrated expansion of the sphenoid sinus around the optic canals.

Results:
Previous reported cases of “sunken eyes, sagging brain” or “silent brain” syndrome and SPD were reviewed. Only 4 of the 17 cases associated with CSF shunting had documented optic neuropathy, 9 cases reported no optic neuropathy, and 4 cases did not specify. In contrast, 23 of the 35 patients with SPD without a CSF shunt noted vision loss. Of these 23, 7 were attributed to bony dehiscence of the optic canal allowing for barotrauma, 6 were attributed to bony compression at the optic canal, and the rest were unknown.

Conclusions:
Optic neuropathy may accompany chronic intracranial hypotension with bony remodeling of the orbit and sphenoid sinus. This case illustrates the potential for marked bony changes of the optic canal, suggesting this as a mechanism.

References: None.

Keywords: Optic neuropathy, Skull Base, Orbit

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Poster 7

A Case Report o Malignant Pleomorphic Adenoma metastasis affecting eye motility and visual acuity.

Macarena Clementi[1], Madeleine Saint Martin[1], Lidia Schiavo[1], Carolina Busquets[1], Marcelo Rivamonti[1], Nicolas Zago[1], Juan Antonelli[1], Mirta Arana[1], Haydee Martinez[1]

[1]*Hospital de Clinicas Jose de San Martin, Buenos Aires, Argentina*

Introduction:
In the presence of compromise of II, III, IV and V cranial nerves, compressive lesions must be suspected in the cavernous sinus or the orbital apex. Imaging and visual field test are useful to identify the location of the lesion.

Methods:
Case report

Results:
A 38-year-old male presented with right eye vision loss, and limitations of all eye movements a week ago. Medical history was significant for malignant parapharyngeal pleomorphic adenoma diagnosed in February 2016. In may 2016 the patient complaint of double vision. VA was 10/10, mild compromise of eye movements was noticed. A neurologist concludes tumor compression; the right eye was occluded to avoid diplopia. Three months later the patient shows motility and vision loss. Symptoms were not noticed because of constant occlusion. The patient brought a post op TC scan that showed a tumor remnant invading the left lower jaw, lung metastasis and a lesion located between the right cavernous sinus and the right orbital apex. On examination, VA was 3/10 OD and 10/10 OS. Eye movement examination showed compromise of eye motion in every direction Pupil: midriatic not reactive. Fundus examination revealed optic nerve superior pallor on the right eye. The patient is currently undergoing chemotherapy.

Conclusions:
In a patient showing compromise of all eye movements, compressive lesions must be searched in the cavernous sinus and orbit vertex. Is important to remember that unilateral visual acuity affection is suspicious of optic nerve damage located rostral to the optic quiasm. Computerized visual field might bring important information regarding the visual pathway affection due to compression of what we conclude was a SNC metastasis. In addition, close follow up is needed in patients with compressive symptoms of cranial nerves involved in eye motility, to diagnose and treat eventual visual impairment.

References: None.

Keywords: Ocular Motility, Orbit, Tumors, Neuroimaging

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Poster 8
VZV-induced optic neuropathy

Monica Ertel[1], Bryan Pham[1], MHD Abdallah Mahrous[1], Cristiano Oliveira[1], Marc Dinkin[1]

[1]*Weill Cornell Department of Ophthalmology, New York, New York, USA*

Introduction:
We present a woman with progressive vision loss from an optic neuropathy after varicella zoster virus (VZV) keratitis.

Methods:
Case Report

Results:
The patient is a 70 year-old woman with a history of hypertension, thyroid cancer, and immunosuppression after kidney transplant for glomerulonephritis. Five weeks prior to presentation, she developed a painful blistering rash over the right side of her face, was diagnosed with herpes zoster, and started on valacyclovir. She developed herpes keratitis one week later which was treated with topical antibiotics. One month later, she developed central vision loss that spread peripherally. Her exam revealed acuity of 20/800 and 20/50 in the right and left eye, respectively, as well as a right eye central visual field defect, dyschromatopsia, and an afferent pupillary defect. Fields, colors, pupil examination were normal in the left eye. Efferent exam was normal. She had mild right eye conjunctival injection. Funduscopic examination revealed pallor and optic nerve edema with vessel obscuration nasally in the right eye. The left fundus was normal. ESR, CRP and platelets were normal. MRI demonstrated mild perineural enhancement of the right optic nerve. Lumbar puncture demonstrated normal contents and negative VZV IgG/IgM, VZV PCR, and HSV PCR. The patient was treated with IV acyclovir and steroids for presumed herpetic etiology.

Conclusions:
The exact mechanism of VZV-induced optic neuropathy remains elusive; however VZV DNA in perineural infiltrate of the posterior ciliary nerves and perivascular infiltrate of the posterior ciliary arteries has been demonstated in enucleated eyes after VZV infection.(1) VZV antigen has also been detected in temporal artery biopsies of patients with anterior ischemic optic neuropathy.(2) Negative lumbar puncture results in this case suggests direct neuronal spread. While the pathogenesis of optic neuropathy secondary to VZV remains uncertain, it is an important clinical consideration in patients with optic neuropathy after recent herpetic keratitis.

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Poster 9
Radiation-induced Optic Neuropathy following Whole-Brain Radiotherapy

Ian Ferguson[1], Leah Levi[2], Gregory Van Stavern[1]

[1]Washington University in St. Louis, St. Louis, Missouri, USA, [2]University of California, San Diego, La Jolla, California, USA

Introduction:
Radiation-induced optic neuropathy (RION) is a rare complication of radiotherapy to the anterior visual pathway (AVP) which results in irreversible vision loss. Experimental data support a dose tolerance for the AVP of 50 Gy. Whole brain radiotherapy (WBRT) is a palliative intervention for patients with multiple brain metastases. The most common WBRT regimen delivers a total dose of 30 Gy, well below the dose tolerance threshold of the AVP. This case series reports three patients who developed RION following WBRT.

Methods:
Case 1. A 64-year-old male underwent WBRT of 35 Gy in 14 fractions of 2.5 Gy. Six months after treatment he reported blurry vision in his right eye rapidly progressing to total blindness, and hand motion vision in his left eye. MRI showed focal enhancement with increased FLAIR signal in both intracranial optic nerves and the left aspect of the optic chiasm. Case 2. A 64-year-old male underwent WBRT of 30 Gy in 10 fractions of 3 Gy. Nine months after treatment he reported abrupt onset of complete visual loss in his right eye, and visual field defect in his left eye. MRI showed focal enhancement with increased FLAIR signal in both intracranial optic nerves and the right aspect of the optic chiasm. Case 3. A 59-year-old male underwent WBRT of 30 Gy in 10 fractions of 3 Gy. Eleven months after treatment he reported progressive vision loss in his left eye. MRI showed showed thickening and enhancement of the intracranial portion of the left optic nerve and the left aspect of the optic chiasm.

Results:
Case series

Conclusions:
This is the first report of RION following WBRT and suggests that the purported dose tolerance of the AVP may overestimate its true threshold. Radiation oncologists should strive to spare the AVP from the full dose delivered to the whole brain.

References: Danesh-Meyer HV. Radiation-induced optic neuropathy. Journal of Clinical Neuroscience. 2008 Feb 29;15(2):95-100. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. Journal of Clinical Oncology. 2006 Mar 10;24(8):1295-304. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose–volume effects of optic nerves and chiasm. International Journal of Radiation Oncology* Biology* Physics. 2010 Mar 1;76(3):S28-35.

Keywords: Chemotherapy and radiation injury, Optic nerve trauma and treatment, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 10
Non-arteritic Ischemic Optic Neuropathy – A Triple Threat?

Aubrey Gilbert[1], Joseph Rizzo[1]

[1]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

Introduction:
Recurrent non-arteritic ischemic optic neuropathy (NAION) in the same eye is very rare.1 There have been only a few prior reports of ipsilateral recurrence of non-arteritic ischemic optic neuropathy happening more than twice.2-4 Sometimes worsening of field loss in the early stage, which is known to occur in around a third of cases, is misclassified as a recurrent event. We present two cases of patients who both suffered three distinct episodes interpreted as NAION.

Methods:
The histories were reviewed for two patients with three distinct episodes of recurrent NAION.

Results:
The first patient experienced acute painless loss of vision in his left eye at age 41. His visual field demonstrated an inferior defect and superior disc edema was noted. Inflammatory markers were normal. He experienced additional episodes one and eight years later. Laboratory work up, fluorescein angiography, and magnetic resonance imaging revealed no other potential etiology. The second patient experienced acute painless loss of vision in his right eye at age 62. An inferior field defect and superior segmental optic disc swelling were noted. Inflammatory markers were normal. He experienced subsequent episodes eight and 10 years later. Atypical features of the case included the degree of edema and the presence of hard exudates. He was followed for a decade before an underlying lesion was identified when MRI showed increased T2 signal at the neuro-ocular junction. A diagnosis of peripapillary combined hamartoma was ultimately made.

Conclusions:
We describe two unique cases of what was interpreted as triply recurrent NAION. While recurrence of NAION more than twice in the same eye is possible, this is still an exceedingly rare diagnosis so alternative etiologies should be considered. One of the two patients was ultimately found to have a peripapillary combined hamartoma.

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Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 11
Compressive optic neuropathy caused by metastases to skull bones from non-small cell lung cancer.

Anna Gruener[1], Alice Milligan[2], Miles Stanford[2]

[1]St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, Great Britain, [2]St Thomas' Hospital, London, Great Britain

Introduction:
Compressive optic neuropathy may result from tumors, inflammatory processes, and rarely, metastases involving the optic canal. Patients with compressive optic neuropathy may have proptosis, mild color deficits and almost normal vision, with or without disc swelling.

Methods:
A young, previously well, woman presented with a 10-day history of gradual left visual loss, not associated with any pain on eye movement. Further questioning revealed a nine-month history of headaches, tiredness and unintentional weight loss. On examination, she had signs of a left retrobulbar optic neuropathy, with reduced colour vision and a left RAPD. She also had a mild left proptosis. An MRI brain showed widespread left calvarial hyperostosis associated with underlying plaque-like dural and orbital enhancement. A left compressive optic neuropathy was diagnosed. A subsequent bone scan displayed multiple metastases in her spine and hip. PET CT showed a pulmonary lesion, that was later identified as a non-small cell lung cancer.

Results:
The patient received chemotherapy for six months, followed by immunotherapy. Two years following her initial presentation to the eye department she died of a pulmonary embolism.

Conclusions:
Despite the patient's initial presentation being suggestive of a typical retrobulbar optic neuritis, red flags that pointed away from this diagnosis were (i) the absence of pain, (ii) her new onset headaches, and (iii) her unintentional weight loss. Although typical optic neuritis is the most common cause of optic neuropathy in a young adult, one should always consider alternative diagnoses, including compressive, infiltrative, inflammatory, toxic and genetic processes.

References: Tamai H, Ishida K, Murakami K, Narita N, Tominaga T, Fuse N. Compression neuropathy caused by cancer metastasis to the optic nerve canal. BMC Res Notes, 6:546, 2013.

Keywords: Optic neuropathy, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 12
Bilateral vision loss with p-ANCA associated lymphocytic vasculitis

Bokkwan Jun[1]

[1]*Mason Eye Institue, University of Missouri, Columbia, Missouri, USA*

Introduction:
To report and review a case presented with bilateral vision loss and p-ANCA associated lymphocytic vasculitis

Methods:
This is a descriptive case report .

Results:
A 73-year-old right handed woman who had a past medical history of rheumatoid arthritis presented with bilateral vision loss. Four days prior to the clinic visit, the patient started noticing dark spots in her vision and on the following morning, the patient woke up with complete vision loss of the left eye and went to a local ophthalmology clinic where optic disc swelling was found and started taking prednisone and on the next morning, the patient woke up with complete vision loss of the right eye. The vision loss was acute, painless, bilateral, simultaneous and the patient had posterior headache radiating to her jaws with no scalp tenderness, no jaw claudication, no weight change no recent history of vaccination, traveling or contact to sick person or animal. On examination at presentation, the visual acuity was NLP in both eyes and funduscopic exam showed pale optic disc swelling with edematous retina in both eyes. The laboratory showed elevated ESR, CRP, LDL, positive p-ANCA and MPO. Optic nerve head OCT showed elevated thickness of retinal nerve fiber layer. CTH/CTA head and neck were unremarkable. Fluorescein angiography showed significant delay in choroidal and retinal circulation in both. Pathology of bilateral temporal artery biopsy showed lymphocytic arteritis, not Giant cell arteritis. The patient received IVMP followed by prednisone and methotrexate was started.

Conclusions:
This is a case of bilateral vision loss with positive p-ANCA (MPO) associated lymphocytic vasculitis. The vision loss was acute, painless, severe, bilateral, simultaneous and occurred with no systemic symptoms or signs and no other intraocular/orbital inflammation at the presentation. Despite the early administration of systemic corticosteroid, the visual outcome was unfavorable.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Vascular disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 13
Optic Nerve Compression Secondary to a Posterior Ethmoid Pyomucocele

Terri Key[1], Josh Gratwohl[2], Micaela Koci[1], Alyssa Eckert[42], Joaquin Arista[2]

[1]University of Nevada Reno School of Medicine, Reno, Nevada, USA, [2]University of Nevada Reno, Reno, Nevada, USA

Introduction:
Optic neuritis is characterized as an acute, unilateral loss of vision associated with orbital pain. It is more prevalent in females, occurs most often in the third and fourth decades of life, and is associated with multiple sclerosis. Importantly, optic neuropathy secondary to other causes should be considered in patients presenting with atypical symptoms. We present a case of a compressive optic neuropathy due to an ethmoidal pyomucocele that was initially diagnosed as optic neuritis.

Methods:
Case Report

Results:
A 44-year-old male with a history of sinusitis and previous sinus surgery presented with a ten day history of sharp, stabbing pain along the medial aspect of his left orbit. Three days after the onset of orbital pain, the patient noticed worsening of his central vision OS accompanied by a blue flickering light and photosensitivity. It is also noteworthy that the patient has a documented history of an ethmoidal mucocele in 2009 documented by CT scan of the orbit. Neuroimaging studies showed no enhancement of the optic nerve OS, which would be indicative of optic neuritis. The MRI scan demonstrated evidence of a pyomucocele involving the left posterior ethmoid sinus and extending into the orbital apex as well as the left anterior clinoid process. The patient was transferred to an outside ENT specialist and an emergent decompression of the pyomucocele was performed. The patient has had an excellent post-operative outcome with a best corrected visual acuity of 20/20 OS and normalization of the visual field.

Conclusions:
This patient had an atypical presentation of optic neuritis associated with a “benign” mucocele. Neuroimaging studies were carefully reviewed and it was ascertained that in fact the patient had a compressive optic neuropathy secondary to a pyomucocele. Prompt decompression of the ethmoidal mucocele resulted in an excellent postoperative outcome.

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Keywords: Optic neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 15
Acute zonal occult outer retinopathy presenting as retrobulbar optic neuritis

sungeun Kyung[1], JunSoo Eun[1], Kyungyoon Shin[1], Moohwan Chang[1]

[1]Dankook University, Cheonan-City, Chungchungnam-Do, Korea, Republic of

Introduction:
Acute zonal occult outer retinopathy (AZOOR) is an inflammatory retinopathy in the category of white dot syndromes characterized by acute loss of one or more zones of outer retinal function associated with photopsia, minimal funduscopic changes and abnormal electroretinography findings. The authors report a case of AZOOR in a patient presenting as retrobulbar optic neuritis.

Methods:
A 33 year-old male without underlying disease was referred with retrobulbar optic neuritis in the right eye. He presented with blurring in the right eye of 2 weeks duration. His visual acuity was 20/20 in left eye and 20/100 in the right eye with no ophthalmoscopic and fluorescein angiographic abnormalities. The cecocentral scotoma was found in the right eye. The amplitudes of pattern visual evoked potential (PVEP) was reduced in the right eye.

Results:
The patient was followed with steroid treatment. Irregularities in the inner segment/outer segment (IS/OS) line of the photoreceptors were observed over the superior fovea by optical coherence tomography (OCT). The amplitudes of the multifocal electroretinographics (ERGs) were reduced in the area of the cecocnetral scotoma. The diagnosis of the AZOOR was made. At 6 months, the reduced amplitude in multifocal ERGs and irregularities in the IS/OS line on OCT were improved. His visual acuity was 20/20 in both eyes.

Conclusions:
The clinical distinction between a retinal versus an optic nerve problem may be difficult in case of subtle retinopathies. The multifocal ERGs and OCT images are helpful in this regards. The abnormalities of the inner/outer segment (IS/OS) junction and reduced amplitude corresponding to the scotoma area can be detected in patient with suspected AZOOR.

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Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields

Financial Disclosures: The authors had no disclosures.

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Poster 16
Bilateral concentric visual field defect as an initial manifestation of multiple sclerosis

sungeun Kyung[1], Junsoo Eun[1], Kyungyoon Shin[1], Moohwan Chang[1]

[1]Dankook University, Cheonan, Korea, Republic of

Introduction:
The lesions in multiple sclerosis have been found in radiological examinations without associated clinical manifestations. However, the symptomatic visual field defects in MS free from optic neuritis is unusual. We report a case with a bilateral concentric visual field defects as the initial manifestation of multiple sclerosis.

Methods:
A 22 year-old male without history of optic neuritis suffering from slowly progressing bilateral concentric visual field defects with duration of 1 year presented to our clinic. His best-corrected visual acuity, intraocular pressures, and anterior segment examination findings were normal bilaterally. Fundus examination showed pale optic disc in both eyes. Humphrey Field Analyzer revealed a bilateral concentric visual field defect.

Results:
The optical coherence tomography (OCT) showed thinning of peripapillary retinal nerve fiber layer (RNFL) and decreased macular volume. The mitochondrial DNA (mtDNA) analysis in the diagnosis of Leber hereditary optic neuropathy (LHON) was negative. The brain magnetic resonance imaging (MRI) showed multifocal bilateral asymmetric T2 hyperintense lesions in left frontal lobe subcortical area, left cingulate gyrus and both frontal lobe subcortical and deep white matter. The diagnosis of probable MS was made.

Conclusions:
Multiple sclerosis is an autoimmune demyelinating disorder of the nervous system. Optic neuritis, the most common ocular manifestation of multiple sclerosis, may be the initial clinical disease manifestation. However, there is a possibility of slowly progressing concentric visual field defect could be a initial signs of multiple sclerosis in a patient without any history of optic neuritis.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Demeylinating disease, Optic neuropathy, Neuroimaging, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 17

CRMP-5 positive Paraneoplastic Optic Neuropathy as Initial Presentation of Small Cell Lung Cancer

Jennifer Lee[1], Igor Bussel[2], Dante Sorrentino[2], Joseph Vojtko[2], Anagha Medsinge[2]

[1]University of Pittsburgh Medical Center: Eye and Ear Institute, Pittsburgh, Pennsylvania, USA, [2]University of Pittsburgh Eye Center, Pittsburgh, Pennsylvania, USA

Introduction:

Paraneoplastic optic neuropathy (PON) is a rare disease entity, it is estimated to occur in less than 0.01% of cancer patients. Despite this, disk edema and associated changes in visual acuity may be the first sign of malignancy. Thus, awareness of these disease entity is vitally important to the ophthalmology community.

Methods:

72 year old Caucasian male presented to the Emergency Department with left eye disc edema and a visual acuity of 20/50. He denied any medical history, but review of systems was positive for cough and ongoing 100 pack year smoking history. Extensive serology, neuro-imaging, CSF studies, and finally core biopsy and paraneoplastic panel revealed Small Cell Lung Cancer with PON.

Results:

MRI/MRA/MRV demonstrated bilateral papilledema, but no abnormal signal enhancement in the optic nerves/ chiasm, no sinus thrombosis or metastatic disease. Negative serologies included: Borrelia burgdorferi, Tuberculosis, Syphilis, Toxoplasmosis, ANA, ANCA, ACE, C3, C4, DsDNA, CRP, RF, ESR, SS-A, SS-B, tissue transglutaminase antibodies. CSF showed an opening pressure of 22 and lymphocyte predominant pleocytosis. Negative CSF studies included: VDRL, Borrelia burgdorferi, AFB, CMV, EBV, HSV, VDRL, NMO, cytology for malignant cells, and culture. He had elevated IgG index, IgG synthesis rate. Chest x-ray showed left hilar opacity. Chest CT confirmed multiple lung and liver nodules compatible with metastatic lung cancer. His liver core biopsy showed metastatic high-grade neuroendocrine cells favoring small cell carcinoma. Paraneoplastic work-up was positive for Collapsin Response-Mediator Protein-5 (CRMP-5) IgG (1:122880).

Conclusions:

PON is an important disease entity to keep on the differential diagnosis in cases of unexplained subacute vision loss, extensive smoking history, and disk edema on exam as it may be the initial presenting symptoms of malignancy that brings the patient to the hospital. Our case is unique as our patient did not have other neurologic sequelae or vitreous cells that are frequently associated with PON.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 18
Reversible Bilateral Optic Neuritis after Influenza Vaccination: A Case Report and Literature Review

Emily Li[1], Adeniyi Fisayo[1]

[1]Yale University School of Medicine, New Haven, Connecticut, USA

Introduction:
Several cases of optic neuritis following influenza vaccination have been reported in literature. The association is rare and pathophysiology unknown. We present post-vaccination bilateral optic neuritis in a patient whose identical twin received the same vaccine without developing visual symptoms.

Methods:
Retrospective case report and literature review.

Results:
A previously healthy 6-year-old girl developed bilateral vision loss one week after receiving the intra-muscular quadrivalent influenza vaccine. Her identical twin received the same vaccination without subsequent vision changes. Visual acuities at presentation were hand motion in the right eye and counting fingers in the left. Ophthalmoscopy revealed optic nerve swelling with vessel obscuration bilaterally and peripapillary hemorrhages on the left. Magnetic resonance imaging with intravenous (IV) contrast showed severe thickening and abnormal enhancement of both optic nerves but no white matter lesions in the brain or spinal cord. Cerebrospinal fluid analysis was unremarkable and negative for oligoclonal bands and Lyme antibodies. Serologic testing was negative for sarcoidosis, Lyme, and aquaporin-4-antibodies. After five days of IV methylprednisolone, visual acuities were 20/20 and and color vision (Ishihara) was10/10 in each eye. Six days after her last dose of IV steroids, she developed vision loss to no light perception in the left eye with a relative afferent pupillary defect and left optic disc swelling. Oral prednisolone (2 mg/kg/day) was restarted and vision improved to 20/20 within one week.

Conclusions:
The influenza vaccine is a rare (10 cases per one million vaccinations), yet significant, cause of bilateral optic neuritis. Vision loss, typically to hand motion or worse, occurs one to four weeks after vaccination and responds to steroid therapy. To the best of our knowledge, the present case is the only report of post-vaccination optic neuritis with a genetically-identical case-matched control in current literature.

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Keywords: Optic neuropathy, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 19
Sphenoid Sinus Mucocele: A Case Series and Review of Literature

Emily Li[1], Martha Howard[1], Eugenia Vining[1], Richard Becker[1], Robert Lesser[1]

[1]Yale University School of Medicine, New Haven, Connecticut, USA

Introduction:
Sphenoid sinus mucoceles are rare, pathologically benign lesions which can expand to cause ocular compromise. We present three cases of compressive optic neuropathy secondary to sphenoid sinus mucocele.

Methods:
Retrospective clinical series and literature review.

Results:
Case 1: A 76-year-old female presented with three months of worsening left eye vision and left-sided headache. Vision acutely decreased six weeks prior to presentation to light perception (LP). Humphrey visual field (HVF) testing and optical coherence tomography (OCT) revealed diffuse field loss and optic nerve thinning. Fluorescein angiography was negative for retinal vasculopathy. MRI demonstrated an expansile mucocele in the left sphenoid sinus compressing the optic nerve. Surgical decompression two weeks later achieved visual improvement to counting fingers at six feet. Case 2: A 13-year-old female presented with left visual loss to no light perception over the course of hours. Examination revealed a left rAPD and normal appearing optic nerves. HVF and OCT showed diffuse defect and optic nerve thinning. Urgent MRI demonstrated a mucocele in the left sphenoid sinus with erosion of the optic canal. She underwent same-day emergent decompression. Her vision recovered to LP. Case 3: An 80-year-old female presented two weeks after acute-onset vision loss in the left eye, which had been preceded by two months of visual "haze" and three weeks of left-sided headache and nasal discharge. Examination revealed only LP. Visual field showed diffuse loss. CT and MRI demonstrated a mucocele in the left sphenoid and ethmoid sinuses. She underwent surgical drainage one day after presentation, but vision never improved.

Conclusions:
Sphenoid sinus mucoceles are pathologically benign lesions that expand, presenting with ocular symptoms—decreased vision, diplopia, visual field defects, proptosis, and external ophthalmoplegia. Prompt imaging enables urgent diagnosis, otolaryngology evaluation, and surgical decompression to maximize visual recovery, which may be limited even in the setting of emergent intervention.

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Keywords: Optic neuropathy, Neuroimaging, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 20
Tacrolimus associated Ischemic Optic Neuropathy

Shuai-Chun Lin[1], Hang Pham[1], Sangeeta Khanna[1]

[1]Saint Louis University, Richmond Heights, Missouri, USA

Introduction:
Tacrolimus is widely used immunosuppressant and though neurotoxicity is well recognized as a side effect, the risk of toxic optic neuropathy is low and described in a few case reports. Tacrolimus related optic nerve toxicity has been reported to present as bilateral1-2,6, asymmetric bilateral3 and even unilateral4-6 optic neuropathy mimicking ischemic or demyelinating optic neuropathy. We report here two patients presenting as unilateral, ischemic optic neuropathy while on tacrolimus therapy

Methods:
Report of 2 cases and review of the literature

Results:
The first patient is 33 year-old male who presented with acute painless decrease in vision right eye with unilateral disc edema mimicking ischemic optic neuropathy after two-year of tacrolimus therapy. The second patient is 51 year-old who presented with holocranial headache and sudden painless decrease in vision left eye with disc edema and peripapillary hemorrhage consistent with ischemic optic neuropathy while using tacrolimus for 7 months. Serial examinations including brain imaging, serologic & CSF tests looking for infectious, inflammatory, and neoplastic etiologies were all negative in both patients. The literature of case reports of tacrolimus-associated optic neuropathy will be reviewed and presented as clinical presentations may vary.

Conclusions:
Our patients highlight that tacrolimus toxicity can present as unilateral ischemic optic neuropathy. We propose that since tacrolimus is known to cause endothelial cell damage and dysfunction, recognition of ischemic optic neuropathy as a possible presentation of toxicity should be considered in patients receiving tacrolimus regardless of bilateral or unilateral presentation.

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Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 21

Idebenona off label- Visual improvement continuing 2 years after surgery of Meningioma with Idebenona.

HAYDÉE MARTINEZ[1], Mirta Arana[1], Mariana De Virgilis[2], Elizabeth Schiavo[1], Lidia Sarotto[1], Carolina Busquets[1], Marcelo Rivamonti[1], Macarena Clementi[1], Juan Antonelli[1], Nicolás Zago[1]

[1]Hospital de Clínicas José de San Martín, Buenos Aires, Argentina, [2]Hospital Oftalmológico Pedro Lagleyze, Buenos Aires, Argentina

Introduction:
Describe the clinical picture of a patient with sellar meningioma, with significant compromise visual function and recovery after a period, than the one determined by various studies, under treatment with Idebenona.

Methods:
Clinical case report

Results:
27-year-old patient who consults (december 2013) due to the progressive decrease in visual acuity (VA) in two months of evolution, with severe headaches, dyslalia and bradyphyquia. VA: RE: hand movement - LE: light perception PUPIL: RE: RAPD- LE: midryatic Ophthalmoscopicy - OCT : Bilateral papilledema VFD: No perception AO Brain MRI: Intracranial mass of 84 to 65 mm, compatible with macroadenoma Surgical behavior (January 2014) Pathological anatomy: Clear cell Meningioma, Grade II according to OMS Postoperative exam: VA: RE 1/10 LE light perception (May 2014) Evolution over 12 months period showed slight recovery (January 2015) VA: RE 3/10 / LE hand movement VDF: OD central remainder / LE peripheral remainder OCT: RE loss and significant flattening of the RFNL - LE nasal RFNL Slight recovery Treatment: Started with IDEBENONA 100 mg/day orally Currently: VA RE 6/10 - LE 1/10. (november 2016) (with Idebenona) VFD: FULL RECOVERY STABLE OCT

Conclusions:
In this clinical case, there was a severe damage in the visual function postoperatively, without recovery in the normal estimated time, evaluated in the last years by Dr SABINO, DANESH MEYER, JACOB, and other. Improvement is seen a year after the surgery when treatment with Idebenoma is started. This result is similar to that observed in other patients treated with Idebenona. Idebenone has been proposed as a free radical scavenger to prevent oxidative damage. Treatments currently undergoing investigation includes ubiquinone analogs, such as idebenone, and provide neuroprotection. There are currently no proven treatments. However, there are novel treatment modalities that are being evaluated, with several clinical trials.

References: 1) Meyerson C, Van Stavern G, Mc Clelland, LEBER HEREDITARY OPTIC NEUROPATHY: CURRENT PERSPECTIVES, (Clin Ophthalmol) 9:1165-76. 2015 jun 26. 2) Peregallo JH, Newman NJ, IS THERE TREATMENT FOR LEBER HEREDITARY OPTIC NEUROPATHY?, (Curr Opin Ophthalmol) 6: 450-7, 2015 Nov 3) Schiff M, Rustin P, IDEBENONE IN FRIEDREICH ATAXIA AND LEBER´S HEREDITARY OPTIC NEUROPATHY: CLOSE MECHANISMS, SIMILARTHERAPY? (Brain) 139 (pt7): e 39, 2016 Jul

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 22

OCT and Ultrasound in a Myopic Patient with Spontaneous Trilaminar Papillary Hemorrhage Without Vitreopapillary Traction

Priya Mathews[1], Megan Ridley-Lane[1], Aakriti Garg[1], Jason Horowitz[1], Jeffrey Odel[1]

[1]Harkness Eye Institute, Columbia University Medical Center, New York, New York, USA

Introduction:

Katz and Hoyt described a syndrome in young Asian female myopes presenting with unilateral tri-laminar hemorrhage: nerve fiber layer, subretinal, and vitreous. These patients typically had a contralateral small dysplastic disc.(1) Katz and Hoyt hypothesized causation by trauma of disc capillaries by vitreopapillary traction (VPT). The role of VPT remains controversial. We describe the use of modern imaging studies in this syndrome.

Methods:

Case report

Results:

A 14-year-old myopic female noticed decreased vision OD after completing a stress test for palpitations. Examination revealed normal vision OU and peripapillary vitreous, nerve fiber layer, and nasal subretinal hemorrhage OD, along with a small hyperemic and slightly elevated disc OS. Ultrasound and spectral domain optical coherence tomography (SD-OCT) showed persistent attachment of the vitreous to the disc OU but no VPT. SD-OCT also showed extensive subretinal hemorrhage OD and a normal RNFL thickness without subretinal fluid or folds OS. Fluorescein angiogram demonstrated mild leakage OD and no leakage OS.

Conclusions:

Our patient's OCT and ultrasound findings possibly support a deep or subretinal source of blood rather than vitreous traction. In addition, the combination of imaging and clinical findings support that the optic disc elevation OS was a congenital variant rather than true RNFL edema. These diagnostic tests may spare patients with similar presentations from invasive procedures such as lumbar puncture.

References: 1) Katz B, Hoyt WF. Intrapapillary and peripapillary hemorrhages in young patients with incomplete posterior vitreous detachment: signs of vitreopapillary traction. Ophthalmology, 1995; 102:349-54.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 23
Infiltrative Tubercular Optic Neuropathy in a Child

Preeti Patil Chhablani[1], Akshay Badakere[1]

[1]L V Prasad Eye Institute, Hyderabad, Telangana, India

Introduction:
Intraocular tuberculosis is not an uncommon entity, especially in regions where the disease is endemic, however primary involvement of the optic nerve is rare. A diagnosis of tubercular optic neuropathy must be considered in a case with infiltrative optic neuropathy in an endemic region.

Methods:
Case Report

Results:
A 12-year-old girl presented with gradual, painless loss of vision in the left eye since 5 days. On examination, she had severe disc edema with exudation around the disc in left eye suggestive of infiltrative optic neuropathy. A magnetic resonance imaging (MRI) scan of the brain and orbits with contrast revealed patchy thickening and enhancement of the retro bulbar portion of the optic nerve. Systemic investigations revealed a highly positive Mantoux test (25 mm) and prominence of hilar lymph nodes on chest x-ray, which pointed towards a diagnosis of tuberculosis. She was treated with intravenous methyl prednisone and a four drug anti-tubercular regimen. She had partial visual recovery with complete resolution of the disc edema and exudation in 8 weeks.

Conclusions:
Tubercular optic neuropathy poses a diagnostic challenge. Precise treatment guidelines for the treatment of tubercular optic neuropathy are not known however prompt institution of a combination of anti tubercular therapy and corticosteroids can result in a favorable outcome.

References: None.

Keywords: Optic neuropathy, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 24
Two Cases of Wolfram-Related Optic Atrophy: A New Mutation and A Misdiagnosis of Normal-tension Glaucoma

Victoria Pelak[1], Kanika Sharma[1]

[1]*University of Colorado School of Medicine, Aurora, Colorado, USA*

Introduction:
The phenotypic spectrum of WFS1-related disorders, spanning from Wolfram syndrome (WFS) to WFS1-related low-frequency hearing loss, are linked to mutations in the WFS1 gene. We describe two patients with WFS1 gene mutations with an incomplete DIDMOAD tetrad and highlight a previously unreported WFS1 mutation in one proband and a misdiagnosis of normal-tension glaucoma (NTG) in the other.

Methods:
Patient evaluation performed by: 1) clinical assessments; 2) retinal imaging; 3) molecular genetics.

Results:
Proband 1: An 8-year-old Hispanic boy presented with congenital hearing loss and optic atrophy. Family history (FH) was remarkable for diabetes mellitus (DM) type-2. VA was 20/40, 20/50 (R,L) with optic nerve pallor OU and decreased OCT RNFL thickness [R: 52µm; L:51µm]. Molecular genetic analysis unveiled a pathogenic sequence variant (c.937C>T;p.His313Tyr.) on exon 8 in the WFS1 gene not reported previously. Disease associated polymorphisms of the Wolfram(p.Val333Ile) and diabetes type-1(p.Val395Va; pSer855Ser; p.Arg456His.; p.Lys811Lys.) variants were detected. A non-autoimmune DM type-1 developed a year later and no other findings noted at 4-years. Proband 2: A 21-year-old Sudanese man presented with a diagnosis of NTG and visual decline over 10 years. History was remarkable for insulin-requiring DM, extensive FH of DM, and visual loss in a sibling. VA was 20/200 OU with optic nerve cupping and rim pallor, and mild background retinopathy bilaterally. OCT RNFL revealed thinning [R:64µm; L:58µm]. Genetic testing demonstrated a homozygous pathogenic variant(c.1511C>T, p.Pro504Leu.) in the WFS1 gene associated with WFS, but no signs of DI, ataxia, psychiatric disease, bladder dysfunction, or other endocrinologic dysfunction at two years of follow-up.

Conclusions:
Genetic testing for mutations in WFS1 gene should be considered in young patients with optic atrophy and the presence of another WFS-related disorder such as hearing loss (including congenital), non-autoimmune DM, or DI. In cases of NTG, particularly in young patients, investigation for WFS1 mutations deserves further investigation.

References: 1. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. J Med Genet. 34(10):838-841,1997. 2. Inoue H, Tanizawa Y, Wasson J, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet. 20(2):143-148, 1998. 3. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc. 9:715–718, 1938. 4. Valero R, Bannwarth S, Roman S, Paquis-Flucklinger V, Vialettes B. Autosomal dominant transmission of diabetes and congenital hearing impairment secondary to a missense mutation in the WFS1 gene. Diabetic medicine : a journal of the British Diabetic Association. 25(6):657-661, 2008. 5. Tranebjaerg L, Barrett T, Rendtorff ND. WFS1-Related Disorders. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews(R). Seattle (WA)1993.

Keywords: Genetic Disease, Optic neuropathy, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 25

Radiation-Induced Optic Neuropathy: Complication Of The Treatment Of Intracraneal Folicular Thyroid Carcinoma Metastases

Simón Quijada Angeli[1], Iulia Pana[2], Belén Gragera Soroa[2], Mónica Hijos Gastón[2], Diego Rincón[3]

[1]Department of Ophthalmology, Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain, [2]Department of Ophthalmology, Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [3]Department of Oncology, Hospital Universitario Puerta de Hierro, Majadahonda, Spain

Introduction:
Radiation-Induced optic neuropathy (RION) is a rare and devastating complication of patients treated with external beam radiation, in which the treatment fields involve head and/or neck

Methods:
We present a case report of a patient with RION after being Ttreated with stereotactic fractionated radiotherapy. Clinical and neuro-radiological findings will be presented

Results:
A 59 Years-Old man was admitted to our hospital, with the diagnose of follicular thyroid carcinoma, Hürthle cell variant, stage IV, treated with stereotactic fractionated radiotherapy (SFRT) plus pazopanib, with metastases to sphenoid greater wings and clivus, who totally lost the visual acuity on his left eye (OS) one year ago, who complained of partial loss of visual acuity on his right eye (OR) during the last five days. On ophthalmologic examination there was Best Corrected Visual Acuity (BCVA) in the OR: 0,4 and OS: light perception (LP), the anterior segment was normal bilaterally, as well as the intraocular pressure. Funduscopy revealed in the OR a normal optic disc and in the OS Diffuse pallor of the optic disc. Magnetic resonance (MR) was performed showing an increase in the signal in T2 sequence in both optic nerves at the intracranial portion, and the optic chiasm, and gadolinium enhancement of these structures. The patient was diagnosed of RION, we stop the therapy with pazopanib, and received steroids, Anti-coagulant and bevacizumab 7,5mg/M2 well tolerated. Despite the initial good response, the patient suffered a decrease of his visual acuity to LP and developed a complete optic atrophy bilaterally

Conclusions:
RION is an infrequent and multifactorial complication produce by a delayed radiation damage to the anterior visual pathways, that severely affects patient´s quality of life, and is really important to consider the develop of this entity after head or neck radiotherapy

References: None.

Keywords: Optic neuropathy, Chemotherapy and radiation injury, Neuroimaging, Tumors, Skull Base

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 26
Atypical Auto-Immune Bilateral Optic Neuritis- Post Multiple Flavivirus Infections.

Carolina Ramos[1], Telemaco Lima[2], Luciana Lima[2]

[1]Hospital da Gamboa-Nossa Senhora da Saude, Rio de Janeiro, Brazil, [2]Faculdade de Medicina Souza Marques, Rio de Janeiro, Brazil

Introduction:
Optic neuritis occurring post-infection may cause direct autoimmune attack to visual structures or indirect damage through occlusive vasculopathy ZIKV is a mosquito-transmitted flavivirus that is closely related to Dengue (DENV), and virological analysis revealed that ZIKV infects the cornea, vascularized choroid, the bipolar and ganglion layers of the retina, and the optic nerve. Although the mechanism by which ZIKV causes eye disease remains undefined. Neurotropic flaviviruses may first invade the brain, then infect the optic tract, and later transit in a retrograde direction into the eye along the optic nerve. Alternatively, ocular infection may result from hematogenous spread of virus across the blood-retinal barrier. Additional studies are needed to define the precise mechanisms of ocular invasion by ZIKV. ZIKV infects both the eyes and testes in humans and in animal models, suggesting that immune privileged organs may support replication even weeks after resolution of viremia and clinical symptoms.

Methods:
59 Y-O male, first had sudden visual loss of his Right Eye 1 month after clinical course and laboratory findings consistent with the diagnosis of Dengue in 2011. BCVA was 20/200 OD and 20/20 OS, after pulsotherapy with methylprednisolone 1g/day for 3 days had partially recovery to BCVA 20/60 OD. In 2016, 45 days after new viral clinical course, was diagnosed as Zika infection and developed OS optic neuropathy with BCVA of 20/200. OD remained 20/60. Visual Fields are very dense with large scotomas compromising almost 30 degrees OU, and OCT showed optic atrophy OD and disc edema OS with complete loss of ganglion cells bilaterally.

Results:
x

Conclusions:
Auto-immune optic neuritis post flavivirus infection can cause deep visual loss, the second infection immune response after having been previous exposed to this kind of virus can be stronger. New studies are needed to understand immune response to multiple flavivirus exposure.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & infectious disease (eg, AIDS, prion)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 27
Optic Disc Edema and Retinal Abnormality Secondary to Dasatinib Treatment in a CML Patient

Reut Singer[1], Anatoly Nemets[1], Eyal Aloni[1]

[1]*Barzilai Medical Center, Ness Ziona, Israel*

Introduction:
Dasatinib (Sprysel) is a new second generation oral Bcr-Abl tyrosine kinase inhibitor, approved for first line treatment of patients with chronic myelogenous leukemia (CML). According to phase 1 and 2 studies published to date ophthalmological secondary effects of dasatinib, are practically non-existent or trivial. Resent literature case report suggest the possibility of secondary optic neuropathy caused by the drug.

Methods:
We present ophthalmic manifestations of a 46 years-old female who was recently diagnosed with CML and started on dasatinib treatment.

Results:
Two and a half months after beginning treatment with Dasatinib, the patient started complaining of photopsias in both eye, exuberated by high pitch sound, and of blurred vision in her inferior visual field of her left eye. On examination the patient had bilateral severe swollen disc with normal sensory and motor visual functions except for a Humphrey visual field showing enlargement of the blind spot in both eyes and a left eye inferior arcuate defect. She underwent extensive complementary tests that ruled out infectious, inflammatory and infiltrative disorders and IIH, following which she was suspected of optic neuropathy secondary to dasatinib treatment. Dasatinib treatment was stopped and treatment with oral prednisone was started with improvement of her symptoms and resolution of the swollen discs. Full field ERG showed slight to moderate depression of the b wave in the left eye while VEP was normal in both eyes.

Conclusions:
To our best knowledge, this is the second case report in the literature describing optic nerve swelling related to Dasatinid treatment and the first to show retinal toxicity as seen on ERG. Physicians treating patients with Dasatinid should be aware of the possibility of severe ophthalmic toxicity related to the drug.

References: Saudi J Ophthalmol. 2015 Jul-Sep; 29(3): 227–231. Optic neuropathy secondary to dasatinib in the treatment of a chronic myeloid leukemia case Katia Sotelo Monge, Alberto Gálvez-Ruiz,, Alberto Alvárez-Carrón, César Quijada, Anna Matheu

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 28

Variable presentation of Leber's hereditary optic neuropathy in a family harbouring a rare mtDNA mutation.

Vasily Smirnov[1], Sabine Defoort-Dhellemmes[1]

[1]Lille University Hospital, Lille, France

Introduction:
We describe in this report 4 patients of the same familiy presented with either typical and atypical clinical picture of Leber's hereditary optic neuropathy.

Methods:
The proband, 5y.o., was adressed for a divergent squint. He was followed by a neurologist for a tremor and a mild gait ataxia. At examination, his VA was reduced and he had a bilateral optic disc pallor. His older brother, 12 y.o., was asymptomatic and was assessed in the settings of the familial survey. Surprisingly, he had a limited VA and the same optic disc pallor on fundus examination. The oldest brother, 15 y.o., was adressed to our consultation few months later with a sudden loss of vision in his RE. Fundus examination revealed a disc swelling and peripapillary telangiectasias in this eye. The LE had not been involved first, but a sequential visual loss happened within 1 month. Finally, we examined their mother, 35 y.o., who had no visual symptoms but she reminded us an episode of self resolved ophthalmoplegia and myopathy at the age of 5 (according to her neurologist, "she had to be dead in the year after diagnosis"). Despite her good VA, she had a mild optic atrophy.

Results:
A standard genetic approach (restriction and sequencing for frequent mutations) was unproductive. Ten years after the first visit, the Whole Genome Sequencing enabled us to discover a m.13051G>A mutation.

Conclusions:
This family reflects quite well the variability of LHON presentation: one patient was suffering from indolent subacute neuropathy typical of early-onset forms, another child had a LHON-plus presentation with motor symptoms similar to the ones his mother displayed at the same age, the oldest one had a classical sequential optic neuropathy with telangiectasias and pseudo-edema. They were harbouring one of the rarest mtDNA mutation, previously described in association with LHON, LHON-like and Leigh-like phenotypes.

References: Barboni P, Savini G, Valentino ML, et al. Leber's hereditary optic neuropathy with childhood onset. Invest Ophthalmol Vis Sci 2006;47:5303–5309. Howell N, Oostra R-J, Bolhuis PA, et al. Sequence analysis of the mitochondrial genomes from Dutch pedigrees with Leber hereditary optic neuropathy. Am J Hum Genet 2003;72:1460–1469. Dombi E, Diot A, Morten K, et al. The m.13051G>A mitochondrial DNA mutation results in variable neurology and activated mitophagy. Neurology 2016;86:1921–1923.

Keywords: Optic neuropathy, Genetic Disease, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 29

Juxtapapillary retinal hemangioma masquerading as optic disc edema as the first manifestation of Von Hippel-Lindau

Kenneth Taubenslag[1], Tarek Shazly[1], Catalina Cleves-Bayon[2], Ellen Mitchell[1]

[1]UPMC Eye Center, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA, [2]Department of Pediatric Neurology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA

Introduction:
Peripheral retinal angiomas are hallmark lesions of Von Hippel-Lindau (VHL) disease. Solitary, juxtapapillary retinal and optic nerve hemangiomas, on the other hand, are comparatively rare. These tumors may be spontaneous or syndromic and may demonstrate nonspecific morphology posing a diagnostic challenge, masquerading as papilledema, optic neuritis, optic nerve granuloma, or peripapillary subretinal neovascularization.

Methods:
Case report.

Results:
A 12 year-old, previously healthy girl was referred for inferior optic disc edema of the right eye, with surrounding retinal edema and exudate in the setting of headache and transient visual disturbance. OCT confirmed inferonasal RNFL thickening, and Humphrey visual fields revealed blind spot enlargement of the right eye consistent with disc edema. MRI brain and orbits was obtained, demonstrating posterior globe flattening bilaterally and protrusion of the optic nerve head on the right, read as concerning for papilledema. However, lumbar puncture measured a normal opening pressure and yielded bland CSF. Laboratory evaluation for typical infectious and infiltrative etiologies was negative. Upon further review we noted subtle post-contrast enhancement at the optic nerve head on MRI suggestive of a vascular lesion, prompting genetic testing for VHL given the appearance of the lesion at the disc. Gene sequencing returned positive for a heterozygous Y98H "Black Forest" founder mutation. Currently as the patient is asymptomatic with 20/20 visual acuity bilaterally we have elected observation.

Conclusions:
Exophytic, juxtapapillary retinal angioma should be considered in the differential diagnosis of unilateral or bilateral papillitis even in children less than 15 years of age with no family history of VHL. Juxtapapillary angioma may be indistinguishable from optic disc edema due to intracranial hypertension based on OCT and formal visual field testing and may also present with optic nerve head protrusion on MRI. This case highlights imaging features that should raise the index of suspicion for the diagnosis and prompt genetic testing.

References: None.

Keywords: Pediatric neuro-ophthalmology, Genetic Disease, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 30
Bilateral Sequential Central Vision Loss in a Young Man

Samuel Thomsen[1], Bokkwan Jun[1]

[1]*University of Missouri - Columbia, Columbia, Missouri, USA*

Introduction:
To report a case of bilateral sequential central vision loss and review possible etiologies.

Methods:
A 19-year-old right handed man who was previously healthy presented with a month history of blurry vision in the right eye. The visual disturbance was described as painless, no change over time. The patient had no history of recent contact to sick person or exposure to animals and no vaccination. The initial exam showed visual acuity was CF in the right eye and 20/20 in the left eye, dyschromatopsia in both eyes, central scotoma in the right eye on HVF and Amsler test and showed no RAPD, no optic disc swelling or no macula edema in either eye. MRI brain and orbit with and without contrast with fat suppression and serologic test including mitochondrial genome were performed. MRI was unremarkable. Coenzyme Q10 was started. About 5 weeks later, the patient returned to clinic with two-week history of blurry vision in the left eye which was described as sudden, painless, no change over time. The exam showed visual acuity was 5/100 in the right eye and 10/200 in the left eye, worsening dyschromatopsia, central scotoma in both eyes on HVF and Amsler test and showed mild disc edema in the left eye. FA showed telangiectatic vessels on both optic discs with no leakage or no staining. ONH OCT showed slight thickening of RNFL in both eyes at their early presentation. Systemic corticosteroid was administered with IVMP followed by oral prednisone tapering with no improvement. Mitochondrial genome analysis returned as negative for mutation but we considered repeating mitochondrial genome test.

Results:
See "Methods"

Conclusions:
The patient had bilateral optic neuropathy with clinical presentation of LHON without mutation of mitochondrial genome which is rare. We reviewed literatures and discussed other possibilities of bilateral sequential central vision loss in a young patient.

References: None.

Keywords: Optic neuropathy, Genetic Disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 31
Nyctalopia as the presenting symptom of new onset alcoholic liver failure

Astrid Werner[1], Thomas Hedges[1], Laurel Vuong[1], Carlos Mendoza-Santiesteban[1]

[1]New England Eye Center, Tufts Medical Center, Boston, Massachusetts, USA

Introduction:
Vitamin A plays a crucial role in retinal phototransduction, and deficiency of this essential nutrient commonly produces nyctalopia as its earliest symptom. In the developing world, vitamin A deficiency is usually due to dietary scarcity, while in the developed world, this occurs rarely, and is confined to patients with psychiatric disease or restricted diets. In the United States, vitamin A deficiency is usually secondary to fat malabsorption or difficulties with Vitamin A metabolism such as in gastric bypass, inflammatory bowel disease or liver disease. We describe a case of vitamin A deficiency that was initially attributed to poor diet, but was ultimately revealed to be the presenting sign of new onset liver failure.

Methods:
Case Summary

Results:
35 year old man with no prior medical or ocular history presented to the neuro-ophthalmology clinic with difficulty seeing in dim light for four weeks. Review of systems was notable for moderate alcohol intake and a diet consisting solely of meat and carbohydrates. Complete ophthalmic exam and OCT of the optic nerve and macula were normal. Electroretinogram revealed complete loss of rod response, and severely diminished cone response bilaterally. Vitamin A levels were severely depleted at 7 mcg/dL (normal 38-98 mcg/dL). Low Vitamin A levels were attributed to dietary deficiency, and oral repletion was initiated with rapid improvement in ERG response and normalization of Vitamin A levels over two weeks. One week later, the patient developed lower extremity swelling and abdominal distention, and was urgently referred to Gastroenterology. Evaluation revealed new onset liver decompensation with transaminitis, hyperbilirubinemia, and ascites secondary to chronic alcohol abuse.

Conclusions:
In the United States, dietary Vitamin A deficiency should be considered a diagnosis of exclusion, and a patient presenting with nyctalopia and ERG changes suggesting vitamin A deficiency should have a systemic evaluation looking for another etiology.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 32
Infantile presentation of Leber's hereditary optic neuropathy 'plus' disease.

Helena Zakrzewski[1], Walla Al-Hertani[2], Milad Modabber[3], Daniela Toffoli[4]

[1]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, Calgary, Canada, [2]Department of Medical Genetics, Alberta Children's Hospital, Calgary, Canada, [3]Department of Ophthalmology, McGill University, Montreal, Canada, [4]Department of Ophthalmology, Montreal Children's Hospital, Montreal, Canada

Introduction:
Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease most often leading to bilateral centroceccal scotoma secondary to preferential loss of papillomacular bundle nerve fibers. Clinical studies suggest that LHON may be a systemic disease ('plus' disease) occasionally associated with neurological, cardiac, and skeletal manifestations. Reports of infantile onset of LHON are rare and LHON 'plus' disease has yet to be described in infancy. We present the case of a 3 year old boy with infantile onset of LHON 'plus' disease.

Methods:
Case report and review of the literature.

Results:
A 3 year old right hand dominant boy presented to the emergency department with a 2 month history of chronic intermittent vomiting and ketosis. He had had a vague history of ataxia 3 months prior. MRI revealed multiple T2 and FLAIR hyperintensities of subthalmic nuclei, ventral aspect of the fourth ventricle, and upper medulla suggestive of a mitochondrial disease as well as caliber asymmetry of the optic nerves. Genetic workup revealed a 11778G>A homoplasmic mitochondrial mutation. Vision was 20/20 OD and hand motion OS. A left relative afferent pupillary defect was appreciated. The patient had a left sensory esotropia. Extraocular movements were full. Dilated fundus examination was unremarkable OD with pronounced optic nerve head pallor OS. Neurological examination revealed decreased tone and muscle bulk in both upper and lower extremities. Gait was normal. There was no evidence of cardiac or skeletal involvement. He was started on coenzyme Q10. Despite ongoing symptoms of decreased energy and fatigue the patient remained clinically stable for 2.5 years thereafter.

Conclusions:
To the best of our knowledge this is the first reported case of LHON 'plus' disease with infantile onset. Clinicians must be sure to consider the disease in the differential diagnosis of this population and to ensure the appropriate investigations of potentially associated systemic disease.

References: None.

Keywords: Genetic Disease, Optic neuropathy, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 33
Can occipital lesions produce pre-geniculate changes in humans?

Kimberly Gokoffski[1], Vivek Patel[1]

[1]*USC Roski Eye Institute, Los Angeles, California, USA*

Introduction:
Retrograde trans-synaptic degeneration (RTSD) has been well documented in animal studies: occipital lobectomies in adult primates leads to atrophy of not only the lateral geniculate nucleus, but also that of the optic nerves (ON). Clinical observations in humans, however, have varied in support of this concept. In one case, five decades after a cerebral vascular accident that resulted in a homonymous hemianiopia, the ON showed no evidence of atrophy. In contrast, a case series of patients with retro-geniculate lesions showed correlating ganglion cell layer (GCL) loss via spectral domain-optical coherence tomography (SD-OCT) in 68% of patients. Although this discrepancy may, in part, be explained by the availability of higher resolution imaging allowing characterization and quantification of neuronal loss in the anterior visual pathway that was previously missed, there may be other undetermined structural or functional changes in the posterior visual pathway that influence which injuries lead to RTSD.

Methods:
Here, we used conventional MRI, tractography, and fMRI imaging, combined with detailed psychophysical tasks to characterize the visual pathway changes in a patient with an occipital lobe infarct. In addition to advanced imaging studies, the patient underwent standard HVF testing and SD-OCT quantification of his GCL.

Results:
This is a case of a patient who presented with a macula-sparing homonymous hemianopia with corresponding GCL loss on SD-OCT. Initially thought to have a pre-geniculate lesion, the patient was found on imaging to have an old occipital lobe infarct, without apparent involvement of the pre-geniculate tissues on conventional MRI. Retrograde atrophy of his visual pathway was characterized with high resolution MRI and fMRI imaging.

Conclusions:
This case provides further evidence for RTSD along the visual pathway. Continual improvements in our ability to image the central visual pathways have the potential to lead to breakthroughs in our understanding of which lesions predispose a patient to RSTD.

References: 1. Miller NR, Newman SA. Transsynaptic degeneration. Arch Ophthalmol. 99, 1654, 1981. 2. Mitchell JR, Oliveira C, Tsiouris AJ, Dinkin MJ. Corresponding Ganglion Cell Atrophy in Patients With Postgeniculate Homonymous Visual Field Loss. J Neuro-Ophthalmol, 35, 353-359, 2015.

Keywords: Stroke Trauma, Neuroimaging, Visual fields, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 34
JC Virus: An Uncommon Infection More Common with Immunosuppression

Ehtesham Khalid[1], Acosta Lealani[1], Paul Moots[1]

[1]*Vanderbilt University Medical Center, Nashville, Tennessee, USA*

Introduction:
Resistant infections have become increasingly more widespread in modern medicine (e.g., HIV). Many patients are immunosuppressed due to either medical conditions or medications to suppress the immune system, making such infections more common in this population. This patient's clinical presentation is unique due to the combination of non-specific MRI changes and a telling history of symptoms, which fits well with diagnosis of progressive multifocal encephalopathy.

Methods:
A 70-year-old man with history of recurrent follicular non-Hodgkin's lymphoma of abdominal and thoracic lymph glands s/p idelalisib developed progressive visual disturbance for a couple of months. He noticed difficulty with depth perception, lane changing while driving, recognizing people other than family members at certain occasions and missing patches of grass while mowing the yard. His examination was significant for prosopagnosia, visual neglect, left homonymous hemianopia, simultanagnosia and diffuse hyper-reflexia. Contrasted MRI showed confluent abnormal T2 signals in subcortical white matter of right parietal, occipital, temporal, frontal and left occipito-temporal areas with faint enhancement. The initial brain MRI was read by radiology as consistent with posterior reversible encephalopathy, but this did not fit with his clinical course because he did not have significant hypertension and his symptoms developed over the period of couple of months. EEG showed focal slowing in right posterior quadrant. CSF analysis for a neoplastic process was normal after three lumbar punctures. Paraneoplastic panel was negative. John Cunningham (JC) virus testing in CSF was positive.

Results:
.

Conclusions:
JC virus is progressive subacute infection of oligodendroglia for which there is currently no treatment. With increased use of immunosuppression, JC virus is more widespread, so should be considered in the differential for an immunocompromised patient with a subacute decline.

References: None.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Higher Visual Cortical functions, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 35
Metastatic Hepatocellular Carcinoma Presenting as Left Homonymous Hemianopia

Hye Jin Lee[1], Soolienah Rhiu[2]

[1]Jeju National University School of Medicine, Jeju-si, Korea, Republic of, [2]Hallym University College of Medicine, Dongtan Sacred Heart Hospital, Hwaseong, Korea, Republic of

Introduction:
Metastasis of hepatocellular carcinoma (HCC) to the central nervous system is rare, although hepatoma is a relatively common malignant tumor in Korea. Much rarer is metastatic HCC presenting as homonymous hemianopia and there have been only 4 cases reported in the past. To the best of our knowledge, this is the first report of occipital lobe metastasis of HCC as homonymous hemianopia in South Korea.

Methods:
A 51-year-old female with a history of liver cirrhosis in the diagnosis of HCC 19 months earlier was referred to our neuro-ophthalmology clinic for evaluation due to headache and decreased visual acuity for the past several months. She underwent hepatectomy for HCC 2 years earlier. Best visual acuities were 20/20, and results of all other aspects of our examination were normal except Humphrey automatic perimetry, which showed complete left homonymous hemianopia.

Results:
Brain MRI showed a large mass in right occipital lobe. Craniotomy and removal of tumor was done. HCC was confirmed by histopathologic examination.

Conclusions:
Metastasis to occipital lobe of hepatocellular carcinoma is extremely rare but it can present as homonymous hemianopia therefore clinicians should be aware of this when examinating a patient with history of HCC.

References: Hsu SY, Chang FL, Sheu MM, Tsai RK. Homonymous hemianopia caused by solitary skull metastasis of hepatocellular carcinoma. J Neuroophthalmol. 2008 Mar;28(1):51-4

Keywords: Tumors, Visual fields, Neuroimaging, Perimetry

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 36

Bilateral Progressive Visual Loss Related to Toxic Leukoencephalopathy Due to Chronic Ingestion of Para-Dichlorobenzene (mothballs)

MHD Abdallah Mahrous[1], Lindsay Smith[1], Monica Ertel[1], Bryan Pham[1], Cristiano Oliveira[1], Marc Dinkin[1]

[1]*Weill Cornell Medicine, New York, New York, USA*

Introduction:
31 year-old female who presented to the Emergency Department reporting progressive bilateral painless vision loss over 3 weeks.

Methods:
Case report.

Results:
Patient's visual acuity was hand motion in both eyes, with no saccades to an optokinetic strip. She had normal eye movements and pupillary function. Her fundus exam was normal. The rest of her neurological exam was unremarkable. Her brain MRI imaging was suggestive of a toxic leukoencephalopathy. Her cerebrospinal fluid analysis was normal. The rest of her blood work was remarkable for a mild microcytic anemia. Upon further questioning, the patient admitted to ingestion of 4-5 mothballs daily for several years. Her urinary 2,5-Dichlorophenol, a Dichlorobenzene metabolite, level was elevated at 1600 mg/L (Normal <50 mg/L).

Conclusions:
Para-dichlorobenzene (p-DCB) is a chemical present in mothballs, urinal cakes, insecticide fumigants, and several chemical cleaning products.1 Chronic or acute exposure to inhaled or ingested p-DCB is associated with severe hematologic, pulmonary, hepatic, renal, and neurologic syndromes.2-4 Unlike a previous report of visual loss related to bilateral toxic optic neuropathy secondary to p-DCB inhalation5, the mechanism of visual dysfunction in the present case was confluent toxic leukoencephalopathy involving bilateral optic radiations. Therefore we present a unique case of cortical blindness due to p-DCB ingestion. Given the widespread use, affordability, and abuse potential of p-DCB-containing products, and the significant morbidity from overexposure, clinicians should consider p-DCB toxicity in patients presenting with leukoencephalopathy of unknown etiology.

References: 1. Rossberg, et. al. "Chlorinated Hydrocarbons". Ullmann's Encyclopedia of Industrial Chemistry, 2006. 2. Avila E, et. al. "Pica with paradichlorobenzene mothball ingestion associated with toxic leukoencephalopathy", J Neuroimaging, 16, 78-81, 2006. 3. Dubey D, Sharma VD, Pass SE, Sawhney A, Stüve O. "Para-dichlorobenzene toxicity – a review of potential neurotoxic manifestations", Therapeutic Advances in Neurological Disorders, 7(3):177-187, 2014. 4. Weidman E, Tsiouris A, Heier L. "Toxic encephalopathy due to paradichlorobenzene toxicity: a case report and review of imaging characteristics", Clin Imaging, Nov-Dec;39(6):1095-8, 2015. 5. Reygagne A, Garnier R, Chataigner D, Echenne B, Efthymiou ML. "Encephalopathy due to repeated voluntary inhalation of paradichlorobenzene", J Toxicol Clin Exp, 12(4-5), 247-50. 1992.

Keywords: Higher Visual Cortical functions, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 37
Lateral Geniculate Bodies: Partners In Crime

SMITA PRAVEEN[1], VEENA NORONHA[1]

[1]MEDICAL RESEARCH FOUNDATION, CHENNAI, India

Introduction:
This is a clinical and radiologic case report documenting an uncommon cause for bilateral vision loss.

Methods:
This is a retrospective chart review. A 13 year old boy presented with sudden painless loss of vision in both eyes since 10 days. There was no preceding fever, rash, trauma, drug intake. He had no systemic diseases. He was diagnosed as retrobulbar neuritis elsewhere and had received steroids as per the Optic Neuritis Treatment Trial study, with no improvement in vision.

Results:
His best corrected visual acuity was counting fingers close to face in both eyes. There was no afferent pupillary defect. Slit lamp examination of the anterior segment was unremarkable. Retinal examination revealed healthy optic discs. VEP showed normal P2 latencies with reduced amplitudes. MRI brain-orbit showed symmetrical T1 and T2 hyper-intense signal in bilateral lateral geniculate bodies (LGB) with bright signals on diffusion weighted images, suggestive of bilateral sub-acute hemorrhagic infarctions. A detailed vasculitis and coagulopathy work up was undertaken including complete hemogram, lipid profile, plasma homocysteine, C- reactive protein, RA, ANA, C-ANCA, P-ANCA, Antiphospholipid antibody, protein C and protein S. All results were within normal range except for neurtorphilic leukocytosis and elevated levels of Protein C.

Conclusions:
It remains unclear why the LGBs were involved in isolation. The postulated mechanisms are hemorrhagic infarction and osmotic demyelination. The infarcts could be due to the disruption of the blood brain barrier in the distribution of anterior and posterior choroidal arteries. It is interesting to note that only 8 cases of bilateral isolated LGB infarctions have been documented in literature so far and those have all been in female patients. Our patient is male and the youngest documented.

References: None.

Keywords: Higher visual functions, Neuroimaging, Vascular disorders

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Grant Support: None.

Poster 38
Is it Glaucoma?

Dr. Sarwat Rahman[1]

[1]*Bangladesh Eye Hospital Ltd, Dhaka, Bangladesh*

Introduction:
A 45 years lady referred by an ophthalmologist for suspicion of glaucoma because her visual field is abnormal.

Methods:
a 45 yrs old lady complaints gradual dimness of vision in left eye for last three yrs. she had on and off headache but no other symptom her past medical history is significant for hypertension, hyperglycemia. her family history is positive for a sister with glaucoma . on examination visual acuity in right eye 6/12 and left eye 6/60, IOP is 21 mm Hg in both eyes with pachymetry of 542 and 549 microns in right and left eye respectably . RAPD and decreased color vision present in left eye, gonioscopy revails open angle in each eye. optic nerve shows cup disc ratio of 0.2 in right eye and 0.5 in left eye with deffuse pallor.VFA shows tubular field. with these findings she was being treated with antiglucoma drugs for last 2 yrs.but the field,disc and vision dose not co-relate with each other.we did an MRI and it showed a large pituitary macroadenoma.

Results:
She was diagnosed as a case of pituitary macroadenoma and referred to Neurosurgeon and operated. —After surgery VAL CF5ft, and RE preserved same vision 6/12.

Conclusions:
—Everyday we face a lot of patient in our practice. A few of them need special attention . —This cases are potentially curable with appropriate treatment, but needs to be identified at an early stage because this conditions can sometimes be life threatening.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 39
Idiopathic Intracranial Hypertension in Addison´s Disease: A Case Report

Mirta Arana[1], Haydée Martínez[1], Macarena Clementi[1], Mariana de Virgiliis[2], Schiavo Elizabeth[1], Lidia Sarotto[1], Busquets Carolina[1], Rivamonti Marcelo[1], Nicolás Zago[1], Juan Antonelli[1]

[1]Hospital de Clínicas José de San Martín, Buenos Aires, Argentina, [2]Hospitla Oftalmológico Pedro Lagleyze, Buenos Aires, Argentina

Introduction:
Idiopathic intracranial hypertension presents with increased lumbar puncture opening presure, normal CSF, normal neuroimaging, and signs and symptoms of intracranial hypertension. Etiology is unknown, although more frequent between women with overweight, certain medications, pregnancy, systemic diseases and venous obstruction. Association with gluco and mineralocorticoids deficiency has been described. We present the case of a woman with Addison´s disease, headache and progressive visual loss.

Methods:
We conducted a 3 years follow up of a 28 years old caucasian woman with Addison´s disease and progressive visual loss. Controls included best corrected visual acuity, visual fields, OCT, neuroimaging, lumbar puncture and immuno-endrocrinology laboratory.

Results:
The initial visual acuity was 1/10 OD and 6/10 OS. MRI showed bilateral globe flattening and optic nerve sheaths dilation. The lumbar puncture informed a 35 cmH2O opening pressure. The laboratory was positive for TPO, 21-alpha-hydroxylase, rheumatoid factor, Immunoglobulin G, total proteins, ACTH, C-Reactive Protein, ANA, Complement C3, Factors VIII, V, and IX. Visual field presented bilateral superior altitudinal defect, and the OCT an abnormal RNFL. Therefore treatment begun with acetozolamide 250 mg b.i.d, fludrocortisone 0.2 mg/day, and idebenone 45 mg/day. Considering no improvement was achieved, derivation valve was implemented. Despite treatment headache and visual parameters fluctuated between controls. Pulse corticosteroid therapy with methylprednisolone 1 g/day for three days was initiated, continuing with 40 mg/day of mepredinsone. Current visual acuity is light perception OD and 7/10 OS, visual field with a constrictive and isolated central defect in the right eye, and a central remanent for the left. OCT confirms optic disc and macular compromise.

Conclusions:
Addison´s disease is a rare cause of idiopathic intracranial hypertension, therefore must be suspected to avoid long term sequels. The immunonologic and endocrinologic disfunction makes it a challenging presentation.

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Keywords: Pseudotumor Cerebri, High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 40

Castleman disease with follicular dendritic cell sarcoma presenting with pseudotumor cerebri and myasthenia gravis

Alexander Fein[1], Humberto Trejo Bittar[2], Ernest Scalzetti[1], Manisha Shende[2], Melissa Ko[1]

[1]SUNY Upstate Medical University, Syracuse, New York, USA, [2]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Introduction:
Castleman disease is a lymphoproliferative disorder that has previously been associated with pseudotumor cerebri (PTC) or myasthenia gravis (MG). This is a rare case of CD with follicular dendritic cell sarcoma (FDCS) presenting with PTC and subsequently MG.

Methods:
Case Summary

Results:
A 21-year-old woman presented with headache, blurred vision and pulsatile tinnitus in the setting of recent weight gain. On exam, she demonstrated VA: 20/20-1 OU, bilateral optic disc elevation, and noted blind spot enlargement OD. MRI brain was within normal limits. Lumbar puncture showed an elevated opening pressure of 38 cm of water with normal CSF composition and a diagnosis of pseudotumor cerebri was made. Acetazolamide was initiated along with a weight loss regimen. On follow-up, she had lost 18 lbs with resolved symptoms and papilledema. However, she reported new symptoms including facial asymmetry and fatigue with extended speech and reading. Due to worsening dysphagia and facial weakness, acetylcholine receptor antibodies were obtained and noted to be elevated. A diagnosis of myasthenia gravis was made, and pyridostigmine was initiated. A CT thorax with contrast was obtained revealing a posterior mediastinal mass. Upon resection, histology of the mass showed follicular dendritic cell sarcoma in the setting of hyaline vascular Castleman disease. The patient has been asymptomatic following treatment with IVIG, pyridostigmine and acetazolamide.

Conclusions:
To our knowledge, this is the first reported case of unicentric CD with FDCS presenting with PTC and MG. A potential unifying pathophysiology could involve the mass abutting the pulmonary artery leading to pulmonary hypertension and subsequent PTC. Another possibility could involve the elevation of interleukin-6, which has been previously described to contribute to lymphoproliferation associated with cases of CD and CD with MG. Elevated IL-6 levels in serum and CSF have been noted in PTC, which may be a linking factor to CD or an epiphenomenon.

References: Feigert JM, Sweet DL, Coleman M, Variakojis D, Wisch N, Schulman J, Markowitz MH. Multicentric angiofollicular lymph node hyperplasia with peripheral neuropathy, pseudotumor cerebri, IgA dysproteinemia, and thrombocytosis in women. A distinct syndrome. Ann Intern Med. 1990; 113(5):362-7 Ishikawa K, Kato T, Aragaki M, Ohbuchi T, Kimura S, Matsui Y, Kaji M. A case of Castleman's disease with myasthenia gravis. Ann Thorac Cardiovasc Surg. 2014;20 Suppl:585-8 Jakubíková M1, Piťha J, Latta J, Ehler E, Schutzner J. Myasthenia gravis, Castleman disease, pemphigus, and anti-phospholipid syndrome. Muscle Nerve. 2013 Mar;47(3):447-51. Westphal FL, Lima LC, Santana LC, Netto JC, Amaral VC, Silva Mdos S. Castleman's disease associated with follicular dendritic cell sarcoma and myasthenia gravis. J Braz Pneumol 2010; 36: 819-23. Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, Aozasa K, Nakahata T, Kawai H, Tagoh H, Komori T. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood. 2000 Jan 1;95(1):56-61.

Keywords: Pseudotumor Cerebri, Myasthenia, Tumors, Visual fields, High intracranial pressure/headache

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Poster 41

Recurrent Idiopathic Intracranial Hypertension in All-Trans Retinoic Acid and Arsenic-Treated Promyelocytic Leukemia

Gerard Hershewe[1], Alyssa Eckert[2], Micaela Koci[1], Josh Gratwohl[2], Jerad Hershewe[2]

[1]University of Nevada, Reno School of Medicine, Reno, Nevada, USA, [2]University of Nevada, Reno, Reno, Nevada, USA

Introduction:
Promyelocytic leukemia is often treated with a combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) per the recommendation of the National Comprehensive Cancer Network, and cases of IIH have been previously reported with this therapy. Our patient was on pulse therapy of ATO and ATRA. The patient became symptomatic with IIH primarily with ATRA. Symptoms improved with discontinuation of ATRA and treatment with acetazolamide.

Methods:
Case report

Results:
Sixteen year old right handed female with a history of promyelocytic leukemia diagnosed in 2015. The patient had been on pulse ATO and ATRA therapy for the past eighteen months. During the course of her therapy, the patient began having bifrontal cephalgia subjective bruit, horizontal diplopia, and transient visual obscurations. Concurrent with ATRA therapy, the patient developed intense headaches, transient visual obscurations, subjective bruit, and blurred vision, which abated following discontinuation of the drug. Best corrected visual acuity 20/20 OU. Normal color vision. Slit lamp examination normal. Motility examination showed a moderate non-comitant exotropia and moderate convergence insufficiency. Fundoscopic examination showed trace of papilledema OS.The Humphrey visual field 30-2 showed a severe temporal defect OD and was essentially normal OS. OCT showed borderline normal RNFL thickness 108 microns OD and 99 microns OS.Following ATRA monotherapy, the patient was reevaluated and was noted to have bilateral papilledema, bilateral blind spot enlargement, and an increase in the RNFL to 127 microns OD and 112 microns OS.

Conclusions:
IIH has been reported in patients taking a combination of ATRA and ATO in the treatment of acute promyelocytic leukemia. The patient's symptoms promptly diminished when ATRA was discontinued.ATRA is a vitamin A analog which increases CSF production and impedes absorption at the arachnoid villi. Increasing the acetazolamide dose prior to ATRA therapy can help to ameliorate recurrent IIH.

References: None.

Keywords: High intracranial pressure/headache, Pediatric neuro-ophthalmology, Pseudotumor Cerebri

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Grant Support: None.

Poster 42

Unilateral adduction deficit in idiopathic intracranial Hypertension from tortuous optic nerve sheath.

Susiani Intan[1], Heather Moss[2], Shilpa Gulati[3], Peter MacIntosh[1], Milena Stosic[4]

[1]University of Illinois at Chicago, Department of Ophthalmology and visual science, Chiago, Illinois, USA, [2]Stanford University School of Medicine, Department of Ophthalmology, Palo Alto, California, USA, [3]University of Illinois at Chicago, Department of Ophthalmology, Chicago, Illinois, USA, [4]Rush University Medical Center, Department of Neurology., Chicago, Illinois, USA

Introduction:

Idiopathic intracranial hypertension (IIH) is a syndrome of elevated intracranial pressure (ICP) without any identifiable brain pathology and with normal cerebrospinal fluid (CSF) composition. Diagnostic criteria allow only for involvement of the 2nd and 6th cranial nerves. Other focal neurological deficits exclude the diagnosis. Common orbital imaging findings include prominent subarachnoid space within the optic nerve (ON) sheaths with flattening of the posterior sclera at the ON insertions, and tortuosity of ONs. We present a case of IIH causing pseudo-INO due to mass effect of the expanded optic nerve sheath on the extraocular muscles.

Methods:

Review of clinical history, neuroimaging and relevant literature.

Results:

A 14-year- old female with BMI 29 presented with headache and decreased vision for 4 weeks and diplopia for 4 days. Medications included doxycycline. On exam she had impaired right eye adduction and abduction, impaired left eye abduction, mild proptosis worse on the right than the left and bilateral papilledema. MRI did not show midbrain lesion to cause INO. MRI orbits demonstrated a tortuous, expanded right optic nerve sheath with mass effect on the medial rectus as a mechanical cause of her impaired adduction. Lumbar puncture had opening pressure greater than 50 cm H2O. She was diagnosed with IIH causing bilateral sixth nerve palsies, papilledema, and mechanical right eye adduction deficit. The latter finding improved after lumbar puncture, which supports a mechanical etiology.

Conclusions:

Tortuous and expanded optic nerve sheaths occur as a consequence of elevated ICP. Though sixth nerve palsies and papilledema are the only focal neurological signs included in IIH diagnostic criteria, it is important to recognize the potential for expanded optic nerve sheaths to cause orbital signs that may be mistaken for focal neurological signs.

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Keywords: High intracranial pressure/headache, Neuroimaging, Ocular Motility, Orbit, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 43
Meningeal carcinomatosis mimicking pseudotumor cerebri

Hanqiu Jiang[1], Lei Yu[1], Lin Fu[1], Hongzhi Guan[2], Xiaojun Zhang[1], Jiawei Wang[1]

[1]Beijing Tongren Hospital, Captial Medical University, Beijing, China, [2]Peking Union Medical College Hospital, Beijing, China

Introduction:
Intermittent visual loss associated with papilledema is a common presentation of pseudotumor cerebri(PTC) or idiopathic intracranial hypertension(IIH). Some rare causes can mimic this condition.

Methods:
case report

Results:
A 64-year-old woman presented intermittent blurred vision for one month, which was progressive and worse when she bent her body forward. She also started to have episodes of loss of consciousness 20 days before she was admitted. Past medical history was significant for chronic hypertension. Her BMI was 17.5. Ophthalmic examination was normal except bilateral papilledema. BCVA was 20/20. No significant neurological findings otherwise. Comprehensive blood work was negative except elevated carcinoembryonic antigen (CEA) level (28.36ng/ml, normal range 0-5). Brain MRI with contrast only showed an empty sella, some non-specific white matter lesions. Lumbar puncture (LP) was done with opening pressure of 330mmH2O. Cell count and biochemistry panel were normal. CEA in CSF was significantly elevated (119.85 ng/ml).CSF cytological study only showed that elevated white count (1000 in 0.5ml CSF with normal range of <200), 20% were lymphocytes, and 80% were monocytes. The second LP was done and a few abnormal cells (tumor cell and heterocyte monocytes?) were found by HE stain. Lung CT revealed a mass lesion in left upper lung. Biopsy and surgical resection confirmed the diagnosis of invasive lung adenocarcinoma. Patient was treated with chemotherapy but died after nine months from her first blurred vision symptom.

Conclusions:
The warning sign of our case is her rapid progressive visual loss and episodes of loss of consciousness. A significantly increased CEA suggested malignancy, which prompted us for a repeat LP that found tumor cell. We conclude that comprehensive screening test is important especially when patient has some atypical clinical findings. Repeat LP is usually needed to find pathological cytological changes for diagnosis of meningeal carcinomatosis.

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Keywords: Pseudotumor Cerebri, High intracranial pressure/headache

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Grant Support: None.

Poster 44
A Case with a TWIST: Not so Benign Type 1 Dural Arteriovenous Fistula

Hang Pham[1], Sangeeta Khanna[1]

[1]Saint Louis University, Saint Louis, Missouri, USA,

Introduction:
Dural arteriovenous fistula (DAVF) is a vascular anomaly formed by a pathologic connection between dural arteries and venous sinuses (1). Type I DAVFs are considered benign lesions since they drain directly into the dural venous sinuses with antegrade flow. Types II and higher are categorized as aggressive. They are characterized by retrograde flow and reflux into cortical veins which increase the risk of intracranial hemorrhage (2,3). Previous case series have described symptoms of idiopathic intracranial hypertension (IIH) as the initial presentation for DAVF (4,5). Most patients in the case series had aggressive DAVFs. We present a patient with type I DAVF with visual impairment from intracranial hypertension.

Methods:
Case summary

Results:
A 30-year-old morbidly obese man presented with bilateral vision loss and headache. Examination revealed bilateral grade V hemorrhagic papilledema. Head CT was negative. Brain MRI and MRV were concerning for venous thrombosis of the right sigmoid sinus and internal jugular vein. However, a second review of the TWIST sequence indicated the additional presence of a DAVF. Cerebral angiogram demonstrated type I DAVF at the right sigmoid and transverse sinuses with antegrade flow and without cortical venous reflux. Additionally, a cerebral venogram confirmed the small, non-occlusive nature of the venous thrombus extending from the right transverse and sigmoid sinus junction to the right internal jugular vein. Venous blood flow was spontaneous with preserved antegrade flow around the venous thrombus. The patient underwent successful Onyx embolization of the DAVF with 90% occlusion. He was also placed on acetazolamide, topiramate, and anticoagulants.

Conclusions:
While Type I DAVFs prove to be benign for brain parenchyma in most circumstances, they may prove aggressive in inducing intracranial hypertension in a predisposed patient. Thus, benign DAVFs may behave aggressive.

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Keywords: High intracranial pressure/headache, Neuroimaging, Interventional neuroradiology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 45
Intracranial Hypotension or Intracranial Hypertension?: A Case Caught in Transition

Sara Reggie[1], Sangeeta Khanna[1]

[1]Saint Louis University Eye Institute, St. Louis, Missouri, USA

Introduction:
Spontaneous intracranial hypotension (SIH) has been known to occur with an underlying structural weakness of the spinal or skull base meninges and has been associated with a postural headache, neck pain, nausea, and vomiting (1). There is increasing evidence that idiopathic intracranial hypertension (IIH) may also cause spontaneous cerebral spinal fluid (CSF) leaks (classified as high-pressure leaks) and thus SIH that prevents overt manifestations of IIH unless the underlying CSF leak is treated (2,3). Accordingly, rebound intracranial hypertension has been shown to occur following treatment of intracranial hypotension, commonly with epidural blood patching (EBP) or surgical repair of the leak (2,4). We present a patient with MRI and clinical evidence of SIH spontaneously transitioning into IIH.

Methods:
Case Summary

Results:
A 24-year-old obese woman presented to our clinic for evaluation of IIH. Work-up had been initiated elsewhere for acute onset of severe headache, and the patient had bilateral papilledema. Head CT and brain MRV were negative; however, initial brain MRI had evidence of brain sagging, such as crowding at the foramen magnum, flattening of the pons, and obliteration of the suprasellar cistern, consistent with intracranial hypotension. Lumbar puncture had been deferred due to concern for cerebellar descent. Hypercoagulable work-up was negative, and the patient had been started on Diamox and Topamax for concern for IIH. The patient's headache responded to treatment, and repeat MRI 4 weeks later showed near interval resolution of signs of intracranial hypotension.

Conclusions:
Given this young obese patient's papilledema and somewhat counterintuitive imaging findings of SIH on initial MRI, we believe that this patient likely had undetected IIH which led to a spontaneous CSF leak, causing the patient to remain symptom-free for some time. This leak may have spontaneously sealed, leading to resolution of brain sagging and manifestations of IIH, such as papilledema and worsening headache.

References: 1. Yoon et al, Clinical experiences with spontaneous intracranial hypotension: a proposal of a diagnostic approach and treatment. Clin Neurology and Neurosurgery, 113, 373-379, 2011. 2. Perez et al, Primary spontaneous cerebrospinal fluid leaks and idiopathic intracranial hypertension. JNO December; 33(4):330-337, 2013. 3. Wang et al, Spontaneous CSF leaks. Otolaryngol Clin N Am 44, 845-856, 2011. 4. Kranz et al, Rebound intracranial hypertension: a complication of epidural blood patching for intracranial hypotension. AJNR Am J Neuroradiol, 35(60):1237-40, 2014.

Keywords: High intracranial pressure/headache, Neuroimaging, Pseudotumor Cerebri

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Poster 46
Bartonella Neuroretinitis Associated With Elevated Intracranial Pressure

Meagan Seay[1], Lisa Lystad[1], Mary Willis[1]

[1]*Cleveland Clinic, Cleveland, Ohio, USA*

Introduction:
Neuroretinitis is an inflammatory disorder consisting of optic neuropathy and a characteristic stellate macular exudate. We report a case of Bartonella henselae neuroretinitis with an unusual finding of elevated intracranial pressure (ICP).

Methods:
Case summary

Results:
A 36 year old, obese, female presented with right eye vision loss, pain with eye movement, and right sided headache. Her right eye visual acuity (VA) was 20/200 with a trace afferent pupillary defect, and constricted visual fields. There was grade 4 optic disc edema with venous dilation and tortuosity and a few flame-shaped hemorrhages. The left eye was normal. MRI of the orbits showed mild elevation of the right optic nerve head with a small focus of enhancement. Her MRI brain showed one nonenhancing right frontal periventricular white matter lesion linear and perpendicular to the ventricle. She was treated with corticosteroids for presumed optic neuritis. Over the next 10 days, she did not improve with steroids and underwent a lumbar puncture, which showed an elevated opening pressure of 28 cm H2O. Her CSF studies were unremarkable. She was treated with acetazolamide for concern for idiopathic intracranial hypertension. One month after presentation she was noted to have a stellate exudate in the right macula. Serum testing revealed elevated Bartonella henselae IgM and IgG titers confirming the diagnosis of neuroretinitis. She was treated with prednisone due to optic disc edema. Her vision improved in the right eye to 20/25 over the next eight weeks.

Conclusions:
A unique feature of this case was the presence of elevated ICP, which has been reported only once in Bartonella henselae neuroretinitis. Enhancement of the optic nerve head, as seen in this case, should raise suspicion for Bartonella henselae neuroretinitis.

References: None.

Keywords: High intracranial pressure/headache, Neuro-ophth & infectious disease (eg, AIDS, prion), Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 47

Transverse Sinus Dural Arteriovenous Fistula Producing Intracranial Hypertension and Choroidal Folds

Stacy Smith[1], Deborah Friedman[1]

[1]UT Southwestern Medical Center, Dallas, Texas, USA

Introduction:

Acquired hyperopia with choroidal folds may occur with intracranial hypertension, occasionally prior to onset of papilledema [1,2,3]. Most reports are in patients with idiopathic intracranial hypertension, with only rare reports due to secondary increased intracranial pressure (ICP) [3,4,5]. We present a case of acquired hyperopia followed by progressively worsening headaches due to secondary intracranial hypertension from a complex right transverse sinus dural arteriovenous fistula (DAVF) found to have choroidal folds and papilledema. Hyperopia and choroidal folds should be recognized as potential early features of increased ICP, and this case highlights the need for a thorough work-up for all possible etiologies.

Methods:

A 49-year-old man began requiring increasingly stronger reading glasses three years before his initial presentation. Two years later, he developed pressure-like headaches associated with nausea and vomiting. His vision declined more rapidly, with loss of peripheral field and distance acuity, as well as further decline in near acuity. Neurological evaluation revealed papilledema, and urgent imaging identified a right transverse sinus DAVF. Following embolization, his visual symptoms improved temporarily. However, due to fistula recurrence, he required two more embolizations. His headaches and vision symptoms persisted after intervention.

Results:

Neuro-Ophthalmology examination confirmed hyperopia and enlarged blind spots with bilateral papilledema and choroidal folds. Imaging showed significant posterior globe flattening, dilated optic nerve sheaths, a partially empty sella, and posterior and anterior circulation venous outflow anomalies. Lumbar puncture opening pressure was 27 cm H2O. His pressure-like headache and disc edema improved with acetazolamide therapy.

Conclusions:

Hyperopia may be the presenting symptom of increased ICP, and with choroidal folds, can indicate posterior globe flattening related to intracranial hypertension. This rare case illustrates the importance of performing a complete evaluation for secondary causes of increased ICP in patients with acquired hyperopia and choroidal folds.

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Keywords: High intracranial pressure/headache, Vascular disorders, Pseudotumor Cerebri, Orbit/ocular pathology

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Poster 48

Iatrogenic pseudotumor cerebri from treatment of metastatic mixed-spindle-cell endometrial sarcoma with leuprolide acetate

Harris Sultan[1], Cyrus Iqbal[2], Andrew Lee[3]

[1]University of Texas Medical Branch, Galveston, Texas, USA, [2]Baylor College of Medicine, Houston, Texas, USA, [3]Houston Methodist Hospital, The University of Texas Medical Branch, Houston, Texas, USA

Introduction:

Pseudotumor cerebri (PTC) is a syndrome characterized by symptoms of increased intracranial pressure including headache, photophobia, blurred vision, nausea, and vomiting. A gonadotropin releasing hormone (GnRH) agonist, leuprolide acetate which is typically used in the treatment of female sterility and prostate cancer, has been reported to be associated with PTC. We present the fifth report of PTC associated with leuprolide, discuss the potential mechanisms for increased ICP, and to our knowledge this is the first reported case of leuprolide associated PTC after treatment for gynecologic malignancy.

Methods:

A 28-year old thin African American female was diagnosed with mixed-spindle-cell endometrial sarcoma for which she was treated with resection followed by leuprolide hormonal therapy. One month after the initial treatment, the patient developed headaches and bilateral eye pain. Ophthalmic exam showed 20/20 vision, an enlarged blind spot on visual field testing, and papilledema OU. Cranial magnetic resonance imaging (MRI) with contrast was normal except for partially empty sella and increased fluid in the optic nerve sheaths and the patient was started on acetazolamide therapy. A lumbar puncture showed normal cerebrospinal fluid contents and a normal opening pressure (18 cm of water) but unfortunately was already on acetazolamide treatment. Leuprolide was discontinued and the patient had gradual resolution of optic disc edema and headache symptoms over the following 14 months.

Results:

N/A

Conclusions:

Leuprolide has previously been associated with PTC. The mechanism remains unknown but raises interesting questions about the role of hormones in the etiology of IIH and secondary PTC cases. To our knowledge, this is the first case describing the use of leuprolide associated with PTC when used as a chemotherapeutic agent. Clinicians treating such patients should be aware of the possible association especially in thin, elderly, or male patients who would represent an atypical demographic for IIH.

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Keywords: Pseudotumor Cerebri, Chemotherapy and radiation injury, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 49

Unilateral Papilledema in Idiopathic Intracranial Hypertension: A Report of Two Cases and Literature Review

Arun Sundaram[1], Pejman Maralani[2], Emily Swinkin[3]

[1]Department of Ophthalmology and Visual Sciences, University of Toronto, Toronto, Canada, [2]Department of Medical Imaging, University of Toronto, Toronto, Canada, [3]Division of Neurology, University of Toronto, Toronto, Canada

Introduction:

Idiopathic intracranial hypertension (IIH) typically presents with bilateral papilledema; however, highly asymmetric and rare unilateral cases have been reported. Several mechanisms behind this asymmetry have been postulated including differences in compliance of the lamina cribrosa, optic nerve sheath anatomy, and bony optic canal diameter.

Methods:

We report two cases of unilateral papilledema in IIH and review the literature on unilateral papilledema in IIH.

Results:

Two young female patients with obesity and recent additional weight gain endorsed headache, transient visual obscurations, and pulsatile tinnitus. Examination revealed preserved visual acuity and color vision, unilateral papilledema (Frisen grade 2 papilledema vs. normal in the fellow eye in both cases) associated with enlarged blind spot on 24-2 Humphrey visual fields, and increased average retinal nerve fiber layer (RNFL) thickness on optical coherence tomography (111 µm OD vs. 245 µm OS and 236 µm OD vs. 97 µm OS). Neuroimaging did not reveal any space-occupying lesions and cerebrospinal fluid (CSF) opening pressures were elevated consistent with IIH. CT of the orbits in case #1 with papilledema OS demonstrated asymmetry in optic canal area (17.3 mm2 vs. 20.0 mm2) with the right optic canal measuring 14% smaller than the left. Case #2 declined CT orbits. Both patients were treated with acetazolamide and had improvement in their symptoms and papilledema and normalization of average RNFL thickness.

Conclusions:

Unilateral papilledema is a rare manifestation of IIH; the mechanism behind its development is uncertain but we support that a smaller optic canal protects against papilledema by reducing transduction of CSF pressure from the suprasellar cistern to the perioptic subarachnoid space. This unique presentation responds well to treatment with acetazolamide.

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Keywords: High intracranial pressure/headache, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 50
A case of Vogt-Koyanagi-Harada

Florentina Berianu[1], Juan Maya

[1]*Mayo Clinic Jacksonville, Jacksonville, Florida, USA*

Introduction:
Vogt-Koyanagi-Harada syndrome (VKH) is often not recognized. The diagnosis of VKH is based upon the clinical presentation; there are no serologic tests or specific histological changes.

Methods:
A 37 year-old asian male presented with an episode of severe headache, fever and neck stiffness. CSF fluid was remarkable for mild protein elevation (48 mg/dl) and lymphocytosis (67 white cells; 98% lymphs). All infectious work up was negative. Shortly after the aseptic meningitis was diagnosed he developed right eye redness and blurry vision. His ophthalmologic evaluation was remarkable for iritis with vitreous cells and bilateral optic disk swelling compatible with the diagnosis of optic neuritis and panuveitis.

Results:
He had no joint inflammation, no mouth or genital ulcers, no rashes, and no spondyloarthritis features. He reported no toxic exposure. CXR and ACE levels were negative for sarcoidosis. Autoimmune rheumatologic work up was negative for ANA, ENA, RF, anti-CCP and ANCA vasculitis. PPD, RPR, HIV, Lyme and rest of infectious work up were negative. MRI brain and orbits were normal. He was also noted to have poliosis (loss of color from a patch of hair). He was diagnosed with VKH. Patient was initiated on high doses prednisone initially and reported significant improvement. He had been stable over the years on Mycophenolate mofetil 2.5 gram daily.

Conclusions:
Even though VKH is a rare entity, clinician should consider the diagnosis when constellations of clinical presentation are suggestive.

References: Diagnosis and classification of Vogt-Koyanagi-Harada disease. Sakata VM, da Silva FT, Hirata CE, de Carvalho JF, Yamamoto JH Autoimmun Rev. 2014 Apr;13(4-5):550-5. Vogt-Koyanagi-Harada syndrome. Greco A, Fusconi M, Gallo A, Turchetta R, Marinelli C, Macri GF, De Virgilio A, de Vincentiis M Autoimmun Rev. 2013 Sep;12(11):1033-8.

Keywords: Genetic Disease, Miscellaneous

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Grant Support: None.

Poster 51

DEFICIENCY OF ADENOSINE DEAMINASE 2: A RECENTLY DESCRIBED AUTOINFLAMMATORY DISEASE WITH NEURO-OPHTHALMIC MANIFESTATIONS

Sean Gratton[1], Aaron Noll[2], Elizabeth Kessler[2]

[1]University of Missouri--Kansas City School of Medicine, Kansas City, Missouri, USA, [2]Children's Mercy Hospital, Kansas City, Missouri, USA

Introduction:
Deficiency of Adenosine Deaminase Tye II (DAD2) is an autoinflammatory disease caused by mutations in the CECR1 gene yielding recurrent fever, livedo reticularis, neuro-ophthalmic and neurological symptoms. We analyzed published cases of DAD2 to provide broader characterization of the neurological manifestations of the disorder, and to assess for a relationship between CECR1 mutation location and neurological findings. We also report a 6-year-old boy who presented repeatedly over several years with a constellation of neuro-ophthlmic findings from DAD2.

Methods:
A literature search yielded 117 DAD2 cases, 90 had sufficient clinical details for analysis. Characteristics such as age, clinical symptoms, imaging findings, labs, and treatments were recorded. The relationship between CECR1 mutation location and neurological symptoms was analyzed. Statistical analysis including chi-square and logistic regression were performed in SAS.

Results:
91 cases were analyzed, 51 male. Median age at neurological symptom presentation was 3 years and ranged from one month to 42 years. Neurological symptoms were found in 59%(54), and categorized as ocular dysfunction(32), appendicular motor or sensory dysfunction(25), coordination disturbances(16), speech difficulty(12), altered mental status(12), headache(10), developmental delay(4), seizure(3), or other(15). MRI findings of an infarction, hemorrhage, or other abnormality were found in 52%(28), 19%(10), and 15%(8) respectively. Lacunar lesions were seen in 44%(24). Hypogammaglobulinemia, elevated inflammatory markers and abnormal immunological labs were most often associated with neurological symptoms but not statistically significant. Neurological symptoms or MRI infarction/hemorrhage were significantly associated with mutations between amino acids 154-204 (OR 3.6, CI 1.097-11.685).

Conclusions:
DAD2 involves a spectrum of neurological symptoms and MRI findings. Mutations at amino acids 154-204 of the CECR1 gene are more likely to cause neurological symptoms than mutations elsewhere inCECR1. A better understanding of these neurological manifestations will aid in earlier diagnosis, which can reduce morbidity, mortality, and unnecessary testing.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility, Vascular disorders

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Grant Support: None.

Poster 52
Homonymous Visual Field Deficit Selected Ischemic Stroke as The Etiology of Transient Amnesia.

Editha Johnson[1], Manas Upadhyaya[1], Swetha Vennavaram[1], Jorge Kattah[1]

[1]*University of Illinois College of Medicine at Peoria, Peoria, Illinois, USA*

Introduction:
Transient global amnesia (TGA), coined by Fisher and Adams over half a century ago, is an episodic, idiopathic neurological event with good prognosis that presents as a diagnostic challenge, particularly among patients with known stroke risk factors in the first hours after the onset of amnesia. Hypothesis surrounding TGA etiology includes acute ischemia involving the hippocampus – often presenting as discrete restricted DWI MRI hyperintensity - venous congestion, migraine, seizures, or strenuous activity. Published TGA MRI findings include uni or bilateral restricted diffusion in the hippocampus, which forms part of the Papez circuit. Accordingly, lesions in any location of this circuitry (anterior thalamus, fornices and hippocampus) have consistently showed anterograde amnesia, specifically for episodic memory, which is diagnostic of TGA.

Methods:
Case report and institutional review of our past TGA patients.

Results:
A 71-year-old male presented with acute onset of memory loss for two days. A complete neurological examination revealed homonymous superior quadrantanopia confirmed by Humphrey visual field testing. Brain MRI/MRA revealed acute ischemic event involving the bilateral anterior thalamus, lateral geniculate nucleus, temporal and occipital lobes. The unique combination of lesions was a result of a variation of the vascular territory supplied by the artery of Percheron. Two days following admission, there was improvement in his memory illustrating reversibility, demonstrating a TGA-like phenomenon. At six weeks, he performed average to above average on neuropsychological testing. On follow-up visit at four months, he scored 30/30 on MMSE.

Conclusions:
The preponderance of TGA in elderly patients with high ABCD2 scores has raised the question of transient ischemia as the etiology. Moreover, MRI abnormalities, when present, support this concept. The unique constellation of symptoms in our patient prompted imaging with MRI/MRA, revealing ischemic brain injury. The subsequent reversibility of his symptoms eloquently provides further support to a possible arterial related etiology for transient amnesia.

References: None.

Keywords: Vascular disorders, Visual fields

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Poster 53
Seronegative progressive encephalomyelitis with rigidity and myoclonus (PERM)

Ehtesham Khalid[1], Patrick Lavin[1], Dago Ordonez[1]

[1]*Vanderbilt University Medical Center, Nashville, Tennessee, USA*

Introduction:
Tactile startle is an uncommon manifestation that localizes to the brainstem. It occurs in pediatric epileptic patients predominantly, but can occur in adults with brainstem disease such as infection, inflammation, and neurodegeneration. Our patient presented with multiple cranial neuropathies and an exaggerated tactile startle response.

Methods:
A 75-year-old man with a remote history of carcinoid lung cancer, and renal cell carcinoma, presented with progressive dysphagia, dysarthria and alternating facial weakness for about 2 weeks. He noticed abnormal tongue sensation, and dysarthria. A video swallowing study demonstrated oropharyngeal dysphagia. He had progressive fatigue, left facial dysesthesia, and frequent brisk startle responses to facial stimulation. He had no fever or weight loss. He developed episodes of tachypnea with oxygen desaturation, episodes of tachycardia-bradycardia, then a cardiac arrest responding to cardiopulmonary resuscitation. Subsequently, he developed ophthalmoplegia, pyramidal extremity weakness, transient hyponatremia responding to fluid restriction, and then stiffness in his lower limbs. Contrasted brain MRI, LP with cytology and flow cytometry, paraneoplastic panel, and HIV testing were negative. Sedimentation rate 78, C-reactive protein 23.3, and serum protein electrophoresis detected monoclonal bands (IgG lambda type). PET scan demonstrated focal mediastinal lymph gland up take. Bronchoscopy with biopsy confirmed small cell lung carcinoma. He received IVIG and high-dose steroids with no response. He began chemotherapy with a plan for radiation of the abnormal mediastinal glands.

Results:
.

Conclusions:
The spectrum of paraneoplastic disorders, particularly affecting the nervous system, is expanding rapidly with the discovery of new antibodies. Because the sensitivity of paraneoplastic antibody testing is low (sensitivity 34%, specificity 86%) neurologists must be aware of, and be vigilant for, such syndromes that often require total body imaging to uncover the offending neoplasm.

References: None.

Keywords: Paraneoplastic syndromes, Tumors

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Poster 54
Down, out, and blown- not always from an aneurysm

Michelle Abou-Jaoude[1], Edward Escott[2], Padmaja Sudhakar[3]

[1]University of Kentucky, Department of Ophthalmology, Lexington, Kentucky, USA, [2]University of Kentucky, Department of Radiology, Lexington, Kentucky, USA, [3]University of Kentucky, Department of Neurology, Lexington, Kentucky, USA

Introduction:
Pupil involving third nerve palsy traditionally raises concern for intracranial aneurysms. We describe an unusual case of a pupil involving third nerve palsy caused by a sphenoid sinus mucocele which have an incidence of only 1%. They usually cause headache followed by visual disturbance, and cranial neuropathies may occur in 50%.

Methods:
Single case report and review of literature

Results:
A 44 year old female with no significant past medical history presented to the emergency department from an outside optometrist with a ten day history of headache, binocular diplopia and right eye ptosis. She had previously been evaluated several times for the headache at other emergency departments and given a diagnosis of migraine or sinusitis, and been treated with migraine cocktails and antibiotics. On development of ocular symptoms she was ultimately referred to our institution where she demonstrated a pupil involving partial third and partial sixth nerve palsies but with otherwise normal ophthalmic exam. Initial neuroimaging was negative for intracranial aneurysm, instead demonstrated an expansile lesion in the sphenoid sinus with bony erosion, with mild bulging into right cavernous sinus abutting the right internal carotid and pituitary gland, as well as extension into the superior orbital fissure and optic strut. The lesion was surgically removed endoscopically and found to be consistent with a sphenoid sinus mucocele. Cultures demonstrated staphylococcus epidermidis and she was placed on appropriate antibiotics. 1 month after surgical excision she demonstrated resolution of the sixth nerve palsy and improvement in her third nerve palsy and maintained normal visual functions . We believe that the mucocoele being contiguous with the internal carotid artery and the cavernous sinus caused the cranial neuropathies.

Conclusions:
This report highlights a rare and unusual case of sphenoid sinus mucocoele that mimicked aneurysmal third nerve palsy.

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Keywords: Ocular Motility, Neuroimaging

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Grant Support: None.

Poster 56
Gradenigo syndrome – maybe not

Ira Perszyk[1], Padmaja Sudhakar[2], Flavius Raslau[2]

[1]Department of Ophthalmology and Visual Sciences: University of Kentucky HealthCare, Lexington, Kentucky, USA, [2]University of Kentucky, Lexington, Kentucky, USA

Introduction:
Dural venous sinus thrombosis is a known but uncommon intracranial extradural complication of chronic suppurative otitis media. It is a life threatening condition, which occurs from spread of inflammation from the middle ear into the sigmoid sinus complex through hematogenous spread or directly through localized bone erosion. In this report, we describe a unique case of an adolescent boy with chronic otitis media who developed venous sinus thrombosis (VST) from mastoiditis. He presented with bilateral abducens palsy and papilledema that was initially mistaken as Gradenigo's syndrome.

Methods:
Single case report and review of literature

Results:
A 14-year Caucasian male presented with fever, myalgia, mild headache and vomiting for 1 month. His pediatrician noted hepatosplenomegaly and a lazy eye. Past medical history was significant for recurrent bilateral ear infections requiring tube placement. Initial physical exam revealed limited abduction OU with incomitant esotropia and bilateral papilledema. Contrast enhanced head MR revealed left mastoiditis with temporal bone involvement and venous sinus thrombosis affecting the left transverse and sigmoid sinus. Anticoagulation and antibiotic therapy were held till he underwent a mastoidectomy and was found to have extensive infection causing a Bezold abscess and cholesteatoma. He was mistakenly given a diagnosis of Gradenigo's syndrome until neurology and neuro-ophthalmology firmly established that he had bilateral sixth nerve palsy and papilledema from his otogenic venous sinus thrombosis. Subsequently with combination of anticoagulation and antibiotic therapy his papilledema and sixth nerve palsy improved . Venous sinus thrombosis improved on follow-up imaging.

Conclusions:
This case illustrates the need for stronger consensus in the management of pediatric patients with otogenic venous sinus thrombosis where there is no good evidence in the literature to support the order of treatment. The limited available data shows that conservative surgery(Mastoidectomy + decompression of bone covering the venous sinus) is most commonly performed and anticoagulation is safe.

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Keywords: High intracranial pressure/headache, Ocular Motility, Pediatric neuro-ophthalmology, Neuroimaging, Visual fields

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Poster 57
Spontaneous Tectal Glioma Regression in an Adult

Evan Schloss[1], Alexis Demopoulos[2]

[1]North Shore University Hospital, Manhasset, New York, USA, [2]The Brain Tumor Center, Center for Advanced Medicine, Lake Success, New York, USA

Introduction:
Tectal gliomas are rare adult brainstem gliomas, typically presenting with Sylvian aqueduct compression and resultant obstructive hydrocephalus. In children, these tumors occasionally regress spontaneously like optic pathway gliomas, usually during the first and second decades of life in the setting of Neurofibromatosis Type 1. We report spontaneous regression of an adult tectal glioma.

Methods:
Case report.

Results:
A 30 year old woman with migraine headaches presented six months after childbirth with dizziness and headache, but no nausea, vomiting, or visual symptoms. She reported no past neurologic symptoms or deficits. Neurological examination was normal and there was no papilledema. Contrast magnetic resonance imaging (MRI) revealed a solitary T1 hypointense, T2 hyperintense, nonenhancing mass lesion in the left tectum. After successful migraine management, serial imaging demonstrated stability of the presumed low grade glioma without tissue diagnosis. She remained asymptomatic with neither neurologic nor ocular symptoms. Nine years after diagnosis, routine MRI showed spontaneous regression.

Conclusions:
While optic pathway gliomas can regress in children and young adults (often with Neurofibromatosis type 1), we found only five reports of spontaneous adult tectal glioma regression. Patients were aged 20-40 and none had pathological diagnosis. Tectal tumors have variable prognoses; serial imaging and follow-up is necessary to evaluate for obstructive hydrocephalus or evidence of demyelination. Tectal gliomas are most often low grade and mirror the indolent behavior of their pediatric counterparts. As demonstrated with this woman, older adults can benefit from conservative management, especially when asymptomatic and diagnosed incidentally.

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Keywords: Tumors, Neuroimaging, Pediatric neuro-ophthalmology, High intracranial pressure/headache

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Poster 58

Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive To Steroids With Lung And Liver Involvement

Tarek Shazly[1], Islam Zaidan[2]

[1]University of Pittsburgh, Department of Ophthalmology, Pittsburgh, Pennsylvania, USA, [2]University of Pittsburgh department of Ophthalmology and department of Neurology, Pittsburgh, Pennsylvania, USA

Introduction:
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently recognized inflammatory central nervous system (CNS) disorder, prominently involving the brainstem. Pulmonary involvement but not hepatic involvement has been previously reported.

Methods:
A 55-years-old Caucasian male who presented in March 2016 with acute onset of binocular horizontal diplopia, dysarthria, ataxia, and occasional dizziness. He was found to have a right sixth nerve and dysarthria. MRI of his brain that showed extensive T2 hyperintensities in the deep white matter of both hemispheres, temporal lobes, brainstem and cerebellar hemispheres. The initial differential diagnosis of his MRI findings included demyelinating disease, neoplastic or infectious etiology. CSF analysis showed increased protein and glucose with negative infectious. CT of the chest, abdomen and pelvis showed multiple lung nodules with small low-attenuation lesions in the hepatic dome measuring up to 6 mm. He underwent a lung biopsy that initially showed intravascular lymphocytic infiltration raising suspicion of systemic histiocytosis. He was not treated with any steroids or other immunomodulatory with spontaneous disappearance of the diplopia, improvement of his speech and gait.

Results:
A few weeks later, a repeat MRI of his brain showed disappearance of most of the T2 and FLAIR hyperintensities in the deep white matter of both hemispheres and upper brainstem. His repeat CT of the chest, abdomen and pelvis showed regression of basilar lung nodules since with increasing ground-glass opacity nodularity throughout the periphery of both lungs with complete resolution of the hepatic lesions.

Conclusions:
CLIPPERS is a rare entity with predominantly CNS involvement with some extra-CNS involvement. This is the first case report of a hepatic lesions associated with CLIPPERS with complete resolution of the hepatic lesions following remission of CLIPPERS .

References: None.

Keywords: Demeylinating disease, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 59
Parry Romberg Syndrome Presenting Initially With Extensive Unilateral Hemorrhagic Brain Lesions

Tarek Shazly[1], Sara Otaibi[2]

[1]University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [2]Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA

Introduction:
Parry–Romberg syndrome (PRS) is a variant of morphea usually characterized by a slowly progressive course. Clinical and radiological involvement of the central nervous system may be observed in PRS.

Methods:
An 8 years-old-male presented initially in 2014 with 3 day history of severe headache and vomiting. This was followed by blurry vision and altered mentation. A Head CT was obtained and was concerning for inferior left frontal lobe edema and hemorrhages. MRI of the brain revealed strictly unilateral left sided multiple hemorrhagic lesions associated with T2 hyperintensities as well as contrast enhancement of left IC lesion with IVY sign (leptomeningeal enhancement and high signal on FLAIR). Spine MRI was negative. CSF was negative for oligoclonal bands, NMO, HSV, VZV, and HHV6.

Results:
He was treated with IV solumedrol with subsequent 4 month course of PO steroid wean. 3 Months later his headaches recurred while weaning steroids and was found to have a new left occipital lesion with T2 hyperintensity and enhancement on MRI. A repeat course of IV solumedrol was given followed by taper. Cerebral angiography was negative. A month later, a purplish rash was noted on the left upper lid as well as a linear left sided forehead rash. Over the upcoming few months he developed more prominent unilateral facial rash and more brain lesions with a resulting right homonomous hemianopsia.

Conclusions:
Parry–Romberg syndrome should be considered in cases of strictly unilateral multifocal hemorrhagic brain lesions.

References: None.

Keywords: Demeylinating disease, High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

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Poster 60
Bilateral Vision Loss Due to Sphenoidal Rhabdomyosarcoma

Swarup Swaminathan[1], Kara Cavuoto[1], Carla Osigian[1], Byron Lam[1], Joshua Pasol[1]

[1]Bascom Palmer Eye Institute, Miami, Florida, USA

Introduction:
Parameningeal sinus rhabdomyosarcoma has been reported at a rate of 16%, with most cases diagnosed between the ages of 5 and 7 years. These malignancies are often challenging to diagnose given their nonspecific signs and symptoms. If untreated, these neoplasms can rapidly progress to affect nearby structures, including the orbit. We hereby present a case of rapid bilateral visual loss, a rarely reported consequence of this aggressive malignancy.

Methods:
A 7-year old female was seen in our institution's ocular emergency room due to double vision accompanied by headache and nausea. She was noted to have a febrile sinus illness for which she was receiving oral antibiotics. CT imaging just 3 weeks prior was interpreted as unremarkable. The patient was found to have a visual acuity of 20/50 in both eyes. On motility exam, she had an esotropia measuring 30 prism diopters with complete abduction deficits of the right and left eyes, leading to a diagnosis of bilateral cranial nerve VI palsies. On fundus examination, her optic nerves were full but without pallor or edema. An orbital MRI showed a 5x3x2cm lesion within the sphenoid sinus extending into the nasal cavity, epidural space, and extraconal space of both orbits. The patient was emergently referred to the pediatric emergency room for neurosurgical evaluation. Transsphenoidal biopsy confirmed the diagnosis of embryonal rhabdomyosarcoma. She underwent chemotherapy with vincristine, dactinomycin, and cyclophosphamide, and subsequent radiation therapy. One month later in the ophthalmology clinic, she was noted to have no light perception in either eye with pale optic nerves.

Results:
.

Conclusions:
Rhabdomyosarcoma can be extremely aggressive with significant sequelae. Rapid diagnosis and treatment is essential to reducing morbidity and mortality; however even with appropriate treatment, severe vision loss can occur. This case highlights the importance of expedited neuro-imaging in children with persistent, new-onset headaches and/or abnormal extraocular motility.

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Keywords: Tumors, Chemotherapy and radiation injury, Optic neuropathy, Pediatric neuro-ophthalmology

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Grant Support: None.

Poster 61
Myelinated retinal nerve fibers of the optic nerve mimicking elevated ICP on MRI.

Michael Vaphiades[1]

[1]*University of Alabama at Birmingham, Birmingham, Alabama, USA*

Introduction:
Pseudotumor cerebri produces a constellation of MR imaging signs that can assist in establishing the diagnosis of elevated intracranial pressure (ICP). The presence of flattening of the posterior sclera is one of several subtle signs of elevated ICP on cranial MRI. Myelinated retinal nerve fibers usually appear continuous with the optic nerve head and in most patients is clinically asymptomatic. We present a case of a man with myelinated retinal nerve fibers OU whose MRI showed flattening of the posterior sclera mimicking a subtle MRI sign of elevated ICP.

Methods:
A 20-year-old man was referred to rule out papilledema prior to lumbar puncture based on an MRI showing a subtle sign of elevated ICP (ordered for headache). He takes no medications that would induce elevated ICP, has no pulsatile tinnitus and his headaches are typical for migraine. The MRI of the brain with and without contrast showed flattening of the posterior sclera, a subtle sign of elevated ICP. On exam his weight was 147 lbs. and height 6 feet. His afferent and efferent examinations were normal except for an enlarged blindspot OD on the automated visual field, and elevated myelinated retinal nerve fibers of both optic nerves.

Results:
This patient had no evidence of elevated ICP on history or examination. The optic nerves were elevated from the myelinated retinal nerve fibers giving the appearance of flattening of the posterior sclera on cranial MRI, mimicking one of the subtle MRI signs of elevated ICP.

Conclusions:
Myelinated retinal nerve fibers of the optic nerves may mimic flattening of the posterior sclera on MRI, a subtle sign of elevated ICP. It is important to obtain an ophthalmic examination before a lumbar puncture in patients with subtle signs of elevated ICP on MRI.

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Keywords: Neuroimaging, High intracranial pressure/headache, Pseudotumor Cerebri, Visual fields, Optic neuropathy

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Poster 62
A Rip on One Side Causes a Lopsided Eye

Mohamed Al-Ameri[1], Jorge Mendoza-Valencia[1], Jose Munoz[1], Rosa Tang[2], Jade Schiffman[3], Nagham Al-Zubidi[4]

[1]Neuro-Ophthalmology of Texas, PLLC, HOUSTON, Texas, USA, [2]Neuro-Ophthalmology of Texas, PLLC, Blanton Eye Clinic, UH college of Optometry, HOUSTON, Texas, USA, [3]Neuro-Ophthalmology of Texas, PLLC, UHC of Optometry, HOUSTON, Texas, USA, [4]Neuro-Ophthalmology of Texas, PLLC, Blanton Eye Clinic HMH, Houston, Texas, USA

Introduction:
Horner's syndrome due to a cervical rib is an extremely rare disorder. Horner's syndrome usually presents with clinical symptoms related to the anatomic location of the underlying disorder. Cervical rib may cause avulsion of the brachial plexus, consequently causing a preganglionic Horner's syndrome. While cervical rib is reported as a cause of Horner's syndrome in the literature, we found only few reported cases. We herein present 34 year-old WM with Horner's syndrome due to cervical rib. Review of current literature, diagnosis and management are discussed.

Methods:
This is a case report with a retrospective chart review. Literature search terms: Horner's syndrome, thoracic outlet syndrome, and cervical rib.

Results:
This is a 34 year- old WM with history of right arm deep vein thrombosis, pulmonary embolism and thoracic outlet syndrome with cervical rib present. Pt reported a chiropractor visit for severe back pain with no neck manipulation. Surgery with thrombolysis and cervical rib resection was complicated by blood loss and arterial hypotension. Following surgery pt noted new right ptosis. Neuro-Ophthalmic exam showed right Horner's with positive response to Apraclonidine. Patient reported subjective sweating decrease on right side of face. CTA head and neck showed right subclavian and supraclavicular scarring from prior surgery.

Conclusions:
Thoracic outlet syndrome is the compression of neurovascular structures traversing the superior aperture of the chest. It affects 8% of the population. In 95% of cases the brachial plexus is affected and in 2-5% is the vascular structures as in this case causing vein thrombosis. Cervical ribs are seen in 0.5% of population and about 10-20% produce symptoms of neural compression. Although Horner's syndrome is rare with this syndrome, the association should be considered in patients with cervical rib resection. Anatomical surgical description is discussed to explain Horner's. Early diagnosis can resolve the anxiety of considering an underling lie-threatening condition.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Pupils Retina, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuroimaging, Miscellaneous

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Poster 63

Homozygous A467T mutation in a patient with gastrointestinal symptoms, Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoplegia

Cesar Alfaro Cruz[1], Imran Jivraj[1], Madhura Tamhankar[1], Jacob Kaufman[2]

[1]The Scheie Eye Institute, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]The Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Introduction:
We report a patient with a homozygous A467T POLG mutation presenting with sensory ataxic neuropathy, dysarthria, and ophthalmoplegia (SANDO) and gastrointestinal symptoms.

Methods:
A 35-year-old male presented to his internist after noticing that he could not feel his feet while driving and had difficulties with balance. He endorsed “droopy eyelids” for years and recalls that others struggled to understand his speech. He did not see it as abnormal and did not seek care. His medical history included a cholecystectomy and multiple small bowel obstructions, which were initially attributed to possible adhesions from prior surgeries. Ophthalmic examination revealed bilateral ptosis and orbicularis weakness with frontalis overaction. Ocular ductions were limited in abduction and adduction in both eyes with slow horizontal and vertical saccades. Dilated fundus examination was normal. Neurologic examination revealed 4-/5 weakness of the extensor hallucis longus and extensor digitorum brevis bilaterally with absent temperature, pinprick, and vibration sensation at the toes and ankles bilaterally. Involuntary toe movements were apparent when he was unable to see his own feet, demonstrating sensory ataxia. He was areflexic aside from +1 brachioradialis jerks.

Results:
MRI of the brain and spine, EKG, and labs to exclude toxic substances and autoimmune conditions were all normal. Electromyography and nerve conduction studies were consistent with a sensorimotor axonal polyneuropathy. Genetic testing was positive for a homozygous A467T mutation in the POLG gene.

Conclusions:
POLG is a nuclear gene that encodes a subunit of DNA polymerase γ, the sole enzyme responsible for mitochondrial DNA repair and replication [2]. Mutations in POLG, PEO1, RRM2B, ANT1, and TYMP result in heterogeneous disorders along the chronic progressive external ophthalmoplegia spectrum [1]. Our patient has a unique combination of SANDO and mitochondrial neurogastrointestinal encephalopathy (MNGIE) symptoms. A high index of suspicion should be maintained for mitochondrial disorders when evaluating patients who present with multisystem involvement.

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2.Rajakulendran S, Pitceathly RDS, Taanman J-W, Costello H, Sweeney MG, Woodward CE, et al. (2016) A Clinical, Neuropathological and Genetic Study of Homozygous A467T POLG-Related Mitochondrial Disease. PLoS ONE 11(1): e0145500. doi:10.1371/journal.pone.0145500

Keywords: Genetic Disease, Ocular Motility

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Poster 64
Ophthalmic findings in a Hunter Syndrome patient on Idursulfase enzyme replacement therapy

Jarstad Allison[1], Austin Meeker[2], Melissa Ko[3]

[1]SUNY Upstate Medical University; Department of Ophthalmology, Syracuse, New York, USA, [2]Drexel University College of Medicine; Department of Internal Medicine, Philadelphia, Pennsylvania, USA, [3]SUNY Upstate Medical University; Departments of Neurology and Ophthalmology, Syracuse, New York, USA

Introduction:
Hunter Syndrome (mucopolysaccharidosis type II) is a rare x-linked recessive enzymatic deficiency characterized by deposition of glycosaminoglycans (GAGs) in a multitude of organs. In the eye, this deposition can lead to optic nerve edema, uveal effusion, epiretinal membrane, retinal degeneration, and visual field defects. Although enzyme replacement therapy (ERT) with idursulfase has led to improvements in morbidity and mortality, there has yet to be an investigation of the benefits of ERT on ophthalmic disease. The present case highlights the ophthalmic findings in a patient on ERT.

Methods:
A case study of a 39-year-old man followed for 4 years while on ERT for Hunter Syndrome was performed.

Results:
A 39-year-old man with Hunter Syndrome presented to neuro-ophthalmology after 4 years of ERT with a complaint of a progressive bilateral visual field defect. Physical examination was relevant for bilateral optic nerve head elevation, and a myelinated nerve fiber-like appearance OS. Visual field testing revealed bilateral ring scotomata. Electroretinography (ERG) showed bilateral ring-patterned signal loss. Optical coherence tomography (OCT) of the maculae demonstrated diffuse bilateral retinal thinning. Over the next three years, the patient's fundus exam, visual field, ERG and OCT remained stable while following at several outside institutions.

Conclusions:
The case presented demonstrates common ophthalmic findings in Hunter Syndrome: retinal degeneration, visual field defects, and optic nerve head elevation. The lack of improvement in this patient's ophthalmic disease despite ERT is attributable to the fact that idursulfase cannot cross the blood-brain-barrier. Presently, an investigation of the utility of intrathecal idursulfase on central nervous system disease in Hunter Syndrome is underway. A study of the ophthalmic response to intrathecal idursulfase would lead to a better understanding of the ophthalmic changes in Hunter Syndrome, and allow for a proper assessment of the potential vision improvement with ERT.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Genetic Disease, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields

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Poster 65
A Complex Arteriovenous Malformation Presenting with Bilateral Abducens Nerve Palsy

Laura Andrews[1], Vivian Rismondo[2]

[1]University of Maryland Medical Center, Baltimore, Maryland, USA, [2]Greater Baltimore Medical Center, Towson, Maryland, USA

Introduction:
Isolated bilateral abducens nerve palsy is uncommon and has a broad differential diagnosis. This includes infectious meningitis/encephalitis, intracranial hemorrhage, cerebrovascular accidents, elevated intracranial pressure secondary to neoplasm, inflammatory conditions, or pseudotumor cerebri, demyelinating disease, vasculitis, and other vasculopathies including aneurysm, carotid-cavernous fistula and arteriovenous malformations. (1) We present a case of a complex arteriovenous malformation causing isolated bilateral abducens nerve palsy.

Methods:
A 67-year-old male with a past medical history of hypertension and hyperlipidemia presented with two months of diplopia, bilateral conjunctival injection and bilateral pulse synchronous tinnitus. On exam he was esotropic with bilateral incomplete abducens nerve palsies. His comprehensive eye exam was otherwise unremarkable. Cerebral angiography demonstrated a complex skull base dural and intraosseous arteriovenous fistula with venous reflux into the cavernous sinuses and bilateral superior ophthalmic veins as well as bilateral inferior petrosal sinuses.

Results:
The patient underwent gamma knife treatment to three areas in the posterior fossa. Cerebral angiography showed improvement of shunting however there was additional venous reflux into the left temporal lobe. Trans-venous embolization of the lesion was unsuccessful given lack of patent connection to either cavernous sinus through the jugular veins. Fortunately, at one-year follow-up, the patient remains stable with near complete symptom resolution.

Conclusions:
The abducens nerve follows a long course as it exits the brainstem at the pontine-medullary junction, past the clivus, through Dorello's canal, over the petrous apex and through the cavernous sinus.(1)This allows for various modalities of nerve compromise. The most common etiology of bilateral palsy is indirect compression from elevated intracranial pressure secondary to trauma, vascular lesions, intracranial hemorrhage, or malignancy.(2,3) Arteriovenous malformation represents an uncommon etiology of isolated bilateral sixth nerve palsy, with few cases reported in the literature. The mechanism is likely related to nerve compression/stretching in the distended sinuses against the petro-clinoid ligament overlying Dorello's canal.(1,2,3,4,5)

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Keywords: Ocular Motility, Vascular disorders, Interventional neuroradiology

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Grant Support: None.

Poster 66
A Case of a Fatal Acute Disseminated Encephalomyelitis with Extensive Optic Pathways Involvement

Tatiana Bakaeva[1], Nicholas Barna[2], Janet Rucker[1], Matija Snuderl[2], Steven Galetta[1]

[1]NYU Langone Medical Center, Department of Neurology, New York, New York, USA, [2]NYU Langone Medical Center, Department of Pathology, New York, New York, USA

Introduction:
A 21 year old man presented with a 2 month history of worsening dizziness, blurred vision, unsteady gait, dysarthria and dysphagia after a flu-like illness.

Methods:
On examination, visual acuity was count fingers in both eyes with bilateral central scotomas. Pupils were sluggish without APDs. There was downbeat nystagmus in the primary position and downgaze, and direction changing horizontal end gaze nystagmus. On fundoscopy, the optic nerves appeared normal. The remainder of the exam was notable for hypophonia, dysarthria, mild appendicular and severe truncal ataxia and brisk reflexes.

Results:
MRI of the brain/orbits with gadolinium revealed diffuse supra- and infratentorial high signal abnormalities and abnormal signal in optic tracts, optic chiasm and prechiasmatic optic nerves with no contrast enhancement. Laboratory analysis of blood and CSF demonstrated non-specific elevation of inflammatory markers; testing for various metabolic abnormalities, autoimmune, paraneoplastic processes and infectious agents was unrevealing. The patient was empirically treated with intravenous steroids with gradual worsening of mental status, dysarthria and dysphagia. He was transferred to ICU for aspiration pneumonia and sepsis. IVIg was administered with no effect. His continued to decline clinically, and despite aggressive vasopressor and antibiotic support, on hospital day 22 he became asystolic and was pronounced dead.

Conclusions:
On autopsy, major gross findings included pulmonary congestion and brain with diffuse white matter lesions. Microscopic evaluation of white matter from cerebrum, cerebellum and spinal cord showed innumerable areas of demyelination with reactive gliosis and relative preservation of axons. Demyelination was predominantly perivenular without microhemorrhages or viral cytopathic change. Immunohistochemical stains demonstrated areas of demyelination filled with myelin digesting macrophages. These findings were consistent with acute disseminated encephalomyelitis (ADEM). There was no malignancy on autopsy, but unexpectedly, sections of testes demonstrated seminiferous tubules with diffuse multinucleated giant cells and nuclear inclusions, which are features of viral infection that may have triggered ADEM.

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Keywords: Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Neuro-ophth & infectious disease (eg, AIDS, prion)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 67
Unusual ocular manifestation of granulomatosis with polyangiitis

Stuart Ball[1], Padmaja Sudhakar[1], Flavius Raslau[1]

[1]*University of Kentucky, Lexington, Kentucky, USA*

Introduction:
Granulomatosis with polyangiitis (GPA) is a systemic disorder characterized by necrotizing vasculitis of small arteries and veins. The classic clinical triad includes upper and lower respiratory system involvement, systemic vasculitis, and necrotizing glomerulonephritis. Ocular involvement occurs in about 30-50% of GPA patients. The orbit is the most frequently involved. Like other autoimmune diseases GPA is associated with an increased risk of thrombosis, though there are less than a handful of patients reported with venous sinus thrombosis. Our patient demonstrated papilledema from venous sinus thrombosis which is an atypical ocular manifestation of GPA.

Methods:
Single case report and review of literature

Results:
A 16-year-old female with an 8-week history of multiple symptoms including loss of appetite, fatigue, diarrhea, oral and perianal lesions, and 30-pound weight loss presented to an outside emergency room after defecating on herself. Previously she was seen by multiple primary care doctors and given diagnoses of sinusitis, infectious mononucleosis, and Steven Johnson syndrome. She was transferred to our hospital when chest X-ray and CT chest showed right lung cavitary lesion. On exam she had severe oral ulcers, excoriated erythematous lesions on bilateral thighs, and 14x14 cm gluteal cleft wound involving the rectum. Lab work revealed leukocytosis, anemia, nephrotic range proteinuria and red blood cell casts. Ophthalmology exam revealed: VA 20/30-1 OU; bilateral conjunctival injection and bilateral severe disc edema concerning for papilledema. Contrast enhanced MRI brain and orbits and MR Venogram with contrast revealed partially occluding thrombus in the left transverse dural sinus, sigmoid sinus, and proximal internal jugular vein. The above clinical picture was concerning for Behcet's disease but unexpectedly her C-ANCA returned positive at 1:80 and subsequent renal biopsy revealed crescentic glomerulonephritis thus confirming GPA.

Conclusions:
This report highlights an unusual and rare presentation of papilledema as the primary ocular finding in systemic GPA.

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Keywords: Vascular disorders, High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 68
Susac syndrome: clinical characteristics, radiological features and treatment

Ruchika Batra[1], Alastair Denniston[2], John Horsburgh[2], Saiju Jacob[3], Susan Mollan[2]

[1]Birmingham Neuro-ophthalmology Unit, Birmingham, Great Britain, [2]University Hospitals Birmingham, Birmingham, Great Britain, [3]University Hospitals Birmingham and Institute of Immunology and Immunotherapy, Birmingham, Great Britain

Introduction:
Susac syndrome (SS) is a rare autoimmune disease characterised by the clinical triad of encephalopathy, sensorineural hearing loss and visual disturbance secondary to branch retinal artery occlusions (BRAOs).

Methods:
A case note review of all patients with a diagnosis of SS presenting to a university hospital within the last 15 years was undertaken. Clinical features at presentation and during the disease course, fluorescein angiography findings, radiological features, treatment and response to treatment are described.

Results:
Eight patients with a diagnosis of SS were identified, that is, seven females and one male (mean age 33.5, age range 21-46). Five patients presented with the complete clinical triad and one developed the full triad within 3 months of presentation. One patient did not develop ophthalmic involvement. The male patient presented with severe neurological symptoms only (without detected hearing and ophthalmic involvement) and died within weeks of presentation, prior to immunosuppressive treatment. The diagnosis of SS was made on post-mortem examination. Four patients had fundus fluorescein angiography and in all four this revealed evidence of bilateral multiple BRAOs. Seven patients had sensorineural hearing loss (five were bilateral and two unilateral). The seven female patients were treated at presentation with intravenous methylprednisolone followed by oral prednisolone plus a second immunosuppressant with good results. Intravenous immunoglobulin was used with success in three cases.

Conclusions:
The diagnosis of SS may be challenging as it is a rare condition and may mimic other neurological disorders. Furthermore, some patients do not present with the complete clinical triad, such as our male patient who was diagnosed on post-mortem, thus adding to the diagnostic uncertainty.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Pupils Retina

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Poster 69
An unusual cavernous mass

Shauna Berry[1], Ama Sadaka[1], Obadah Nakawah[2], Andrew Lee[1]

[1]Houston Methodist Hospital, Houston, Texas, USA, [2]Houston Methodist, Houston, Texas, USA

Introduction:
This is a case report of a 37 year-old female on chronic immunosuppressive therapy that developed a right cavernous sinus mass.

Methods:
This is a 37 year-old Hispanic female on chronic immunosuppressive therapy with methotrexate for rheumatoid arthritis that then developed right facial pain in the V1 and V2 distribution. Imaging study was performed which showed a lesion in the right cavernous sinus leading to a subsequent biopsy. The biopsy showed inflammatory cells and the patient was treated for inflammation. A year later, she developed a right sixth nerve palsy along with the persistent right facial pain. She then underwent extensive testing.

Results:
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Conclusions:
This patient on chronic immunosuppressive therapy was diagnosed with mucosal associated lymphoid tissue lymphoma with leptomeningeal dissemination.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility

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Poster 70
Characterization of Optic Neuropathy in Charcot-Marie-Tooth Disease

Benjamin Botsford[1], Laurel Vuong[1], Thomas Hedges, III[1], Carlos Mendoza-Santiesteban[1]

[1]Tufts Medical Center/New England Eye Center, Boston, Massachusetts, USA

Introduction:
Charcot-Marie-Tooth disease, also known as hereditary motor and sensory neuropathy (HMSN), is an inherited, progressive disease of the nerves resulting in weakness and numbness more pronounced in the legs than the arms. There are several sub-types of Charcot-Marie-Tooth disease based on myelin or axonal abnormalities and patterns of inheritance. Optic neuropathy has been described to some extent in some sub-types, including HMSN I and HMSN VI. To better characterize optic neuropathy in Charcot-Marie-Tooth disease, we evaluated retinal nerve fiber layer and ganglion cell layer complex thicknesses, visual evoked potentials and pattern electroretinograms in four patients.

Methods:
Two patients with HMSN I and two with HMSN VI were evaluated. All patients underwent a complete neuro-ophthalmic examination. Ancillary testing included, Humphrey visual fields, retinal nerve fiber layer and ganglion cell layer thickness measurements. Pattern visual evoked potentials and pattern electroretinogram were also obtained.

Results:
Our HMSN VI patients demonstrated functional abnormalities in addition to their structural abnormalities, as both patients showed impaired best corrected visual acuities as well as diminished P50-N95 amplitudes on pattern electroretinograms suggestive of retinal ganglion cell dysfunction. Additionally, one patient with HMSN VI demonstrated delayed pattern visual evoked potential latencies. Both patients with HMSN I had normal pattern electroretinograms, though one patient had delayed pattern visual evoked potnetionals in one eye consistent with previous reports of underlying delay in some patients due to the demyelinating nature of the disease

Conclusions:
Our findings indicate that in HMSN VI, there can be significant optic nerve damage, even though most patients have mild to moderate loss of visual function. The retinal nerve fiber layer and ganglion cell layer complex findings closely resembles that seen in other mitochondrial optic neuropathy and corresponds with the recent discovery of underlying mitochondrial dysfunction that results in the other neurologic manifestations in patients with Charcot-Marie-Tooth disease.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 71
Episodic Unilateral Mydriasis – Malignancy Or Lyme Induced?

Mayur Chalia[1], William Cantore[1]

[1]*Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA*

Introduction:
To describe an unusual presentation of episodic anisocoria with leptomeningeal metastatic colorectal cancer presumed to be neuroborreliosis.

Methods:
A 20-year-old Caucasian male with known history of signet ring cell colorectal cancer status-post resection and chemotherapy four years prior presented to OSH with one month history of headache, fever, nuchal rigidity, photophobia and horizontal diplopia concerning for aseptic meningitis with bilateral 6th nerve palsy. Serum and CSF evaluation was negative except for positive Lyme antibodies. Brain MRI showed mild meningeal enhancement. He was treated for Lyme meningitis with IV antibiotics but showed no improvement after two weeks. After transfer to our center for further management, patient had an event in which right pupil measured 5mm diameter reactive to neither light nor accommodation, left pupil measured 4mm with brisk reaction to light and accommodation. There was no afferent pupillary defect by reverse testing. Re-examination performed within 10 minute of the initial examination showed briskly reactive bilateral pupils to light and accommodation with neither efferent nor afferent defects. On the following day, again the same episodic of right pupillary involvement was observed. Repeat work up with MRI Brain/Spine revealed multiple enhancing lesions, lumbar puncture showed an opening pressure > 55 cmH20, atypical tumor cells positive for AE1/AE3 and CK20 (consistent with colorectal adenocarcinoma), and elevated carcinoembryonic antigen level concerning for leptomeningeal carcinomatosis. Intraventricular chemotherapy with methotrexate and gemcitabine through an Ommaya reservoir was initiated with subsequent improvement of symptoms.

Results:
Case Report

Conclusions:
In northeast USA, Lyme antibodies can be positive from routine exposure to ticks. For this reason, other etiologies of meningitis should be explored despite positive Lyme antibodies, particularly when there is poor response to treatment and a concern for an elevated intracranial pressure. Transient anisocoria is one of the life threatening neurophthalmological emergencies due to brainstem involvement compressing the third cranial nerve.

References: None.

Keywords: High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 72
Isolated Third Nerve Palsy as a Presenting Sign of Multiple Sclerosis

Sona Chaudhry[1], Christina Scelfo[1], Clotilde Hainline[1], Crandall Peeler[1]

[1]Department of Ophthalmology, Boston Medical Center, Boston, Massachusetts, USA

Introduction:
Common ocular manifestations of multiple sclerosis (MS) include optic neuritis, internuclear ophthalmoplegia, and nystagmus. Isolated cranial nerve palsies in the setting of MS are much less common, with third nerve (CNIII) palsies occurring least often. We report two cases of CNIII palsy as a presenting sign of MS.

Methods:
Case series.

Results:
A 24-year-old male presented with a ten day history of binocular diplopia and ptosis of the left eye. Extraocular motility testing demonstrated supraduction, infraduction, and adduction deficits on the left consistent with CNIII palsy. Pupils, afferent visual function, and dilated ophthalmoscopy were normal. Another patient, a 40-year-old female, presented with a four day history of binocular diplopia and ptosis of the right eye. Motility testing showed a supraduction deficit on the right consistent with a partial CNIII palsy. Visual acuity was 20/20 OD, 20/30 OS with an afferent pupillary defect and moderate optic nerve pallor on the left, presumably resulting from previous subclinical optic neuritis. In both cases, MRI of the brain and orbits with gadolinium demonstrated enhancement of the ipsilateral cerebral peduncle in addition to multiple non-enhancing lesions elsewhere in the CNS. Both patients were ultimately diagnosed with MS.

Conclusions:
CNIII palsy is estimated to occur in only 0.07% of MS patients over the course of their disease(1). Among all patients presenting with an isolated CNIII palsy, MS is determined to be the cause in 1.7% of cases(2). Although rare, this case series (and the few available case reports in the literature) demonstrate the importance of considering MS in the differential diagnosis of an isolated CNIII palsy and distinguishing this from other efferent manifestations such as internuclear ophthalmoplegia(2-5).

References: (1)Thömke F, Lensch E, Ringel K, Hopf HC. Isolated cranial nerve palsies in multiple sclerosis. J Neurol Neurosurg Psychiatr. 1997;63(5):682-5. (2) Bhatti MT, Schmalfuss IM, Williams LS, Quisling RG. Peripheral third cranial nerve enhancement in multiple sclerosis. AJNR Am J Neuroradiol. 2003;24(7):1390-5. (3) Beleza P, Machado A, Soares-fernandes J, et al. Isolated oculomotor nerve paresis as the presenting sign of multiple sclerosis. Arq Neuropsiquiatr. 2008;66(2A):254-5. (4) Newman NJ, Lessell S. Isolated pupil-sparing third-nerve palsy as the presenting sign of multiple sclerosis. Arch Neurol. 1990;47(7):817-8. (5) Uitti RJ, Rajput AH. Multiple sclerosis presenting as isolated oculomotor nerve palsy. Can J Neurol Sci. 1986;13(3):270-2.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Demeylinating disease

Financial Disclosures: The authors had no disclosures.

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Poster 73
Systemic Lupus Erythematosus Presenting as Monocular Elevation Deficiency

Seung Ah Chung[1]

[1]*Department of Ophthalmology, Ajou University School of Medicine, Suwon, Korea, Republic of*

Introduction:
To report a case of monocular elevation deficiency as the presenting manifestation of systemic lupus erythematosus (SLE).

Methods:
A 23-year-old, otherwise healthy female presented with a 3-day history of vertical diplopia and headache. She had a left hypotropia, which worsened in adduction and supra-duction and a profound inferior oblique underaction (-3). Magnetic resonance imaging showed an enhancement around the left superior oblique muscle and multiple infarctions in the left midbrain. On repetitive serological tests, anemia, lymphopenia, and anti-phospholipid antibody were positive. A presumptive diagnosis was a myositis of left superior oblique muscle and hyper-coagulation related with anti-phospholipid antibody. Two months after high-dose steroid treatment, the vertical diplopia was resolved. Five months later, the left hypotropia recurred as a more severe form with the inability to elevate the left eye in all directions. In addition, the infarction associated with vasculitis recurred in the left midbrain. As the treatment with high-dose steroid failed to relieve her ocular symptoms, recession of the left inferior rectus was performed 8 months later. One month after the surgery, she developed multiple lesions of erythematous nodosa with tenderness.

Results:
Skin biopsy of the lesion in the fingers showed the histological findings consistent with lupus.

Conclusions:
Eye movement abnormality can be an initial manifestation of SLE, which should be considered as a differential diagnosis especially in young female patients.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility

Financial Disclosures: The authors had no disclosures.

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Poster 74

Intractable "Idiopathic Intracranial Hypertension" as the clinical presentation for Bardet-Biedl Syndrome

Catalina Cleves-Bayon[1], Ellen Mitchell[2], Hannah Scanga[2]

[1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA, [2]UPMC Eye Center, Eye and Ear Institute, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Introduction:

Bardet Biedl syndrome (BBS) is ciliopathy characterized by rod-cone dystrophy, polydactyly, obesity, genital/renal anomalies and cognitive impairment, resulting from dysfunctional cilia. Obesity is frequently found in these patients and as in the general population, can lead to intracranial hypertension and papilledema. Recognizing symptoms of retinal dystrophy vs. those from papilledema and IIH allows the clinician to promptly diagnose the condition, institute surveillance for comorbidities and provide patients with adequate visual resources

Methods:

Case summary

Results:

14 y/o obese boy with cognitive impairment referred for consideration refractory IIH surgical treatment. Diagnosed 8 years prior, on Acetazolamide intermittently due to enuresis. Patient reported headaches, loss of peripheral vision and depth perception, difficulty navigating familiar areas in dim light and color vision deterioration. Dilated examination showed retinal pigmentary changes consistent with retinal dystrophy in addition to chronic papilledema. ERG confirmed retinal dystrophy. Further questioning revealed polydactyly and hypogonadism. Genetic testing for BBS was positive. Visual rehabilitation services and multidisciplinary care were instituted to address potential comorbidities. Headaches and papilledema are medically managed with weight loss and acetazolamide which he has tolerated

Conclusions:

Obesity is a common IIH risk factor and may be part of a wide array of multisystem disorders, including ciliopathies. Intracranial findings of IIH may be related to the dysfunctional cilium as surface cilia of ependymal cells play a role in CSF movement. Furthermore, animal studies demonstrate that BBS gene mutations disrupting ciliary structure hinder the beat frequency of ependymal motile cilia and CSF flow. The ubiquity of cilia and the systemic consequences of defective cilia may result in a complex phenotype including obesity, increasing the risk for IIH papilledema. In this case, distinguishing progressive visual loss as a result of a primary retinal process rather than chronic papilledema, allowed correct identification of BBS, institution of multidisciplinary treatment and prevented unnecessary shunting

References: Sawamoto K et al. Science 2006;311:629-32 / Marshal WF, Nonaka S. Curr Biol 2006;16:R604-14 Carter CS et al. Nat Med 2012;18:1797-804

Keywords: Pupils Retina, Pseudotumor Cerebri, Pediatric neuro-ophthalmology, Genetic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 75
Trochlear nerve palsy in Multiple Sclerosis

Sneh Dhannawat[1]

[1]*Metropolitan Hospital Center, New York, New York, USA*

Introduction:
Symptomatic involvement of trochlear nerve by multiple sclerosis is rare. The relative short intracranial course of the nerve is exposed to little myelin which is the reason for this rare association.

Methods:
An 18 years old male with no pertinent past history admitted with vertical diplopia on attempting gaze to the right. Ocular exam showed right superior oblique palsy. Posterior segment examination showed normal optic discs and vessels. On further work up MRI brain showed demyelinating lesions at periventricular white matter consistent with multiple sclerosis. CSF cell count, protein and glucose and cell count were normal. He was treated with intravenous steroids for 5 days. Diplopia improved at the end of treatment.

Results:
Multiple sclerosis can present with isolated trochlear nerve palsy.

Conclusions:
Though rare, isolated trochlear nerve palsy can be presenting feature of MS. Treatment with intravenous steroids leads to resolution of the symptoms.

References: Jacobson DM, Moster ML, Eggenberger ER, Galetta SL, Liu GT. Isolated trochlear nerve palsy in patients with multiple sclerosis. Neurology. 1999 Sep 11;53(4):877-9. PubMed PMID: 10489061

Keywords: Demeylinating disease

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Grant Support: None.

Poster 76
Neuromyelitis optica associated with atypical pigmentary retinopathy

Abdenour Djellaoui[1], Elias Attal[1]

[1]Ait Idir Hospital of Neurology, Algiers, Algeria

Introduction:
Neuromyelitis optica (NMO) and NMO spetrum disorder (NMOSD) is a severe demyelinating disease of the central nervous system. The manifestations of the brainstem can be inaugural and make erroneous the diagnosis. The association with other ophthalmological pathologies is exceptional.

Methods:
We report the case of an 18-year-old patient who presented severe and recurrent bilateral retrobulbar optic neuritis, concomitant transverse myelitis and brainstem signs like incoercible vomiting with persistent hiccups and recurring balance disorders for 8 years. In total, there were five outbreaks.

Results:
The MRI displayed a T2 and FLAIR hyperintense lesion with edema located in chiasma and optic bands and longitudinally extensive spinal cord lesion with involvment of the area postrema. Repetitive MRI shows atrophy of the optic pathways and spinal cord "syringomyelia-like" lesions.The ophtalmological assessment reveals a bilateral afferent pupillary defect. Visual acuities were counting fingers in both eyes. Fundoscopy demonstrated an arteriolar attenuation and bilateral optic atrophy without excavation and without osteoblasts. OCT showed a significant thinning of the RNFL with discrete pigment blade. ERG shown an Increase in latency and decrease in amplitude of the waves "a" and "b".The patient's brother presents a similar symptomatology with notably an optical atrophy.In the light of these data, the diagnosis of atypical pigmentary retinopathy with secondary atrophy was retained. Genetic study is underway.

Conclusions:
In view of the optico-spinal and brainstem damage in the foreground, recurrent development and MRI lesion characteristics, the diagnosis of multiphasic seronegative NMO was established and treatment with azathioprine and prednisolone. The evolution was marked by the reduction of the number of relapses. This observation highlights the flexibility of the currently accepted diagnostic criteria of the NMO and the usefulness of an early diagnosis essential to the therapeutic initiation.The association of NMO and a pigmentary retinopathy has not been described to the best of our knowledge.

References: None.

Keywords: Demeylinating disease, Pediatric neuro-ophthalmology, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Genetic Disease

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Poster 77
40kD (CAR) Retinal Autoantibodies in Autoimmune Syphilitic Neuroretinitis

Ryan Gise[1], Thomas Slamovits[2], Donald Hood[3], Charles Thirkill[4], Joyce Mbekeani[5]

[1]Department of Ophthalmology, Montefiore Medical Center and Albert Einstein COM, Bronx, New York, USA, [2]Albert Einstein College of Medicine, Bronx, New York, USA, [3]Columbia University Medical Center, New York, New York, USA, [4]University of California - Davis, Sacremento, California, USA, [5]Dept of Surgery, Jacobi Medical Center, Dept of Ophthalmology, Albert Einstein COM, Bronx, New York, USA

Introduction:
Antiretinal antibodies can occur in the setting of paraneoplastic visual loss. Autoimmune retinopathy has also been reported in the absence of cancer, at times in association with infections such as onchocerciasis, toxoplasmosis and coronavirus. We present a case of an HIV-positive man with syphilis-related neuroretinitis associated with presence of the CAR (cancer-associated retinopathy) 40kD autoantibodies.

Methods:
A 52 year old man with HIV (CD4=417, viral load=5750), on HAART therapy, presented with episodic painless vision loss and was diagnosed with mild posterior uveitis. He initially responded to topical steroids but later developed constant nyctalopia, photophobia, photopsia and dim central vision. Examination revealed visual acuities of 20/30 OD and 20/40 OS (declining to 20/70 OD and 20/100 OS over one month). Ishihara color vision was absent OU. Anterior segments were normal and ophthalmoscopy revealed mild optic nerve swelling and vitreous cells. Humphrey visual fields revealed enlarged blind spots and central defects. OCT (SD) showed disruption of sub-foveal ellipsoid bands while multi-focal ERGs showed attenuated central waveforms. The workup included testing for possible paraneoplastic retinopathy and led to the finding of 40kD anti-retinal antibodies. Subsequent systemic work up for cancer was negative. Further testing revealed positive VDRL and FTA-ABS and the patient was treated with a course of IV penicillin.

Results:
Following treatment of syphilis there was resolution of entoptic phenomena and visual acuity recovery to 20/15 OD and 20/20 OS. The disc edema resolved, visual fields improved and OCT and electrophysiologic test results normalized. Post-treatment retinal autoantibodies became undetectable.

Conclusions:
In the absence of an underlying malignancy, the finding of retinal autoantibodies in the setting of active syphilis may be coincidental, however, their simultaneous presence and then clinical and laboratory test improvement after antibiotic therapy strongly suggests syphilis-related immune dysregulation. We are not aware of any reports of syphilitic neuroretinitis associated with 40kD anti-retinal antibodies.

References: Hooks JJ, Tso MO, Detrick B. Retinopathies associated with antiretinal antibodies. Clin Diagn Lab Immunol 2001;8(5):853-8. Grange L, Dalal L, Nussenblatt RB, Sen HN. Autoimmune retinopathy. Am J Ophthalmol 2014;157(2):266-72. Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management. Surv Ophthalmol 2013:58(5):430-58. Davis, Janet, Ocular Syphilis. Curr Opin Ophthalmol 2014; 25: 513-518. Kiss, Szilard et al. Ocular manifestations and treatment of syphilis. Seminars in Ophthalmology 2005; 20: 161-167. Parc CE, Azan E, Bonnel S et al. Cone dysfunction as a paraneoplastic syndrome associated with retinal antigens approximating 40kD. Ophthalmic Genet 2006;27(2):57-61. Espander, Ladan et al. Successful treatment of cancer associated retinopathy with alemtuzumab. J Neurooncol (2007) 83: 295-302.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Paraneoplastic syndromes, Pupils Retina

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Poster 78

Susac Syndrome: Clinical Presentation and Therapeutic Management, Concerning Two Cases Reports

BELÉN GRAGERA SOROA[1], MÓNICA HIJÓS GASTÓN[1], IULIA PANA[1], SIMÓN QUIJADA ANGELI[2], MARTA SÁNCHEZ DEHESA-SAEZ[3], DIEGO URQUÍA PÉREZ[3], JAVIER ITURRIA SOLER[3], VANESSA GERENA ARÉVALO[3]

[1]HOSPITAL PUERTA DE HIERRO MAJADAHONDA MADRID, MADRID, Spain, [2]HOSPITAL UNIVERSITARIO FUNDACIÓN JIMÉNEZ DÍAZ, MADRID, Spain, [3]HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA, MADRID, Spain

Introduction:

Purpose: to present two different clinical cases of Susac Syndrome with different clinical presentation and therapeutic management.

Methods:

Two different clinical cases of Susac Syndrome. The first case, a female 53 year old, with Susac Syndrome diagnosis since 2010 who presents the complete clinical triad (hearing loss, vertigo and tinnitus right ear affection; retinal microangiopathy both eyes in different moments and headache, mental confusion and memory loss with MRI typical findings). The second case, a female 38 years old, begins with unilateral branch retinal arterial occlusion, headaches and tinnitus since 2008, with bilateral sensorineural hearing loss since 2012 and MRI small white matter pericallosum lesions.

Results:

Each case had a different clinical presentation and evolution, as they also had different therapeutic management. In the first case was treated with gamma globulin intravenous (IVGG) and prednisone 5mg/Kg. The second case only has been treated with Magnesium and oral steroids for the acute episodes. Both of them had a good response to each treatment and remain clinically stable.

Conclusions:

Although Susac Syndrome is a weird illness, with around 200 cases described all over the world, the clinical debut and manifestation could vary leading us to a more difficult diagnosis. There are incomplete forms and there is not an international clinical guide to treat these cases as there in not enough caseload to make clinical randomized trials. We also pretended to show different therapeutic managements with good response in both cases as an example to show how individual can be the treatment approach.

References: None.

Keywords: Vascular disorders, Neuroimaging, Visual fields, Vestibular

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 79
The Importance of Complementary Test in Horner Syndrome: a Case Report.

BELÉN GRAGERA SOROA[1], MÓNICA HIJÓS GASTÓN[1], SIMÓN QUIJADA ANGELI[2], IULIA PANA[1], MARTA SÁNCHEZ DEHESA-SAEZ[1]

[1]HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA, MADRID, Spain, [2]HOSPITAL UNIVERSITARIO FUNDACIÓN JIMÉNEZ DÍAZ, MADRID, Spain

Introduction:
Purpose: to attach importance to the complementary studies needed in a suspected Horner Syndrome as it has an straight relationship with supra-aortic trunks diseases.

Methods:
We present a case report of a 47 year old male who came to Emergency area for ptosis and ipsilateral miosis for the last 9 days. No relevant information in his medical history. EKG, chest X-ray, cranial CT scan and supra-aortic trunk Eco-doppler were made in that moment after suspecting Horner Syndrome diagnosis.

Results:
All the complementary tests had normal results but supra-aortic trunks Eco-doppler, in which a carotid´s blockage suggestive image was found out. Asupra-aortic trunk CT scan was made in which a carotid dissection was seen in the right internal carotida branch (from 3 cm next to carotid bulb to the carotid channel) with an eighty percent blockage of the lumen. A acetylsalicylic acid 100 mg treatment was scheduled and carotid angioplasty and double stenting were done 7 days later (Stent Surpass123 FPP and Stent Precise PC1020XCE) without complications. Two months later follow - up with cervical CT scan showed stents overlapping missing. This lead to anticoagulation and double antiaggregation for 6 months and double stenting for second time for the defect covering. By now, the patient is on follow- up with antiaggregation.

Conclusions:
this case report remains the prime importance of complementary image testing in Horner Syndrome suspecting as an internal carotid blockage is one of the main ethiologies to exclude due to the clinical implications it has.

References: None.

Keywords: Vascular disorders, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Interventional neuroradiology

Financial Disclosures: The authors had no disclosures.

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Poster 80
Twists and Turns May Break My Bones...

Arezu Haghighi[1], Kim Gokoffski[1], Vivek Patel[1]

[1]*USC Eye Institute, Los Angeles, California, USA*

Introduction:
A case report of a 45-year-old previously healthy male presenting with bilateral subacute vision loss found to have extensive infiltrating soft tissue masses (including orbital) with histology consistent of foamy, hemosiderin-laden macrophages, rare S-100, and CD68 positivity consistent with a diagnosis of Erdheim-Chester disease. This case is atypical in the absence of long-bone involvement.

Methods:
Patient initially presented to an outside ophthalmologist, diagnosed with posterior uveitis, exudative retinal detachment OS and treated with an unknown laser procedure. Weeks later, he developed bilateral painless vision loss, nausea/emesis, black stools, and truncal petechia. pan-CT scan revealed extensive soft tissue densities along the pericardium, lungs, adrenal glands, kidneys, and pre-sacral space with sparing of the osseous structures and lymph nodes. A biopsy of the perinephric mass revealed numerous foamy as well as hemosiderin-laden macrophages with CD68 positivity, CD1a negativity, and rare S-100.

Results:
VA was HM OD and 20/400 OS, IOP wnl, pupil was fixed/dilated with 2+ RAPD OD. Anterior segment exam unremarkable. DFE revealed 360 bilateral, hyperemic disc edema OU and hemorrhagic choreo-retinal scar OS. OCT macula was notable for drusenoid changes and retinal atrophy OD as well as choroidal atrophy and hemorrhagic fibrosis OS. IVFA without evidence of retinal vasculitis or peripheral non-perfusion. A vasculitis/infectious panel was negative other than an elevated ESR/CRP (44/74.3) and slightly elevated p-ANCA (1:40). MRI orbits w/ and w/out contrast revealed a uniformly enhancing nodular soft tissue collection inferior to the optic nerve OD with calvarial medullary expansion causing bilateral optic canal narrowing.

Conclusions:
Given extensive soft tissue masses showing characteristic lipid-laden macrophages (rare S-100, pos CD68), papillitis, and nodular orbital soft tissue density, patient was diagnosed with Erdheim-Chester disease (ECD) and started on high dose oral steroids and PEG-Interferon. One month later, VA improved to 20/100 OD and 20/400 OS with improvement in disc edema OU.

References: [1] Veyssier-Belot et al. “Erdheim-Chester Disease: Clinical and Radiologic Characteristics of 59 Cases.” Medicine (1996): 75(3): 157-169. [2] Adawi et al. “Erdheim-Chester disease (ECD): Case report, clinical and basic investigations, and review of literature.” Medicine (2016): 95:42 (e5167). [3] Cavalli et al. “ The multifaceted clinical presentations and manifestations of Erdheim-Chester disease: comprehensive review of the literature and 10 new cases.” Ann Rheum Dis (2013): 72: 1691-1695. [4] Sedrak et al. “ Erdheim-Chester Disease of the Central Nervous System: New Manifestations of a Rare Disease.” American Journal of Neuroradiology (2011): 32:2126-31. [5] Abdellatief et al. “Choroidal Involvement in Erdheim-Chester Disease.” Ophthalmic Surgery, Lasers, & Imaging Retina (2015): 46(6): 674-676.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 81
Painful Multiple Cranial Neuropathies due to Lyme Disease as Opposed to Tolosa-Hunt Syndrome

Eman Hawy[1], Phil Aitken[1]

[1]*University Of Vermont, Burlington, Vermont, USA*

Introduction:
Painful cranial neuropathy is sometimes attributed to inflammatory idiopathic disorder called Tolosa-Hunt syndrome which often responds to steroids. In case of steroid poor response alternative infectious or inflammatory etiology should be investigated. Sarcoidosis, Tuberculosis, and Lyme are only a few conditions that can present with painful cranial neuropathies.

Methods:
A 44 years old lady who was admitted to the hospital with multiple cranial nerve palsy, severe pain, double vision and an abnormal MRI. The MRI had multiple areas that enhanced involving the right base of the brain and the cranial nerves. At first, this was diagnosed as a Tolosa-Hunt syndrome. Investigations were carried out and a specific etiology was not found. The testing included serum Lyme antibodies which tested disease negative. She was placed on prednisone and continued to be followed. Patient didn't improve and over a week developed facial palsy on the affected side. repeat serum testing for Lyme showed conversion to seropositive and with the CSF positive as well. She was subsequently diagnosed as Lyme disease. She was then subsequently treated with IV antibiotics and then treated as well at the direction of the Lyme Center in Bennington.

Results:
Patient has improved with complete recovery of extraocular muscle movement but with residual facial nerve palsy.

Conclusions:
Lyme disease can present with painful cranial neuropathies including optic nerve, oculomotor, abducent and facial nerves. Close follow up to patients is needed especially when diagnised with Tolosa-Hunt syndrome that is not responsive to steroids.

References: 1. Prete B, Sowka Painful ophthalmoplegia as an initial presentation of sarcoidosis. J.Clin Exp Optom. 2016 Sep 15. doi: 10.1111/cxo.12468. 2. Jain R, Sawhney S, Koul RL, Chand P. Tolosa-Hunt syndrome: MRI appearances. J Med Imaging Radiat Oncol. 2008 Oct;52(5):447-51. doi: 10.1111/j.1440-1673.2008.01988.x. 3. Gladstone JP. An approach to the patient with painful ophthalmoplegia, with a focus on Tolosa-Hunt syndrome. Curr Pain Headache Rep. 2007 Aug;11(4):317-25. R 4. La Mantia L, Curone M, Rapoport AM, Bussone G; International Headache Society.. Tolosa-Hunt syndrome: critical literature review based on IHS 2004 criteria. Cephalalgia. 2006 Jul;26(7):772-81

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Lyme, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 82
Tilt-A-"Whorl": A Rare Meningeal Variant of a Glial Neoplasm Causing Foster Kennedy Syndrome

Danielle Isen[1], Marc Dinkin[2]

[1]UPMC Eye Center, Pittsburgh, Pennsylvania, USA, [2]Weill Cornell Medical College, New York, New York, USA

Introduction:
Foster Kennedy Syndrome is a constellation of signs that classically includes unilateral compressive optic atrophy, contralateral papilledema, anosmia, and the presence of an intracranial lesion. The syndrome is most frequently from meningiomas but may also be due to gliomas, frontal lobe abscesses, plasmacytomas, nasopharyngeal angiofibromas, cholesteatomas, and neuroblastomas. We describe a case of Foster Kennedy Syndrome secondary to an atypical neoplasm possessing characteristics of both a glioma and meningioma.

Methods:
Case report and review of literature

Results:
A 65-year-old Saudi man who was status post resection of an olfactory groove mass in 2012 and again for a recurrence in 2014 presented to us in 2016 with vision loss in the left eye. Best-corrected visual acuities were 20/40, OD, and light perception, OS. Review of systems was positive for anosmia, gait ataxia, urinary incontinence, insomnia, and poor concentration. A left relative afferent pupillary defect was elicited. The left eye had restriction with lateral gaze and partial restriction with vertical gaze. Examination revealed papilledema, OD, and severe optic atrophy, OS. Magnetic resonance imaging showed an expansive, multi-compartmental mass with invasion of the left orbital apex and optic foramen and lateral deviation of the right optic nerve. Resection of the tumor was again performed. Histopathology showed spindled cells with round to ovoid nuclei and prominent angiocentric whorled patterning, resembling a meningioma. However, immunostaining was strongly positive for glial fibrillary acidic protein (GFAP) and only weakly positive for epithelial membrane antigen (EMA). GFAP+ staining is highly specific for tumors of a glial origin, so a glioma was suspected despite the histopathologic findings.

Conclusions:
We present a rare case of a glioma with meningioma-like features. Recognizing this variant may assist in initiating a more aggressive treatment plan.

References: 1. Harberler C, Jarius C, Lang S, et al. Fibrous meningeal tumours with extensive non-calcifying collagenous whorls and glial fibrillary acidic protein expression: the whorling-sclerosing variant of meningioma. Neuropath Appl Neurobiol 2002;28:42-47. 2. Li J, Hu W, Zhang Z, Wei D. Clinical and Pathological Studies of Meningioma-Glioma Mixed Tumor. Surgical Science 2011;2:140-143. 3. Wanschitz J, Schmidbauer M, Maier H, et al. Suprasellar meningioma with expression of glial fibrillary acidic protein: a peculiar variant. Acta Neuropathol 1995;90:539-544.

Keywords: Tumors, Orbit/ocular pathology, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 83
77 year old male with diplopia and facial swelling

Brooke Johnson[1]

[1]*Advocate BroMenn Medical Center, Normal, Illinois, USA*

Introduction:
This case presentation describes an atypical presentation of giant cell arteritis that unfortunately resulted in a unilateral complete loss of vision due to misdiagnosis.

Methods:
A 77-year-old male presented with one week of binocular diplopia worst on right gaze with associated headache and confusion after a fall. On examination a right lateral rectus palsy and mild confusion were noted and presumed due to post-concussive syndrome. On hospital day two, the patient developed a new left lower motor neuron facial palsy with facial swelling and chemosis in both eyes. Several imaging and laboratory studies were done including MRI brain and orbits with and without contrast and MR venogram most of which were unremarkable except Sodium 123, AST 82 and ESR 72 drawn on the day of admission and CRP 269.9 drawn on hospital day four. Patient had extensive infectious and autoimmune workup that was mostly negative and was discharged without a concrete diagnosis after nine days. He returned two days later with blurry vision and visual hallucinations but was discharged without seeing neurology after symptoms resolved. Unfortunately, he returned again ten days later with complete loss of vision in his left eye that started the day after he was last discharged. He was given one gram of methylprednisolone daily for three days. He had a temporal artery biopsy after one dose of the steroids that was positive for giant cell arteritis. He was subsequently placed on a long taper of prednisone but never recovered vision in his left eye.

Results:
Not applicable.

Conclusions:
Multiple uncommon presentations of temporal arteritis were found in our patient including multiple cranial nerve palsies, visual hallucinations, facial swelling, and transaminitis. The differential diagnosis for diplopia with these associated but uncommon findings, especially in the elderly, should include giant cell arteritis and be treated promptly to avoid permanent visual loss.

References: Docken WP, Rosenbaum JT. Clinical manifestations of giant cell (temporal) arteritis. UpToDate. http://www.uptodate.com/contents/clinical-manifestations-of-giant-cell-temporal-arteritis?source=search_result&search=temporal arteritis&selectedtitle=3~113. Published August 9, 2016. Accessed April 10, 2016. Hunder GG. Diagnosis of giant cell (temporal) arteritis. Diagnosis of giant cell (temporal) arteritis. https://www.uptodate.com/contents/diagnosis-of-giant-cell-temporal-arteritis. Published October 7, 2014. Accessed August 10, 2016. Hunder GG. Treatment of giant cell (temporal) arteritis. Treatment of giant cell (temporal) arteritis. http://www.uptodate.com/contents/treatment-of-giant-cell-temporal-arteritis. Published March 14, 2016. Accessed August 10, 2016. Miller NR, Subramanian PS, Patel VR. Walsh and Hoyt's Clinical Neuro-Ophthalmology: The Essentials. 3rd ed. Philadelphia, PA: Wolters Kluwer; 2016. Savino PJ, Danesh-Meyer H. Neuro-Ophthalmology. 2nd ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2012.

Keywords: Optic neuropathy, Ocular Motility, Vascular disorders

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Grant Support: None.

Poster 84
Visual Field Defect As The Presenting Symptom Of A Serious Systemic Condition

Syed Karim[1]

[1]*University of Maryland Department of Ophthalmology, Baltimore, Maryland, USA*

Introduction:
The sellar and parasellar regions are rich in vital neurovascular structures, and as such may be the location of the first presentation of a systemic disease or malignancy. Primary tumors represent the vast majority of lesions in this area, and metastatic lesions comprise a rare minority.

Methods:
A 62 year old African American female presented to the neuro-ophthalmology clinic with complaints of two weeks of decrease in visual acuity and visual field loss in both eyes. Past medical history was significant for rheumatoid arthritis and interstitial lung disease. Ocular history was remarkable for bilateral cataract surgery. Review of systems was positive for intractable cough and cold symptoms three months prior to presentation. Exam revealed visual acuity of 20/200 and CF at 1 foot in the right and left eyes, respectively. Pupils and all optic nerve testing were normal, and extraocular movements were full. Tonometry, external and slit lamp exam, as well as dilated fundus exams were unremarkable. Optic nerves appeared pink and healthy with normal cup to disc ratios.

Results:
Humphrey visual field analysis showed complete bitemporal hemianopia and additional field loss nasal to the vertical midline in the left eye. The test was reliable, and results were consistent with an optic chiasm lesion. Urgent brain MRI showed a large suprasellar mass completely encasing the optic chiasm. There was mass effect upon the hypothalamus and the pituitary infundibulum, and extent into the posterior pituitary gland. CT chest showed a mass in the right hilum, and axillary lymph node biopsy confirmed the primary tumor to be adenocarcinoma of the lung. The patient was treated with palliative therapy, including whole brain radiation.

Conclusions:
In older patients who display rapid progression of signs and symptoms localizing to the sellar and parasellar regions, the possibility of metastasis must be investigated.

References: Altay, Krisht, Couldwell, Sellar and Parasellar Metastatic Tumors, International Journal of Surgical Oncology, Volume 2012, 2012.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Tumors, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 85
Smartphone Esotropia

Marilyn Kay[1]

[1]*University of Wisconsin Department of Ophthalmology and Visual Sciences, Madison, Wisconsin, USA*

Introduction:
Acquired double vision in an adult can be due to serious neurologic entities. I discuss a relatively unrecognized cause for acquired esotropia in an adult

Methods:
A 36 yo male came for a second opinion about the cause of his horizontal double vision for the last 8 months, occurring when looking up from his E book or phone. findings included a 9 diopter esotropia at distance, with normal exam, MRI, and cycloplegia refraction similar to his refractive correction

Results:
I diagnosed "Smartphone Esotropia", reported primarily in the Asian literature, due to excessive near use of his electronic media at the distance of 12 inches, with glasses on. This induced convergence over-action when the activity occurred 4 or more hours a day for many weeks.

Conclusions:
acquired esotropia can occur from overuse of electronic media , inducing convergence over action. The treatment will be discussed as will other cases with similar induced double vision.

References: Lee, HS et al, Acute acquired comitant esotropia related to excessive Smartphone use, BMC Ophthalmology(2016) 16:37

Keywords: Adult strabismus with a focus on diplopia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 87
Cavernous Sinus Syndrome as the presenting sign of Burkitt's Lymphoma in a child

Jenna Kim[1], Adeniyi Fisayo[2]

[1]Department of Ophthalmology and Visual Science, Yale School of Medicine, New Haven, Connecticut, USA, [2]Department of Neurology, Ophthalmology and Visual Science, Yale School of Medicine, New Haven, Connecticut, USA

Introduction:
Cavernous sinus syndrome (CSS) is rare in the pediatric population. Even less frequent is CSS as the presenting symptom of lymphoma. Of the 14 cases reported in the English literature, only five have been identified as Burkitt lymphoma. We report the 6th case of primary central nervous system (CNS) Burkitt's lymphoma presenting as unilateral, cavernous sinus syndrome in a child.

Methods:
Retrospective case report and literature review

Results:
A previously healthy 8-year-old boy developed binocular diplopia, painless proptosis, and ptosis of left eye over three days. There were severe deficits of supra-, infra-, and adduction of the left eye with a fixed, dilated left pupil. Visual acuity was 20/20 in both eyes and there was a left relative afferent pupillary defect. The optic nerves appeared normal. The remainder of the examination was unremarkable. Brain Magnetic Resonance Imaging (MRI) showed enlargement of the left cavernous sinus and enhancement of the left trigeminal nerve. Bone marrow biopsy was normal. A chest X-ray and PET-CT of the whole body were unremarkable. Cerebrospinal fluid (CSF) showed WBC 43/uL (59% lymphocytes, 40% blasts), protein 143 mg/dL with clonal B cells expressing CD-10, CD-20 and CD-38 and positive immunostain for c-myc, all diagnostic of Burkitt's lymphoma. After four weeks of chemotherapy, eye movements and anisocoria improved significantly, and initial MRI findings resolved.

Conclusions:
Lymphoma is a rare, yet important, cause of cavernous sinus syndrome in children. Isolated CSS as the presenting sign of lymphoma is even more rare with only five pediatric cases in the literature. It is notable that in our case the diagnosis was reached by CSF analysis after a negative bone marrow biopsy. To the best of our knowledge, the present case is the only report of isolated CS Burkitt's lymphoma that was diagnosed solely by CSF analysis.

References: None.

Keywords: Pediatric neuro-ophthalmology, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 88

Two Cases of Unilateral Transient Ptosis Presumed Myasthenia Graves of Childhood Associated with Viral Infection

Sakang Kim[1]

[1]Kangwon University Hospital, Chuncheon, Korea, Republic of

Introduction:
To report unique cases of unilateral, recurrent, transient and variable level of ptosis during viral illness.

Methods:
We describe 2 cases of transient ptosis that developed during viral illness. The first is 3-year-old girl who developed unilateral recurrent transient ptosis during hospitalization for treatment of pneumonia. Most of day her MRD (margin reflex distance) was +2/+2 but she developed unilateral transient ptosis (MRD 0/2) lasting few seconds several times a day (we can show movie if possible for e-poster). Number of ptosis events was related to severity of her illness. After 4 days of hospitalization, fever and pneumonia symptoms were resolved with medication. Several events of ptosis persisted during hospitalization period. One or two days after discharge, her ptosis symptom has resolved spontaneously without any medication for ptosis. After this event, she visited hospital several times for enteritis, cough and sinusitis but she didn't develop ptosis again. The second is 34-month-old boy who developed unilateral ptosis during upper respiratory tract infection. His MRD of right eye was +4 and MRD of left eye was variable (+1~+4). He showed fatigue on his left eye. Unilateral ptosis persisted after resolving cough and fever. Ptosis last 2 months and resolved gradually without medication. After resolving ptosis, we couldn't follow up this boy because he moved away. In both cases, ophthalmic examination shows no abnormal findings except ptosis. They didn't develop any neurologic deficits.

Results:
(-): case report

Conclusions:
Several papers stated that viral infection can induce myasthenia gravis but the reported cases are limited. We additionally report two more cases of ptosis presumed to myasthenia gravis which developed during viral illness and resolved spontaneously.

References: None.

Keywords: Myasthenia

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Poster 89
An Unusual Case of Homonymous Hemianopia and a Sellar Mass

Kyle Kovacs[1], Adeniyi Fisayo[2]

[1]Yale School of Medicine, Department of Ophthalmology and Visual Science, New Haven, Connecticut, USA, [2]Yale School of Medicine, Department of Ophthalmology, and Department of Neurology, New Haven, Connecticut, USA

Introduction:
Posterior cortical atrophy (PCA) typically manifests clinically with higher order visual dysfunction and radiologically with occipito-parietal atrophy and/or hypometabolism, usually in the setting of Alzheimer's disease. Patients can rarely present with homonymous hemianopia and advanced visual field deficits.

Methods:
We report a case of a 72-year-old man with a sellar mass and left homonymous hemianopia who was referred for pre-operative neuro-ophthalmology evaluation.

Results:
Examination revealed visual acuities of 20/30 in each eye with normal pupils and optic nerves. Automated perimetry showed an incongruous left homonymous hemianopia. He was unable to read any color plates - including the control plate - in either eye. This prompted further evaluation for higher order visual processing impairment. He was found to have simultagnosia, optic ataxia, mild optic apraxia, agraphia, alexia/dyslexia, and left sided neglect. MRI of the brain with and without contrast showed a 10 mm rim enhancing cystic mass contacting and displacing the left optic chiasm. It also showed diffuse cortical atrophy in the frontal, temporal, parietal and occipital lobes. PET CT scan of the head showed hypometabolism of the parietal and occipital lobes, worse on the right, confirming a diagnosis of PCA. Neuropsychiatric testing confirmed Alzheimer's disease. Surgery was not recommended.

Conclusions:
Our patient was found to have homonymous hemianopia and Balint's syndrome along with other disorders of higher visual processing during pre-operative evaluation of a sellar mass. While visual field defect due to PCA is a known entity, this case is unique because of the presence of an intracranial mass lesion that, in other settings, might also conceivably cause a visual field defect. This illustrates the importance of thoughtful neuro-ophthalmology evaluation which can rescue patients from the morbidity of unnecessary surgical intervention.

References: Beh SC, Muthusamy B, Calabresi P, Hart J, Zee D, Patel V, Frohman E. Hiding in plain sight: a closer look at posterior cortical atrophy. Pract Neurol. 2015 Feb;15(1):5-13 Delamont RS, Harrison J, Field M, Boyle RS. Posterior cortical atrophy. Clin Exp Neurol. 1989;26:225-7. Formaglio M, Krolak-Salmon P, Tilikete C, Bernard M, Croisile B, Vighetto A. [Homonymous hemianopia and posterior cortical atrophy]. Rev Neurol (Paris). 2009 Mar;165(3):256-62. doi: 10.1016/j.neurol.2008.10.010. Epub 2009 Jan 4. French. Müller KI, Bekkelund SI. Visual impairment and posterior cortical atrophy preceding rapid progressive dementia. BMJ Case Rep. 2013 Jan 2;2013. Pelak VS, Smyth SF, Boyer PJ, Filley CM. Computerized visual field defects in posterior cortical atrophy. Neurology. 2011 Dec 13;77(24):2119-22. Sadun AA, Chu ER, Boisvert CJ. Neuro-ophthalmology Safer Than MRI? Ophthalmology. 2013 Apr;120(4):879. Suárez-González A, Crutch SJ, Roldán Lora F, Franco-Macías E, Gil-Néciga E. Can patients without early, prominent visual deficits still be diagnosed of posterior cortical atrophy? J Neurol Sci. 2016 Aug 15;367:26-31.

Keywords: Higher visual functions, Higher Visual Cortical functions, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Visual fields, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 90
Central Retinal Artery Occlusion As A Rare Complication of Compressive Optic Neuropathy From Sarcoidosis

Cindy Lam[1], Edward Margolin[1]

[1]*Department of Ophthalmology & Vision Sciences, University of Toronto, Toronto, Canada*

Introduction:
We describe a case of central retinal artery occlusion (CRAO) as a rare complication of compressive optic neuropathy from sarcoidosis.

Methods:
Case report.

Results:
A 79-year-old man was referred for progressive vision loss in the right eye over three weeks. Vision was light perception (LP) with right RAPD, right optic nerve was pink but diffusely elevated with numerous peripapillary hemorrhages and cotton wool spots. MRI demonstrated concentric enhancement in the right optic nerve sheath surrounding the anterior two-thirds of the intraorbital portion of the optic nerve and extending to the posterior surface of the globe. Indistinct margins suggested an inflammatory etiology. CT of the thorax revealed bilateral hilar, mediastinal, and paratracheal lymph nodes. Transbronchial biopsy demonstrated non-caseating granulomas confirming diagnosis of sarcoidosis. The patient was pulsed with intravenous methylprednisolone 1 gram daily for 3 days and then started on oral prednisone 40 mg daily. There was no improvement in visual acuity. When examined two weeks later, fundoscopy demonstrated CRAO with neovascularization of the iris and the anterior chamber angle in the right eye. There was no posterior uveitis or retinal vasculitis. Fluorescein angiography demonstrated severely delayed arterial perfusion (> 1 minute) consistent with CRAO. Intravenous steroids were administered again but visual acuity remained at LP.

Conclusions:
CRAO is an extremely rare complication of sarcoidosis. Only one other case in the literature described a patient with CRAO secondary to sarcoidosis-related intraconal inflammation, but the patient presented with excellent vision (20/25) and improved with steroids, thus it is likely that the cilioretinal artery perfusion was spared [1]. In our case there was severe, concentric inflammation within the optic nerve sheath encasing the intraconal portion of the optic nerve that we believe severely compressed the central retinal artery, causing a CRAO with anterior and posterior segment ischemia that was recalcitrant to treatment.

References: 1) Kim DS, Korgavkar K, Zahid S, et al. Vision Loss After Central Retinal Artery Occlusion Secondary to Orbital Sarcoid Mass. Ophthal Plast Reconstr Surg. 32(2):e37-40, 2016.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 91

Vision Loss with Retinal Periphlebitis and Negative Waveform ERG as Presentation of Cancer-Associated Retinopathy

Michael Lewen[1], Shelly Lee[2], Kevin Sitko[2]

[1]Tufts Medical Center / New England Eye Center, Boston, Massachusetts, USA, [2]University of New Mexico, Albuquerque, New Mexico, USA

Introduction:

Cancer-associated retinopathy (CAR) involves aberrant antibodies against retinal antigens, such as recoverin and enolase, leading to retinal degeneration. Clinical exam is often unremarkable despite visual symptoms. Retinal vascular abnormalities are rare and typically end-stage manifestations. Electroretinography (ERG) demonstrates reduced rod and cone responses. We report an unusual presentation of CAR leading to the diagnosis of lung cancer.

Methods:

Case summary and review of the literature

Results:

A 64 year-old man presented with bilateral vision loss, prolonged dark adaptation and photopsias. He had no ocular history or family history of blindness. His visual acuity was 20/30 OD and 20/250 OS. A relative afferent pupillary defect was present in the left eye. Color plates were full. Optic disc exam revealed temporal pallor OU. The maculae were unremarkable, and scattered areas of venous sheathing were present peripherally OU. OCT demonstrated normal macular architecture and nerve fiber layer thickness. Humphrey visual fields were severely depressed with paracentral sparing OD and stimulus V testing was required OS. Fluorescein angiography showed delayed arterial filling and late staining at the sites of venous sheathing. Full-field ERG demonstrated markedly reduced b-waves on scotopic rod response and negative waveforms on combined rod-cone testing OU. Cone response was decreased OS. Bloodwork for inflammatory and infectious etiologies was negative. CT chest revealed a suspicious lesion, which was determined to be small-cell lung cancer. Anti-retinal antibodies were positive for anti-enolase (46-kDa), anti-GAPDH (36-kDa) and others. Anti-recoverin antibody was not identified.

Conclusions:

Small-cell lung carcinoma, breast, and ovarian cancers are most commonly associated with CAR. Retinal periphlebitis and negative waveform ERG have rarely been reported in CAR. It is important to consider CAR in patients with vision loss out of proportion to exam findings especially when supported by electrophysiologic testing. A high index of suspicion and appropriate testing may lead to detection of an underlying malignancy.

References: Grewal, Fishman, Jampol, Autoimmune retinopathy and antiretinal antibodies: a review, Retina, 34,827-45, 2014. Weleber, Watzke, Shults, Trzupek, Heckenlively, et al, Clinical and electrophysiologic characterization of paraneoplastic and autoimmune retinopathies associated with antienolase antibodies, American Journal of Ophthalmology, 139, 780-94, 2005. Anastasakis, Dick, Damato, Spry, Majid, Cancer-associated retinopathy presenting as retinal vasculitis with a negative ERG suggestive of on-bipolar cell pathway dysfunction, Documenta Ophthalmologica, 123, 59-63, 2011. Kim, Toma, Thirkill, Dunn, Cancer associated retinopathy with retinal periphlebitis in a patient with ovarian cancer, Ocular Immunology and Inflammation,18, 107-9, 2010. Lee, Vrabec, Baldassano, Cancer-associated retinopathy with unusual retinal whitening, Retinal Cases and Brief Reports, 9, 21-4, 2015.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Paraneoplastic syndromes, Pupils Retina, Tumors, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Poster 92

Acute cerebral venous sinus thrombosis (CVT) presenting with papilledema and complete vision loss

Anagha Medsinge[1], Dante Sorrentino[1], Jennifer Lee[1], Luis Gonzalez-Gonzalez[1], Lance Bodily[1], Gabrielle Bonhomme[1]

[1]UPMC Eye Center, Eye and Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Introduction:

The evaluation of optic disc edema can be a diagnostic challenge. It is important to perform thorough work-up to rule-out vascular, infectious, inflammatory, toxic, metabolic, and compressive causes. Papilledema is present in only approximately 28% of patients with CVT. Papilledema commonly causes transient visual impairment, but if left untreated, can lead to permanent loss due to optic atrophy. Severe vision loss in the setting of acute CVT is rare and reported in only 2%-4% of cases.

Methods:

Thirty three-year-old male with history of stage IA germ-cell testicular cancer presented to the emergency department with acute onset bilateral progressive painless vision loss to the point of no light perception with bilateral Frisen grade 5 disc edema.Extensive infectious, inflammatory, toxic, and metabolic serologies were normal.

Results:

Neuroimaging revealed acute CVT including superior sagittal sinus, right transverse and sigmoid sinus thrombosis. Formal angiography confirmed elevated intracranial pressure (ICP) with thrombus. He was treated with therapeutic lumbar puncture, venous thrombectomy, anticoagulation, ventriculoperitoneal shunt, acetazolamide, and high dose steroids. At 3 month follow up, visual acuity was 20/200 and 20/60 in right and left eye respectively with improvement in visual fields.

Conclusions:

Given the history of cancer and immunocompromised state of our patient; infection, adverse reaction to chemotherapeutic agents, carcinomatous meningitis, and intracranial metastatic lesion causing raised ICP were considered as differential diagnoses including CVT. Prompt diagnostic work up including laboratory and neuroimaging helped us in establishing the diagnosis in this case. With timely interventional neuroradiology and neurosurgical management, we were able to salvage the vision and prevent the development of irreversible visual loss. Although controversial, high dose corticosteroids may be considered as an adjuvant in the setting of acute optic nerve damage. We believe that this is a rare presentation of recovery from profound visual loss secondary to CVT in a young patient with known cancer.

References: 1.Ferro, Canhao, Stam, Bousser, Barinagarrementeria. Prognosis of cerebral vein and dural sinus thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), Stroke, 35,664-70,2004. 2.Baumgartner, Studer, Arnold, Georgiadis, Recanalisation of cerebral venous thrombosis, J Neurol Neurosurg Psychiatry,74, 459-461,2003. 3.Ferro, Canha˜o , Stam, Bousser, Barinagarrementeria, ISCVT Investigators. Delay in the diagnosis of cerebral vein and dural sinus thrombosis: influence on outcome. Stroke,40,3133-3138,2009.

Keywords: Optic neuropathy, High intracranial pressure/headache, Vascular disorders

Financial Disclosures: The authors had no disclosures.

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Poster 93
Ophthalmic Artery Occlusion Without Retinal Manifestations

Kannan Narayana[1], Damian Berezovsky[1], Virender Sachdeva[1], Frank Tong[1]

[1]Emory University School of Medicine, Atlanta, Georgia, USA

Introduction:
Ophthalmic artery occlusion typically results in ischemia to both the retina and the optic nerve. Typical early manifestations include retinal whitening without cherry red spot and late manifestations include diffuse disc pallor, severe attenuation of retinal vessels, diffuse opacification of the retina with a 'featureless' appearance, and RPE changes. We report an unusual patient with ophthalmic artery occlusion confirmed by catheter cerebral angiography. His optic nerve, retina and retinal vasculature initially had a normal appearance. Optic nerve pallor developed a month later, but his retina did not show any abnormalities

Methods:
A 53-year-old man suffered a right carotid artery injury during trans-sphenoidal pituitary surgery. Dissection in the cavernous portion of the right ICA was confirmed by CT angiography. He underwent two angiographic procedures, first a balloon test occlusion, followed by coil embolization of the right ICA (supraclinoid segment to the junction of the cavernous and petrous segments). Interval development of a carotid-cavernous fistula was noted 2 days later. Upon awakening, he reported vision loss in the right eye. On examination, he had no light perception right eye and normal vision left eye. Fundus examination was normal. One month later, the right optic disc was pale, but his retina did not show any visible abnormalities.

Results:
Initial catheter cerebral angiogram showed absence of ophthalmic artery opacification, confirming ophthalmic artery occlusion. Choroidal blush was identified on external carotid artery injection, indicative of collateralization from the external carotid artery system to the ophthalmic artery.

Conclusions:
Our patient did not show clinical evidence of retinal ischemia, despite the presence of confirmed ophthalmic artery occlusion. The absence of expected retinal findings can be explained by the presence of collateral circulation and this case highlights the importance of understanding the collateral circulation between the external and internal carotid arteries. Differential diagnosis will be discussed.

References: None.

Keywords: Vascular disorders, Neuroimaging, Interventional neuroradiology, Optic neuropathy, Skull Base

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 94
Multiphasic neuromyelitis optica: A case report in Senegal

Patrice Ntenga[1], Kamadore Touré[2], Mohamed Lelouma Mansare[1], Soumaila Boubacar[1], Daniel Gams Massi[1], Mouhamadou Mansour Ndiaye[1]

[1]Fann national teaching hospital-Cheikh Anta Diop University, Dakar, Senegal, [2]Fann national teaching hospital-Thies University, Dakar, Senegal

Introduction:
Neuromyelitis optica (NMO) is a neurological inflammatory disease leading to limb paralysis and blindness. It is a rare disease with an unequal world distribution and a prevalence that varies geographically. We report the observation of a patient admitted to the neurology department of Fann national teaching hospital in Dakar, Senegal.

Methods:
A 32 year old male patient was admitted in the department in June 2016 for upper and lower limbs muscle weakness that had evolved for 8 months. At the beginning he was complaining of right cervico-brachial neuralgia followed by a right and left upper limbs weakness. He mentioned also a left monocular loss of visual acuity that disappeared spontaneously within 4 months. Clinical examination revealed signs of transverse myelitis, left eye's diplopia. Spinal cord MRI showed an extended cervical hypersignal, the dosage of anti-aquaporin 4 antibodies was positive and and the CSF analysis was inflammatory. Visual evoked potentials demonstrated an elongation of P100 latency. Thus the diagnosis of an multiphasic NMO was made according to the criteria of Wingerchuk DM et al. The patient was under corticosteroid and his short-term evolution was stable.

Results:
Most authors agree that NMO is a globally rare and geographically diverse disease with prevalence varying from 0.05 to 5/100,000 (95% CI). In our environment the low prevalence is multifactorial, especially the inaccessibility of the anti-aquaporin 4 antibodies test and the low socio-economic level thus limiting the availability of MRI. Spinal cord MRI shows in more than 70% of cases an extended lesion including several metameres producing an extensive transverse myelopathy as in our case.

Conclusions:
This pathology of unknown etiology still poses a problem of functional and mental outcome, possible recurrences and socio-economic burden for the family and society. The patients with multiphasic clinical form seems to have better outcome than those with monophasic form.

References: Wingerchuk DM et al, Revised diagnostic criteria for neuro-myelitis optica, Neurology, 66, 1485-1489, 2006. Wingerchuck D, Hogancamp WF, O'Brien PC, Weinshenker B. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology, 53, 1107-1114, 1999 De Seze J, Stojkovic T, Ferriby D, et al. Devic's neuromyelitis optica: clinical, laboratory, MRI and outcome profile. Journal of Neurological Sciences,197, 57-61, 2002.

Keywords: Demeylinating disease, Optic neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 95
Retrobulbar optic neuritis due to Hodgkins Lymphoma

Benjamin Osborne[1]

[1]*Medstar Georgetown University Hospital, Washington, Maryland, USA*

Introduction:
21 yo male went to the student health clinic complaining of a worsening pain/pressure behind both eyes and headache. He had no photophobia or vision changes. His medications were ibuprofen, flonase and singulair. Initial exam was nonfocal except for tenderness along the posterior neck muscles. He was diagnosed with tension headaches and prescribed prednisone 50mg qd for five days and cyclobenzaprine prn. After the headaches resolved, he developed blurred vision OS. VA was 20/20 OD and 20/50 OS. Color vision was 10/10 OD and 6/10 OS. There was an RAPD OS. Slit lamp exam and remainder of dilated eye exam were normal. HVF 24-2 showed temporal field loss OS MD -9.82 db. A diagnosis of retrobulbar optic neuritis was made.

Methods:
Case report

Results:
MRI brain with gad showed enhancement of the left optic nerve. There were some non enhancing hyperintense T2/FLAIR signal changes in the corpus callosum which did not meet the McDonald criteria for MS. He received 3 days of solumedrol 1000mg followed by a prednisone taper but no improvement in his vision . NMO Ab negative. CSF normal cell count, TP, glucose, VDRL negative, OCB absent and cytology negative. At follow up visit VA 20/20 OD and 20/80 OS. HVF showed worsening visual field loss OS. Further work up included an MRI of the spine. No cord signal abnormalities were found however there was bilateral lower neck, mediastinal and right hilar lymphadenopathy. Excisional biopsy of the right cervical lymph node showed classical hodgkins lymphoma nodular sclerosing type stage 2A. Chemotherapy was initiated in August and by September, 2016 he had improvement in his vision. VA 20/20 OD and 20/20 OS, color vision 10/10 OD and OS and normal HVF OD and OS.

Conclusions:
Hodgkins lymphoma rarely has been reported to present with optic neuritis, mimicking ON associated with multiple sclerosis.

References: 1. Litvak, John, Max M. Leder, and A. J. Kauvar. "Hodgkin's disease involving optic nerve and brain." Journal of neurosurgery Vol 21, page 798, 1964. 2. Miller, Neil R., and W. Jackson Iliff. "Visual loss as the initial symptom in Hodgkin disease." Archives of Ophthalmology Vol 93, page 1158, 1975. 3. Kattah, Jorge C., et al. "Optic neuritis and systemic lymphoma." American journal of ophthalmology Vol 89, page 431, 1980.

Keywords: Optic neuropathy, Tumors, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Grant Support: None.

Poster 96

Pupil sparing incomplete oculomotor palsy due to intracraneal space-occupying lesions in the Emergency Department

Iulia Pana[1], Simon Quijada Angeli[2], Belén Gragera Soroa[3], Marta Sánchez-Dehesa Sáez[3], Vanessa Gerena Arevalo[3], Maria Gabriela Cruz Gutierrez[3], Mónica Hijós Gastón[3]

[1]Hospital Universitario Puerta de Hierro, Madrid, Majadahonda, Madrid, Spain, [2]Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain, [3]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

Introduction:
The diagosis of incomplete third nerve palsy can be clinically challenging beacause the presentations could be subtle and the etiology can vary from local ischemia to a life threatening condition.

Methods:
A retrospective case review of two patients with partial oculomotor nerve palsy due to intracranial space-occupying lesions. Ophthalmological, neurological and imagistic examination will be presented.

Results:
Two patients seen in the Emergency Department presented acute onset of ptosis of the upper eyelid and binocular diplopia.The ophthalmological and neurological examination showed no other neuromuscular dysfunction other than a pupil sparing incomplete oculomotor palsy.Non-Contrast head CT showed in both cases an intracranial space-occupying lesion in the cavernous sinus.The patiens were a female of 51 years old and a male of 40 years old with no systemic disease or treatments.A MRI was performed for better visualization and the female was diagnosed of meningioma of the right cavernous sinus with intraselar extension.She was treated with radiotherapy with good evolution until now.The other patient was diagnosed with a MRI of meningioma of the right cavernous sinus with affectation of the sella turcica, the pituitary gland, the optic chiasm and intracranial optic nerve.He is treated with radiotherapy.After a six months follow up in the ophthalmology department they continue to present the partial oculomotor nerve palsy with no changes.

Conclusions:
These cases highlight the importance of prompt diagnosis of an oculomotor palsy and its cause.Especially in patients younger than 50 with no other diseases.The dilemma of obtaining or not neuroimaging in these patients is faced very often, but we consider that the risk of missing a potentially severe disease is higher in this group of patients.

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Keywords: Tumors, Ocular Motility, Neuroimaging

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Poster 97
Anti-titin reactive Paraneoplastic Cerebellar degeneration with thyroid papillary cancer

JIYUN PARK[1]

[1]Ulsan university hospital, Ulsan, Korea, Republic of

Introduction:
Paraneoplastic neurogenic disorders are syndromes caused by an autoimmune pathogenesis against 'onconeural antigens' shared between a tumor and the nervous system. They are rare but important and can cause severe neurologic disability if not recognized and treated early. Here we describe the first reported case of anti-titin reactive cerebellar syndrome as paraneoplastic phenomenon in association with papillary thyroid carcinoma without myasthenia gravis.

Methods:
A seventy- nine year-old woman presented with a 2 weeks history of progressive unsteadiness and dysarthria. There was bilateral dysdiadocholkinesia and dysmetria, scanning speech. Her gait was broad-base and she can't stand and gait independently. She showed DBN and gaze-evoked nystagmus. Her muscle tone and power were normal. Pathological reflexes are not checked. Her vibration, pain and temperature were normal. She had hypertension for 15 years with regular medication and old smoker (25PYS). She was diagnosed with thyroid cancer three months ago and undergoing observation without treatment.

Results:
MRI of the brain was normal but mild enhancement of cerebellum. A whole body PET/CT scan showed focal hypermetablism lesion in left thyroid gland, bilateral cerebellar hemisphere and vermis and hypometabolism in bilateral occipital lobes. Titin antibody was detected in the serum. The patient underwent total thyroidectomy, pathologic diagnosis was papillary thyroid cancer 6.3mm size. CT scan 6th month post-operation showed no residual malignancy. She can stand independent and DBN and limb ataxia were disappeared, but she could not walk without any help can't walk without any help.

Conclusions:
Anti-titin antibodies indicate a paraneoplastic etiology pointing towards a thymoma in myasthenia gravis but their potential diagnostic value in patients with other paraneoplastic neurological syndrome is unknown. One study first reported the presence of anti-titin antibodies in paraneoplastic cerebellar syndrome associated with papillary thyroid carcinoma without myasthenia gravis.

References: None.

Keywords: Paraneoplastic syndromes

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Grant Support: None.

Poster 98
Neuro-Ophthalmic Manifestations Of Metastases - 8 Snapshots

SMITA PRAVEEN[1], VEENA NORONHA[1], AMBIKA SELVAKUMAR[1]

[1]MEDICAL RESEARCH FOUNDATION, CHENNAI, India

Introduction:
This report describes a series of 8 cases of metastases seen at our institute that had neuro-ophthalmic manifestations.

Methods:
4 male and 4 female patients aged between 22 and 77 years were studied. Of these, 6 presented with vision loss (unilateral or bilateral, ranging from nil perception of light to hand movements), 1 with binocular diplopia and 1 with constricted visual fields. 3 had normal optic discs, 2 had bilateral disc oedema, 2 had unilateral pallid disc edema and 1 had bilateral pale discs. 1 patient had constricted visual field in one eye and inferior defects in the other, while 3 patients with unilateral vision loss had normal fields in fellow eye. 1patient had acquired vertical squint and 2 had multiple cranial nerve palsies. 6 of the 8 patients had a history of treated prior systemic malignancies (duration ranging from 1-25 years earlier). These included Carcinoma stomach, lung, bone, breast, ovary and kidney. Treatment included surgery, chemotherapy and radiotherapy.

Results:
Neuro-imaging was suggestive of intra-cranial metastases in all cases. All patients were referred for further investigations including PET scans, CSF analysis and biopsies wherever indicated.

Conclusions:
In our series, the metastases were in the form of ill defined lesions encasing optic nerve from canal to chiasm, superior orbital fissure, cavernous sinus and orbital apex bony destructions with altered marrow signals, frontal lobe mass, leptomeningeal enhancement and cerebellar spread. These presented variably as infiltrative optic neuropathy, atypical optic neuritis, papilloedema and acquired cranial nerve palsies. Neuro-ophthalmic (ocular and brain) involvement is a frequent and early manifestation of metastasis and it may mimic different diseases making early clinical diagnosis challenging.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Tumors, Optic neuropathy

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Poster 99
Vanishing Act - Gorham Disease Leading to CSF Dynamic Abnormalities

Jason Peragallo[1]

[1]*Emory University, Atlanta, Georgia, USA*

Introduction:
Gorham-Stout disease, also known as vanishing bone disease, is a rare disorder of unknown etiology that presents with proliferating lymphatic tissue and massive osteolysis. Affected patients are most frequently children or young adults.

Methods:
A 14yo girl presented to an otolaryngologist with progressive right-sided hearing loss. A right supraclavicular mass was noted and aspirated, but was non-diagnostic. A CT of the temporal bones and neck revealed a large transspatial multiloculated low-density cystic lesion in the right neck, an ill-defined low-density soft tissue mass with cortical erosion through the right temporal bone, and multifocal lytic expansile lesions with cortical dehiscence and lysis along the right mandible. At 18yo, she developed recurrent bacterial meningitis and was diagnosed with a CSF leak on a CT cisternogram. The leak was not repaired and she was treated with zolendronic acid. An MRI of the brain performed 12/2014 revealed lymphangiomatosis of the right temporal bone and mandible, partial remineralization of the right mandible, brainstem sagging, effacement of the suprasellar cistern, and low lying cerebellar tonsils indicating intracranial hypotension. At 20yo, she developed severe headaches, neck pain, blurry vision, and diplopia. She was found to have severe optic nerve edema and a partial right sixth nerve palsy.

Results:
MRI/MRV of the head revealed decreased effacement of the prepontine cistern, decreased brainstem sagging, decrease in cerebellar tonsillar descent, narrowing of the bilateral transverse and sigmoid dural venous sinuses. A lumbar puncture OP was >56cm H2O and otherwise unremarkable. Acetazolamide was started. She developed bilateral sixth nerve palsies and visual fields worsened. A lumbar drain was placed which improved her examination and symptoms, but she eventually required bilateral optic nerve sheath fenestrations and VP shunting.

Conclusions:
This case demonstrates rebound intracranial hypertension following chronic intracranial hypotension from closure of CSF leak due to Gorham-Stout disease after remineralization from zoledronic acid.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), High intracranial pressure/headache

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Poster 100
Visual improvement following stenting of subclavian artery in Takayasu's Arteritis

Kumudini Sharma[1]

[1]*Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India*

Introduction:
Takayasu's Arteritis (TA) is an idiopathic chronic inflammatory disease of major branches of aorta and results in stenosis of the arteries. We report two cases of TA, with ocular ischemic syndrome OU.

Methods:
Case I: Fifteen years female patient TA, was referred for decreased vision OU. Examination visual acuity - no perception of light OD and finger counting (FC) at 3 meter OS with signs of ocular ischemia, more marked in OD > OS. Fluorescein angiography (FA) OS revealed retinochoroid, optic disc hypoperfusion. Diagnostic digital subtraction angiography (DSA) showed diffuse high grade narrowing of brachiocephalic trunk, right and left common carotid and right subclavian artery. Left subclavian artery shows narrowing at its ostium and proximal segment, origin of left vertebral artery. Balloon angioplasty with stenting of proximal left subclavian was performed. After stenting visual acuity in left eye improved to 6/18. Case II: Eighteen years female of TA was referred with sudden worsening vision OU after cessation of oral steroid therapy. On examination vision - light perception in OD, FC at four meter in OS with signs of ocular ischemia OU. FA showed retinochoroidal, optic disc hypoperfusion. Doppler scan revealed stenosis of bilateral common carotid and subclavian arteries. Intravenous methylprednisolone was started, she noticed improvement in vision OD count finger at 2 meter and 6/24 in OS. DSA and angioplasty with stenting of occluded carotid vessel is planned.

Results:
Case I - following balloon dilation and stenting of left subclavian artery patient noticed gradual improvement in vision, ocular perfusion. Case II - shows improvement in vision on systemic steroid but vascular intervention is planned as there are symptoms and sign of retinal ischemia.

Conclusions:
Vascular intervention of the occluded subclavian artery results in flow of blood through circle of Willis to ophthalmic artery.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Interventional neuroradiology, Neuroimaging, Optic neuropathy, Pupils Retina

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Poster 101

Case of aquaporin-4 immunoglobulin-G positive neuromyelitis optica spectrum disorder associated with small cell lung carcinoma

Rahul Sharma[1], Sangsu Han[2], Harman Sekhon[3], David Munoz[4], Danah Albreiki[1]

[1]Department of Ophthalmology, Eye Institute, The Ottawa Hospital, Ottawa, Ontario, Canada, [2]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, [3]Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, Canada, [4]Division of Pathology, St. Michael's Hospital, Toronto, Canada

Introduction:
Recent findings of the aquaporin-4 (AQP4) immunoglobulin G (IgG) in cancer patients' serum have indicated neuromyelitis optica spectrum disorder (NMOSD) as a potential paraneoplastic immune response. While 38 cases of AQP4-IgG positive paraneoplastic NMOSDs have been reported, none has been associated with small cell lung carcinoma (SCLC). We report the first case of SCLC-associated seropositive NMOSD.

Methods:
A 66-year-old female presented with left vision loss and pain on eye movements for 2 days. Her past medical history included: thymoma resected 21 years ago, left breast intraductal carcinoma (IDC) diagnosed 10 months ago, and a lung mass detected on computed tomography (CT) chest 3 months ago. The patient's IDC was managed by lumpectomy, sentinel node biopsy, and radiation completed 3 months prior to presentation; the lung nodule was diagnosed as SCLC two months after the initial visit. On examination, her visual acuity was 20/20 oculus dexter (OD) and counting fingers oculus sinister (OS). Color vision was full OD, but nil OS. A relative afferent pupillary defect OS was present. The pupils, efferent visual system and the anterior segment were normal bilaterally. The posterior segment OD was normal, but mild-to-moderate left ON head swelling was seen. The Humphrey Visual Field test demonstrated a bitemporal hemianopia. A CT head showed no suprasellar lesion. Magnetic resonance imaging of the orbits/brain demonstrated hyperintensity of both ONs, left ON enhancement, and non-specific subcortical white matter lesions. AQP4-IgG serology was positive. We diagnosed the patient with NMOSD, and started her on intravenous methylprednisolone 1 gram/ day for three days, followed by oral prednisone 60mg daily.

Results:
Hematoxylin and eosin, and immunohistochemical stainings of formalin-fixed paraffin embedded sections with AQP4-IgG revealed AQP4-negative IDC but AQP4-positive SCLC.

Conclusions:
We report the first case of seropositive NMOSD with a paraneoplastic association to SCLC, in a patient with history of multiple malignancies.

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Keywords: Paraneoplastic syndromes, Optic neuropathy, Demeylinating disease

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Poster 102
Antisaccade Deficits in Stiff Person Syndrome

Amrita Singh[1], Wangzikang Zhang[1], Jeffrey Odel[1], Michael Goldberg[1], Linus Sun[1]

[1]Columbia University, New York, New York, USA

Introduction:
The antisaccade task is a clinically useful sign of frontal cortical dysfunction (Hallet,1978). In this task, subjects must make a saccade away from a salient stimulus to a spatial location reflected 180° away. Normal subjects make about 10% errors in this task, but frontal patients make many more. Stiff Person Syndrome (SPS) is a disorder characterized by muscle rigidity, spasm, and ataxia, in which 85% of patients have antibodies against glutamic acid decarboxylase (GAD) an enzyme necessary for GABA synthesis. Previous studies of these patients have identified oculomotor abnormalities, including esotropia (Economides, 2005), multi-component and slow vertical saccades, decreased smooth pursuit gain, downbeat nystagmus (Ances, 2005), and ophthalmoplegia (Pittock, 2006).

Methods:
We used an SMI infrared tracker to measure the horizontal and vertical saccades of a 25 yo intellectually intact student presenting with SPS (anti-GAD65 positive) on immunotherapy.

Results:
She made very slow but accurate 10° prosaccades in all 4 directions, with a median latency of 242 ms. Her main sequence showed deceased velocity for all saccade amplitudes and directions. Attempting to do 20° antisaccades, she made 22/31(71%) prosaccade errors. However, because her saccades were so slow, few of her prosaccades actually reached the target. Instead, she often made midflight corrections to turn initially inaccurate prosaccades into accurate antisaccades. Her prosaccade error median latency was 285 ms and the midflight correction median latency was 462ms which was similar to trials when she made a single initially correct antisaccade with a median latency of 458ms.

Conclusions:
The high percentage of prosaccades in the antisaccade task suggest that our patient has a frontal cortical deficit in addition to the more usual cerebellar and basal ganglia deficits found in SPS. The midflight correction to slow saccades provides further evidence for an intrasaccadic feedback mechanism in the generation of saccades (Zee, 1976).

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Keywords: Paraneoplastic syndromes, Higher Visual Cortical functions, Ocular Motility, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Nystagmus

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Poster 103
POEMS Syndrome as a Rare Cause of Bilateral Optic Disc Edema

Kevin Sitko[1]

[1]*University of New Mexico, Albuquerque, New Mexico, USA*

Introduction:
POEMS syndrome is a rare paraneoplastic condition that occurs in the context of a plasma cell neoplasm. Although the acronym stands for Polyneuropathy Organomegaly -Endocrinopathy Monoclonal plasma cell disorder and -Skin changes, all features are not always seen nor necessary to make the diagnosis. "Papilledema" is a minor diagnostic criterion. Controversy exists as to whether the optic disc swelling is secondary to elevated intracranial pressure or mediated by increased vascular permeability in the context of elevated VEGF levels.

Methods:
Case summary with OCT findings and review of the literature.

Results:
A 76-year-old woman experienced a constellation of symptoms including progressive lower extremity pain, decreased sensation, difficulty ambulating, chronic diarrhea, anasarca, dyspnea, and a violaceous rash of her trunk and extremities. An eye care provider noted bilateral disc swelling which prompted an MRI of her brain and MRV, which were unremarkable. Perimetry was initially normal. Lumbar puncture showed normal opening pressure and only elevated protein in the CSF. At presentation visual acuities were 20/50 OD and 20/40 OS, without an RAPD. Funduscopic examination revealed diffuse disc swelling in each eye with scattered peripapillary hemorrhages and retinal whitening. Retinal nerve fiber layers were diffusely swollen as measured by OCT and raster line scans showed a downward angulation of the peripapillary RPE, suggestive of non-ICP dependent disc swelling. VEGF level was elevated at 258 pg/ml and SPEP revealed a lambda M-component, both consistent with POEMS.

Conclusions:
POEMS syndrome is a rare condition but should be considered in atypical cases of bilateral optic disc edema without dysfunction with normal opening pressure on LP. Knowledge of the systemic findings and appropriate testing is necessary to make the diagnosis. This case provides anecdotal evidence based on both multiple LP findings and OCT of optic disc and RPE morphology that intracranial hypertension is not the mediating force for disc swelling.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy, Paraneoplastic syndromes

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Poster 104
Kearns-Sayre Syndrome at Seventy; an Update in the Era of Personalized Genomics

Obada Subei[1], Howard Chang[1], Linda Hasdasri[2]

[1]Michigan State University, East Lansing, Michigan, USA, [2]Mayo Clinic, Rochester, Minnesota, USA

Introduction:
We report the oldest onset of Kearns-Sayre Syndrome (KSS) to date at age seventy, utilizing the latest genetic sequencing technology.

Methods:
A 76-year-old female presented with bilateral ophthalmoplegia, ptosis, and dyschromatopsia. She was investigated for myasthenia, had negative antibody titers and a single-fiber EMG indicating increased jitter and blocking. An electroretinogram showed diminished cone function with preserved rod function bilaterally. A quadriceps muscle biopsy showed only a few ragged red fibers (RRF) normally found in her age. The patient's entire mitochondrial genome was sequenced, confirming the diagnosis of KSS. Interestingly, the criteria defining KSS includes an age of onset younger than 20 years [1]. Paradoxically, the largest single institution review of 35 KSS cases in 2014 showed that 20% had an age of symptom onset older than 20, with a range between 4 to 40 [2]. Mitochondrial myopathies including KSS characteristically have many RRF on muscle histopathology and are considered a confirmatory finding of the disease process [3]. Precedently, a 5 kb mitochondrial deletion has been probed for in patients with KSS via traditional PCR sequencing [4]. With the advent of Next Generation Sequencing (NGS) technology, we are now able to sequence entire genomes versus targeted strands, with a thousand-fold increased efficiency allowing exact coordinates identification at a lower cost, which has allowed us to confirm our patient's diagnosis [5].

Results:
KSS diagnosis.

Conclusions:
Kearns-Sayre Syndrome consists of progressive external ophthalmoplegia, cone dysfunction, and a mitochondrial DNA deletion known as the "common deletion" with coordinates between nucleotides 8482-13460. Cases clinically suspicious of KSS with age of onset later than 20 years old should not be excluded from the diagnosis in light of most recent data. NGS technology facilitates affordable personalized genomics. We encourage clinicians to utilize the emerging technology in confirming the diagnosis of clinically suspicious KSS cases and other mitochondrial DNA diseases.

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Keywords: Genetic Disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility

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Grant Support: None.

Poster 105
Getting a HaNDL on Papilledema

Aimee Szewka[1], Carrie Grouse[1]

[1]Rush University Medical Center, Chicago, Illinois, USA

Introduction:
We describe a case of a patient presenting to an academic institution with recurrent episodes of headache, aphasia and neurologic symptoms who was diagnosed with HaNDL(headaches, neurologic deficits and CSF lymphocytosis) and noted to have papilledema. Literature on the subject is reviewed to increase awareness of this issue and the comorbidities that could complicate the syndrome.

Methods:
A 34 year old man without significant past medical history presents with recurrent episodes of headache, acute aphasia and right hand paresthesia. No acute stroke was seen on MRI brain and CT angiogram was completely unremarkable. CSF evaluation revealed opening pressure of 33cm H_2O, protein of 188, and lymphocytic pleocytosis with 115 WBCs. EEG showed slowing but no epileptiform activity and MRI showed asymmetry of the susceptibility of vessels along the right cerebral sulci of uncertain significance. He presented a total of 4 times over 2 months with acute aphasia, headache, and agitation, each episode resolving over 24 hours. Given negative workup for other causes, HaNDL syndrome was diagnosed. He has had no further episodes since that time.

Results:
During his 3rd admission, routine funduscopic evaluation revealed Grade 2 papilledema. Visual acuity was 20/20 in both eyes and Humphrey Visual Fields were full. He was closely monitored for improvement and papilledema resolved at his 2 month follow visit without any visual complications.

Conclusions:
This is an illustrative case of an important neuro-ophthalmologic manifestation seen in a rare but important neurologic disease felt to have an infectious or autoimmune etiology. It is suspected that the elevated CSF protein is the cause for increased intracranial pressure and hence, papilledema. Given risk of vision loss in the setting of papilledema, this could cause permanent morbidity in an otherwise “benign” and self-limited syndrome and should be assessed in all patients with suspected HaNDL syndrome.

References: None.

Keywords: High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 106
Bilateral Papilledema as Initial Presentation of Subarachnoid Neurocysticercosis

Aubrey Tirpack[1], Geetha Athappilly[2]

[1]Tufts Medical Center, Boston, Massachusetts, USA, [2]Lahey Medical Center, Burlington, Massachusetts, USA

Introduction:
Neurocysticercosis (NCC), caused by larval cysts of the tapeworm Taenia solium, is the most common helminthic infection of the central nervous system worldwide. NCC can lead to increased intracranial pressure presenting with the nonspecific symptoms of headache and vision change.

Methods:
Retrospective case report.

Results:
A previously healthy 39-year-old male, with history of recent travel to Mexico, presented to the ophthalmology clinic with a three-month history of headaches and blurred vision. Exam revealed a best corrected visual acuity (BCVA) of 20/70 OD and 20/25 OS with decreased color vision OD. Fundus examination showed bilateral pallid optic disc edema. Visual fields demonstrated bilateral blind spot enlargement and dense peripheral field loss. MRI/MRV was significant for ventricular prominence with low-lying cerebellar tonsils. Subsequent lumbar puncture confirmed an elevated opening pressure of 37cm/H2O. CSF analysis revealed a leukocytosis with eosinophilic predominance. Repeat MRI with FIESTA (fast imaging employing steady state acquisition) sequence showed small cysts in the subarachnoid space, consistent with a diagnosis of neurocysticercosis. CSF Cysticercosis IgG antibody subsequently returned positive. The patient was started on albendazole, dexamethasone, and acetazolamide with subjective improvement in symptoms. Repeat imaging seven weeks after initial presentation showed interval decrease in size of the subarachnoid cysts. Repeat ophthalmic exam demonstrated decreased optic disc edema, improved color vision, and a BCVA of 20/40 OD and 20/20 OS.

Conclusions:
This report describes a unique case of bilateral papilledema as the initial presenting sign of subarachnoid neurocysticercosis. Though once considered a disease of developing countries, growing travel and immigration have led to an increasing incidence in the United States. In this case, a high clinical suspicion for occult disease was required given the absence of characteristic cysts on initial imaging studies. Healthcare providers must be diligent to consider NCC in order to facilitate early diagnosis, prompt initiation of treatment, and improved clinical outcomes.

References: None.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

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Poster 107
Hodgkin's Lymphoma Masquerading As Intermediate Uveitis And Bilateral Optic Disc Edema

Mindy Wang[1], Fouad El-Sayyad[1], Hazem Samy[1]

[1]*University of Florida, Gainesville, Florida, USA*

Introduction:
While previous case reports have documented Hodgkin's lymphoma patients to have granulomatous posterior uveitis, periphlebitis, focal chorioretinitis, and vitritis, our case uniquely presents with bilateral optic disc edema and intermediate uveitis in addition to retinal vasculitis on intravenous fluorescein angiography.

Methods:
A 55 year old patient presents with complaints of floaters in the left eye and blurry vision. She was found to have bilateral disc edema and intermediate uveitis in the left eye. She also had retinal vasculitis on intravenous fluorescein angiography. Following a comprehensive work-up, her axillary lymph node excisional biopsy showed classical Hodgkin Lymphoma of mixed cellularity type, diagnosing her with stage 3 Hodgkin's disease. She was started on the ABVD chemotherapy regimen and has been in remission following its completion. Her intermediate uveitis and bilateral disc edema resolved following chemotherapy treatment.

Results:
Hodgkin's lymphoma can present with intermediate uveitis and bilateral optic disc edema. These ocular findings can resolve following appropriate treatment of Hodgkin's lymphoma.

Conclusions:
It is essential to consider that Hodgkin's lymphoma may initially present with ocular impairment, and that one should have a high index of suspicion to promptly diagnose and treat the masquerading syndrome. Hodgkin's lymphoma should be considered in the differential diagnosis when a patient presents with unexplained disc edema with uveitis.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 108
Hunting for an Answer

Ashley Webb[1], Eric Crowell[1], Lin Zhang[2], Emilio Supsupin[3], Ore-ofe Adesina[1]

[1]Ruiz Department of Ophthalmology and Visual Science, McGovern Medical School, Houston, Texas, USA, [2]Department of Pathology and Laboratory Medicine, McGovern Medical School, Houston, Texas, USA, [3]Department of Diagnostic and Interventional Imaging, McGovern Medical School, Houston, Texas, USA

Introduction:
We describe a patient with Burkitt lymphoma metastatic to the cavernous sinus initially diagnosed as Tolosa-Hunt syndrome.

Methods:
A 31-year-old Hispanic man with a history of HIV and hypertension presented with 1 week of diplopia, ptosis, and numbness in the V1 distribution. Pupils were equal and reactive without RAPD. Vision was 20/25 OD and 20/20 OS with normal IOPs and full confrontational visual fields bilaterally. He had complete external ophthalmoplegia OD and full motility OS. MRI brain with and without contrast showed a non-enhancing, low T2 signal lesion within the right cavernous sinus without other intracranial abnormalities. CD4 count was 110 with a normal CBC. He was started on broad-spectrum antibiotics and antifungals without improvement. Full workup for infectious and inflammatory causes was performed with no identifiable cause. A presumed diagnosis of Tolosa-Hunt syndrome was made. He was started on high dose PO steroids with improvement in his pain, but without improvement in EOM. He was discharged home in stable condition, but returned to the hospital 3 days later with severe abdominal pain. CT abdomen showed perforated ileitis with aneurysmal dilation of the ileum and marked wall thickening concerning for mass lesion. A diagnostic procedure was performed.

Results:
Biopsy of the ileum was consistent with Burkitt lymphoma. PET-CT showed avid FDG uptake in both the ileum and cavernous sinus, consistent with metastatic disease. He regained full motility OD after receiving several cycles of chemotherapy with dose-adjusted cyclophosphamide, doxorubicin, vincristine, and prednisone.

Conclusions:
This is a rare case of Burkitt lymphoma initially presenting with ophthalmologic symptoms. Diagnosis was complicated by the presence of HIV, which masked the B symptoms characteristic of the disease. Although initial presentation of Burkitt lymphoma in an extranodal site is uncommon, it is one of the AIDS-defining malignancies and should be included in the differential for any unidentified mass.

References: Bao, Yang-Yang, et al. "Case Report Diffuse large B-cell lymphoma of the maxillary sinus in a patient with acquired immunodeficiency syndrome." Int J Clin Exp Med 9.6 (2016): 12227-12232. Boukobza, Monique, and Jean-Philippe Brouland. "Burkitt's lymphoma with bilateral cavernous sinus involvement: A Case Report." JMED Research (2016). Huisman, T.A.G.M., Tschirch, F., Schneider, J.F.L. et al. "Burkitt's lymphoma with bilateral cavernous sinus and mediastinal involvement in a child." Pediatr Radiol (2003) 33: 719. Levy, J., A. Kratz, and T. Lifshitz. "Burkitt's lymphoma presenting as oculomotor palsy in an hiv-positive patient." European journal of ophthalmology 16.1 (2006): 186. Tanaka, Yuji, et al. "Burkitt lymphoma presenting rapid progression from unilateral to bilateral cavernous sinus syndrome as the initial symptom." Neurology and Clinical Neuroscience 2.6 (2014): 204-206.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Ocular Motility

Financial Disclosures: The authors had no disclosures.

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Poster 109

Severe Vision Loss with Optic Atrophy from IgG4-Related Hypertrophic Pachymeningitis with Steroid-Sparing Response to Rituximab

Emily Wright[1], Kevin Sitko[2]

[1]Tufts Medical Center / New England Eye Center, Boston, Massachusetts, USA, [2]University of New Mexico, Albuquerque, New Mexico, USA

Introduction:
IgG4-related disease is a multisystem condition originally described in the context of autoimmune pancreatitis which can have neuro-ophthalmologic manifestations. These include hypertrophic pachymeningitis, hypophysitis, and orbital inflammation. Hypertrophic pachymeningitis can occur in the context of multiple conditions, infectious and inflammatory, and can result in severe vision loss when it involves the optic nerves.

Methods:
Case summary and review of the literature.

Results:
A 60-year-old, Hispanic man with hypertension initially presented with chronic headache of one-year duration and worsening vision in his left eye more than his right. Brain MRI showed dural thickening interpreted as "intracranial hypotension." Initial ophthalmology visit revealed no light perception OD and 20/80 OS with positive right RAPD. Dilated funduscopic examination revealed optic atrophy OD and a normal optic disc OS. ESR and CRP were elevated at 58 mm/hr and 13.1 mg/dl. Temporal artery biopsy was negative. Lumbar puncture showed normal opening pressure of 18.5 cm of water with lymphocytic pleocytosis (11 nucleated cells) and elevated protein at 172 mg/dl. IgG index was elevated at 1.33 and 2 oligoclonal bands were seen. Serologic and CSF microbiologic testing was all negative except for positive Quantiferon gold. AFB CSF cultures were negative. Rheumatologic testing was negative including ACE level and serum IgG4 which measured 22 mg/dL. Left eye vision improved to 20/25 with steroids and subsequently decreased to 20/40 with worsening headache upon steroid taper. Dural biopsy was performed and showed lymphoplasmocytic chronic inflammation without granulomata. Immunostaining for IgG4-specific plasma cells estimated at 20%. Rituximab treatment was commenced with allowance for tapering of steroids to 5mg daily without clinical deterioration.

Conclusions:
IgG4-related hypertrophic pachymeningitis is a rare cause of severe vision loss. Diagnosis requires a high index of suspicion and pathologic meningeal assessment. Use of rituximab in this condition is supported by the literature and proved highly effective in this case.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy, Neuroimaging

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Grant Support: None.

Poster 110
A Case of Third Nerve Palsy following Infliximab Treatment

Moira Altszul[1]

[1]*Hospital Italiano de Buenos Aires, Buenos Aires, Argentina*

Introduction:
Infliximab, a monoclonal anti-TNF α antibody prescribed for treatment of inflammatory and autoimmune diseases (1), may cause neurological adverse reactions, including demyelinating conditions such as multiple sclerosis, optic neuritis, mononeuritis multiplex, Guillain Barré and Miller Fisher syndromes (2, 1, 3, 4, 5). Third nerve palsy with cisternal enhancement with gadolinium on MRI has been reported (6). Whether anti-TNF α blockers unmask preexisting or induces de novo demyelination was addressed by a prospective study. New demyelinating events, which improved with cessation of TNF alfa antagonists and re-emerged with reintroduction of them, supports anti-TNF alfa evoked pathophysiology. Incidence is controversial, some authors conclude it isn´t clear if TNF alfa antagonists increase demyelinating diseases, while others found 30% increased risk. MRI findings without typical demyelination symptoms is recognized as radiologically isolated syndrome (RIS) (2). If demyelination emerges during treatment, discontinuation of anti TNF alfa is mandatory, with close clinical and MRI follow-up (1) .

Methods:
Single Case Report

Results:
A 43 year-old man presented with permanent diplopia. Due to psoriasis, he had been treated with infliximab during 6 months.Examination revealed bilateral ptosis, limited upgaze in both eyes, and adduction restriction in the left eye. MRI showed a hiperintense image in central midbrain in T2 and Flair, hipointense in T1 with anular enhancement with gadolinium. He also presented a left frontal cortical and subcortical lesion, of similar behavior. Infectious and oncohematologic diseases were excluded by serology, lumbar puncture and brain biopsy. Bilateral third nerve palsy resolved 4 months after discontinuation of infliximab. Follow-up MRI showed no new lesions, edema or enhancement.

Conclusions:
There is potential association between infliximab and demyelinating events. Before treatment, subclinical preexisting demyelinating diseases should be excluded by neurological examination, MRI, and electrophysiological tests. Follow-up is essential. Anti TNF alfa should be immediately discontinued if demyelination occurs.

References: 1. Andreadou E et al. Demyelinating disease following anti-TNFa treatment: a causal or coincidental association? Report of four cases and review of the literature. Case Rep Neurol Med 2013. 2013:671935. 2. Kaltsonoudis E et al. Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Research and Therapy 2014; 16: 1-7. 3. Faillace C et al. Optic neuritis after infliximab therapy. Rheumatol Int 2013; 33: 1101-1103. 4. Cocito D et al. Multifocal motor neuropathy during treatment with infliximab. J Peripher Nerv Syst 2005; 10:386-387. 5. Shin IS et al. Guillán-Barré and Miller Fisher syndromes occurring with tumour necrosis factor alpha antagonist therapy. Arthritis Rheum 2006; 54: 1429-1434. 6. Farukhi F et al. Infliximab-associated third nerve palsy. Arch Ophthalmol 2006 jul. 124(7): 1055-7.

Keywords: Demeylinating disease, Ocular Motility, Adult strabismus with a focus on diplopia, Neuroimaging, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 111
Bilateral Internuclear Ophthalmoplegia as a First Presentation of Neuro-Sweet Syndrome.

Supanut Apinyawasisuk[1], Supharat Jariyakosol[2], Sanchawan Wittayakornrerk[3], Montida Veeravigrom[3], Therdpong Tempark[3]

[1]King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [2]Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3]Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Introduction:
To describe a patient with Neuro-Sweet syndrome presented with bilateral internuclear ophthalmoplegia (INO)

Methods:
Case report and a literature review

Results:
A 3-year-old girl was referred to Neuro-ophthalmologist for eye movement evaluation. She presented with erythematous edematous papules and plaques at face, trunk, and lower extremities for 8 months. Skin biopsy showed prominent interstitial neutrophilic infiltrate, perivascular lymphohistiocytic infiltrate in the upper dermis consistent with the diagnosis of Sweet syndrome. Topical and oral corticosteroid was administered and her symptom was primarily responded to the treatment. After cessation of oral corticosteroid for 3 months, the new skin lesions developed at cheek and forehead. Oral dapsone was additionally prescribed combining with re-challenged oral corticosteroid (1 mg/kg/day). Two weeks after administration of oral dapsone, she developed a new-onset horizontal diplopia and limited eye movement noticed by her grandmother. She reported no eye pain, headache, and visual loss. On examination, visual acuity was 20/30 in both eyes, anterior and posterior segment were normal. She has 70 prism diopter exotropia at distance and 50 prism diopter exotropia at near. There was a marked limited adduction with abducting nystagmus on both eyes. Convergence was partially involved. MRI of the brain and cerebrospinal fluid analysis were within normal limits. She was diagnosed as bilateral internuclear ophthalmoplegia as a first presentation of Neuro-Sweet syndrome. Intravenous pulse methylprednisolone was administered, follow with oral prednisolone and dapsone. Three months after the treatment, she had a flick exotropia with dramatic improvement of adduction deficit.

Conclusions:
Neuro-Sweet syndrome is a very rare condition affecting central nervous system in pediatric patient with Sweet syndrome. Common presentations include encephalitis and meningitis involving brainstem. Eye movement abnormality has been limitedly reported. Our study describes the first case of Neuro-Sweet syndrome with bilateral internuclear ophthalmoplegia.

References: None.

Keywords: Ocular Motility, Pediatric neuro-ophthalmology, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 112
Delayed Onset Cranial Nerve Palsies After Endovascular Coil Emboization of Direct Carotid-Cavernous Fistulas

Alaa Bou Ghannam[1], Prem Subramanian[1]

[1]*University of Colorado School of Medicine, Aurora, Colorado, USA*

Introduction:
Late recurrence of carotid-cavernous fistula with associated visual symptoms, including diplopia, is quite uncommon and raises concern for new or recurrent fistula formation. However, in the absence of a new or recurrent fistula, the mechanism by which diplopia recurs is not clear.

Methods:
Case 1: A 31-year-old previously healthy male was in a motorcycle accident. One week later he developed diplopia and right eye proptosis with redness. Direct right carotid-cavernous fistula was found and treated by coil embolization. Diplopia resolved over 1 month. Five years later, the patient developed new diplopia and had combined right 3rd and 6th nerve palsies. Angiography confirmed no recurrence of the fistula. When symptoms did not abate, he underwent successful strabismus surgery. Case 2: A previously healthy 20-year-old male was thrown from a vehicle and suffered closed head trauma. Several weeks later, he developed left eye swelling and proptosis, was diagnosed with left direct C-C fistula, and had coil embolization with complete regression of eye findings. He developed new diplopia and mild left eye ptosis five years later and was found to have partial left 3rd and 6th nerve palsies. Angiography did not show any fistula recurrence, and the patient underwent strabismus surgery with postoperative symptom resolution.

Results:
N/A

Conclusions:
The cause of delayed onset diplopia after successful coil embolization is unknown. Theories include late compression of cranial nerves within the cavernous sinus due to coil mass that can cause chronic ischemia, delayed inflammation due to a thrombophilic nidus created by the fistula, or permanent injury to the cranial nerves that manifest later due to decompensated strabismus. Patients should be made aware of the potential for late-onset double vision.

References: None.

Keywords: Adult strabismus with a focus on diplopia, Interventional neuroradiology, Orbit

Financial Disclosures: The authors had no disclosures.

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Poster 113
Prolonged Patching: A Diagnostic Tool for Intermittent Diplopia

Marc Bouffard[1], Nurhan Torun[2]

[1]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA, [2]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Introduction:
Decompensated phoria is a common cause of intermittent diplopia without associated symptoms. Conventional wisdom suggests that adults presenting with intermittent diplopia due to decompensation of a phoria will have an abnormal alternate cover test at the time of examination. There are no data in the literature to suggest that prolonged patching may be required in adults to elicit a phoria.

Methods:
We reviewed 3 cases of adults who presented to our institution with intermittent diplopia and were found to have a phoria only after prolonged patching.

Results:
Three patients, aged 51-67 years, reported intermittent diplopia as an isolated symptom and were found to have an explanatory phoria only after prolonged patching. The onset of symptoms prior to evaluation ranged from several months to 8 years. The duration of each episode of diplopia ranged from 15 seconds to 1 hour. No patients were on sedating or neurotoxic medications. No explanatory deficit was seen on the initial sensorimotor examination. After 30 to 45 minutes of patching, patient 1 developed a right hypertropia of 2 prism diopters (PD) and an exotropia of 1 PD; patients 2 and 3 were each found to have left hyperphoria measuring 2 PD. Work-up in one patient, including MRI/MRA brain, ESR, and acetylcholine-receptor antibodies, had been negative years previously.

Conclusions:
The presence of a phoria cannot be definitively ruled out in an adult without prolonged patching. Given that fatigue is a common trigger for decompensation of a phoria, it is not unusual for these patients to be suspected of having ocular myasthenia and, on occasion, treated as such. Thus we recommend prolonged patching to confirm a provisional diagnosis of decompensated phoria in patients where there is very low suspicion for other causes of intermittent diplopia such as transient ischemia, giant cell arteritis, or myasthenia based on history and exam.

References: None.

Keywords: Ocular Motility, Adult strabismus with a focus on diplopia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 114
A Case of Permanent CN VI Palsy Following Carotid-Cavernous Fistula Embolization

Jana Bregman[1], Vivian Rismondo[2]

[1]University of Maryland, Baltimore, Maryland, USA, [2]Greater Baltimore Medical Center, Baltimore, Maryland, USA

Introduction:
Cranial nerve (CN) palsy following carotid-cavernous fistula (CCF) embolization is a rare complication that is not frequently described in the literature. Diplopia secondary to CN palsies that precede intervention is the more common clinical finding. Only a handful of cases of ophthalmoplegia after CCF embolization have been described. In a majority of these cases the CN palsy, and therefore the patient's diplopia, are transient.

Methods:
We present a case of prolonged abducens nerve (CN VI) palsy in a 72 year old woman after embolization of a dural CCF. The patient's unique clinical presentation contributes to our current understanding of the risks associated with CCF treatment.

Results:
The patient initially presented with right eye pain, injection, and a sensation of hearing her own heartbeat. Brain MRI revealed dural CCF and she underwent embolization of the CCF under radiologic guidance. One day following the procedure, she represented with acute onset diplopia and was diagnosed with a CN VI palsy resulting in 55 prism diopters of esotropia in primary gaze. Repeat imaging confirmed that there was no evidence of ischemic stroke, ventricular enlargement to suggest elevated intracranial pressure, or new cavernous sinus lesion. Her ophthalmoplegia was determined to be a complication of the embolization procedure. Unfortunately, expected resolution of the palsy did not occur and she was ultimately schedule for strabismus surgery to help relieve the persistent diplopia.

Conclusions:
Our patient suffered a rare complication of CCF embolization. While intervention for CCF is imperative to help reduce associated morbidity, CN palsy is not a well known complication. When described, CN deficits typically resolve over weeks to months. However, as is demonstrated here, CN VI palsy may persist as a permanent deficit requiring prisms or surgery to reduce diplopia. Therefore, CN palsy a potential temporary or permanent complication should be routinely included during the procedure consent.

References: Kim, Kim, Suh, Kim, Lee et al. Results of transvenous embolization of cavernous dural arteriovenous fistula: a single center experience with emphasis on complications and management, AJNR, 27, 2078, 2006. Kurata, Takano, Tokiwa, Miyasaka, Yada et al. Spontaneous carotid cavernous fistula presenting only with cranial nerve palsies, AJNR, 14, 1097, 1993. Leonard, Moseley, and Sanders. Ophthalmoplegia in carotid cavernous sinus fistula, BJO, 68, 128, 1984. Nishnino, Ito, Hasegawa, Kikuchi, Shimbo et al, Cranial nerve palsy following transvenous embolization for a cavernous sinus dural arteriovenous fistula: associated with the volume and location of detachable coils, J. Neurosurgery, 109, 208, 2008. Tjoumakaris, Jabbour and Rosenwasser, Neuroendovascular management of carotid cavernous fistulae, Neurosurgery Clinics of North America, 20, 447, 2009. Yoshida, Melake, Oishi, Yamamoto and Arai, Transvenous embolization of dural carotid cavernous fistulas: a serious of 44 consecutive patients, AJNR, 31, 651, 2010.

Keywords: Adult strabismus with a focus on diplopia, Interventional neuroradiology, Ocular Motility, Vascular disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 115

Involuntary multidirectional saccades- myoclonus-ataxia: an opsoclonus-myoclonus-ataxia syndrome variant and a new pattern of saccadic intrusion

François Evoy[1], Elisabeth Fortin[1]

[1]*Université de Sherbrooke, Sherbrooke, Canada*

Introduction:
Opsoclonus are involuntary, arrhythmic, chaotic, multidirectional saccades without intersaccadic intervals. Opsoclonus-myoclonus-ataxia syndrome (OMS) consist of opsoclonus, myoclonic jerks of the limbs and trunk, cerebellar ataxia and encephalopathy. The pathophysiology is not clearly understood. The two plausible hypotheses are: 1) a dysfunction of omnipause cells or 2) a malfunction of Purkinje cells and their inhibitory projection to the fastigial nucleus. In studies, inactivation of fastigial nucleus produces saccadic overshoot dysmetria with intervals between saccades

Methods:
We present a healthy 25-year-old female who came to the hospital because of one-week progression of binocular diplopia and gait unsteadiness. At the initial neurological examination, the patient had mild dysarthria, severe ataxia and gazed-evoked nystagmus in all directions. Two weeks later, she developed myoclonus and multidirectional saccades with intersaccadic interval without opsoclonus or flutter despite prolonged ENG monitoring.1 Investigations to exclude the presence of tumor, infection or systemic diseases came back all negative. Final diagnosis was an idiopathic OMS despite the absence of opsoclonus. She was treated with intravenous immunoglobulin for a total of 8 days and improved progressively. Few years after this first case, we documented the same kind of abnormal ocular movements in a classical case of OMS showing both opsoclonus and involuntary multidirectional saccades confirming the links.

Results:
This is the first case reporting involuntary multidirectional saccades with intersaccadic intervals in a patient with OMS. This saccadic intrusions are similar to macro square- wave jerks but with a multidirectional components. This case supports the second hypotheses that opsoclonus may be caused by disinhibition of the fastigial nucleus. The report of a clinical case showing both opsoclonus and involuntary multidirectional saccades reinforced this hypothesis.

Conclusions:
1 Videos of the clinical cases are available

References: 1. Sharpe JA, Fletcher WA. Saccadic intrusions and oscillations. Can J Neurol Sci 1984; 11:426–433. 2. Wong AM, Musallam S, Tomlinson RD, et al. Opsoclonus in three dimensions: oculographic, neuropathologic and modelling correlates. J Neurol Sci 2001; 189:71–81. 3. Helmchen C, Rambold H, Sprenger A, Erdmann C, Binkofski F. Cerebellar activation in opsoclonus: an fMRI study, Neurology, 2003; 12:412-415. 4. Robinson FR, Straube A, Fuchs AF. Role of the caudal fastigial nucleus in saccadic generation. II Effects of muscimol inactivation. J Neurophysiol 1993; 70:1741–1758. 5. Ramat S, Leigh RJ, Zee DS, Optican LM, What clinical disorders tell us about the neural control of saccadic eye movements. Brain 2007; 130:10-35.

Keywords: Ocular Motility, Neuro-ophth & infectious disease (eg, AIDS, prion), Paraneoplastic syndromes

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 116
Continuous Convergence Retraction Nystagmus in a Patient with Severe Hydrocephalia in Neurocysticercosis

Graciela Garcia-Briones[1]

[1]*Hospital de Nuestra Señora de la Luz, Mexico, Mexico*

Introduction:
To describe neuro-ophthalmic eye movement disorders occurring in Neurocysticercosis Case report. A 55-year-old woman presented with recent onset of unsteady gait. Physical examination showed continuous convergence-retraction nystagmus . (video). Head tilt to the righ, and right lateropulsion was evident during walking. Pupils were normal. She underwent a brain MRI that revealed severe hydrocephalia and Paquimeningitis due to neurocysticercosis, and a ventriculoperitoneal shunt.

Methods:
After treatment with albendazol and betametasone followed by oral prednisone, she made good recovery in 2 months, she remained with ocular tilt reaction (OTR) with skew deviation, excyclotorsion of the left eye and slight right head tilt (video). The complete neuro ophthalmological examination will be shown in the poster

Results:
none

Conclusions:
Continuous convergence-retraction nystagmus is an uncommon presentation of neurocysticercosis. Probably a disorder of vergence rather than of opposing adducting saccades. Differential diagnosis must be made with oclulopalatal termor, observing abnormal palatal movement. · These clinical findings may be related to the damage of supranuclear fibers having an inhibitory effect on the convergence neurons or the divergence neurons in midbrain, which could result in a sustained discharge of medial rectus neurons.1,2 · Continuous convergence nystagmus was attributed to the involvement of the rostral interstitial medial longitudinal fasciculus (riMLF), the interstitial nucleus of Cajal (INC) and the nucleus of the posterior commissure system.

References: 1. See-saw nystagmus, convergence-retraction nystagmus and contraversive ocular tilt reaction from a paramedian thalamomesencefhalic infarct. Man BL, Fu YP. BMJ Case Reports 2014; doi:10.1136/bcr-2014-206851 2. Rambold H1, Kömpf D, Helmchen C Convergence retraction nystagmus: a disorder of vergence? Ann Neurol. 2001 Nov;50(5):677-81.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Nystagmus, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 117
Cavernous carotid fistula masquerading as microvascular ischemic cranial nerve VI palsy

Adaku Idika[1], Andrea Stahulak[1], Ryan Walsh[1]

[1]*Medical College of Wisconsin, Milwaukee, Wisconsin, USA*

Introduction:
An abducens palsy which spontaneously resolves within months is typically microvascular ischemic in etiology. We present 2 cases of abducens palsy that initially followed this expected course, but in whom the palsies subsequently recurred and cavernous carotid fistulas were diagnosed.

Methods:
Case Report

Results:
Patient 1: 62-year-old male with a remote history of traumatic brain injury and right orbital trauma who presented with a right cranial nerve VI palsy in November 2015. He had no significant vascular risk factors. Brain MRI and MRA head/neck were normal. The diplopia resolved January 2015. In subsequent follow-up, he had recurrent right abducens palsy with periorbital edema, injection, and increased IOP OD. Cerebral angiography confirmed the presence of a low flow carotid cavernous fistula. The patient was treated with coil embolization of the fistula with resolution of all ocular symptoms. Patient 2: 40-year-old male with no previous trauma presented with a left cranial nerve VI palsy April 2016. Testing revealed HbA1C 11.4%, BP 148/51, BMI 36.8. He was diagnosed with microvascular sixth nerve palsy. The diabetes and hypertension were treated and within 1 month his vision normalized. July 2016, he presented with recurrent abducens palsy, elevated IOP, conjunctival injection, and ptosis OS. Cerebral angiography confirmed a low flow carotid cavernous sinus fistula that was treated by coil embolization. All symptoms resolved 1 week after treatment and have not recurred.

Conclusions:
In patients with abducens palsy suspected of being microvascular ischemic in etiology, but in whom the palsy recurs after resolution, one should consider a cavernous carotid fistula. This is especially true in patients without the typical microvascular risk factors, or in patients with a prior history of head trauma. In such patients we would recommend continued clinical monitoring for a period beyond the point of symptomatic resolution to monitor for recurrence or the development of orbital signs.

References: None.

Keywords: Ocular Motility, Neuroimaging, Orbit

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 118
Bilateral oculomotor nerve palsy secondary to diffuse large B-cell lymphoma

Sachin Kedar[1], Krishnamourya Galla[1], Sara Bares[2], Michael Punsoni[3], Kirk Foster[4], Alexander Braun[4], Jason Helvey[5]

[1]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]Department of Pathology/Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, USA, [4]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, USA, [5]Department of Radiology, University of Nebraska Medical Center, Omaha, Nebraska, USA

Introduction:
We describe a rare presentation of diffuse large B-cell lymphoma with bilateral sequential 3rd nerve palsy.

Methods:
A 56-year-old Sudanese male with HIV well-controlled on cART (CD4=368/22.6%; HIV RNA <20 copies/mL) returned from Ethiopia with fevers, chills, myalgia and a painful pupil-sparing left 3rd nerve palsy. MRI showed left 3rd nerve cisternal enhancement. Serum PCR was positive for P. falciparum and blood smears showed gametocytes. CSF showed lymphocytic pleocytosis. He was treated with antimalarials for presumed Plasmodium falciparum malaria associated 3rd nerve palsy. Two weeks later he returned with painful right 3rd nerve palsy, facial and palatal anesthesia. MRI brain showed new right CN3 cisternal enhancement and multi-focal T2 signal abnormality. CSF showed lymphocytic pleocytosis without atypical cells. Low titers of EBV DNA was seen in serum and CSF. He had elevated anticardiolipin antibodies. Brain biopsy was deferred due to difficult lesion location. He was treated with high dose steroids for possible post-EBV related vasculitis. Shortly, he developed pneumonia and somnolence. CSF now showed CMV and EBV DNA. CD4 counts had declined to 59 (13.7%) but HIV RNA remained undetectable. MRI brain showed interval progression of multifocal lesions. He developed a pulmonary embolus and expired from multi-organ failure.

Results:
Autopsy revealed diffuse large B-cell lymphoma (DLBCL) involving cerebral cortical and subcortical structures, cerebellum, and brainstem with atypical cells positive for CD79a and hemorrhagic pericarditis with DLBCL.

Conclusions:
DLBCL is the most common HIV-associated lymphoma with a 650-fold increased risk in HIV/AIDS. EBV, an oncogenic virus, is found in 40% of all HIV-lymphoma. Although low CD4 increases risk of HIV-related lymphoma, DLBCL may occur at higher CD4 counts. CNS lymphoma presenting as isolated oculomotor palsy is extremely rare with fewer than 20 reported cases in literature.

References: None.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 120
SIXTH NERVE PALSY FOLLOWING EPIDURAL ANESTHESIA FOR C-SECTION

Iris Krashin-Bichler[1], Adi Brenner[1]

[1]Tel Aviv Medical Center, Tel Aviv, Israel

Introduction:
We describe a rare case of a young woman who presented with severe headache and diplopia a few days after a C-section.

Methods:
Case report and a review of the literature

Results:
We describe a case of a 39 years old woman, with a history of pre-eclampsia and HELLP syndrome during her previous pregnancy. She presented with severe headache followed by horizontal diplopia a few days after giving birth with epidural anesthesia. On exam she was diagnosed with bilateral sixth nerve palsy. Due to her past history the differential diagnosis included a cerebrovascular accident as well as a demyelinating disease and thus she underwent an extensive workup including full coagulation profile and an MRI scan of the brain that revealed diffuse pachymeningeal enhancement. The MRI findings were highly suggestive of intracranial hypotension leading to the diagnosis of dural puncture and CSF leakage. Intracranial hypotension causes the descent of the brain and stretching the sixth nerve along its long course resulting in palsy and diplopia. During a 6 months follow up, her symptoms resolved completely.

Conclusions:
We describe an uncommon case of sixth nerve palsy following epidural anesthesia. The combination of epidural anesthesia, postural headache and acute esotropia should alert to the possibility of the uncommon but benign diagnosis of dural puncture and prevent unnecessary workup.

References: None.

Keywords: Ocular Motility, Adult strabismus with a focus on diplopia, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 121
Bilateral Horizontal Gaze Palsy Caused By Unilateral Midbrain Infarction

Joao Lemos[1], Joana Parra[1], Cristina Duque[1], Cesar Nunes[1], Carla Cecilia[1]

[1]Coimbra University Hospital Center, Coimbra, Portugal

Introduction:
The descending cortical pathways for horizontal saccades are believed to pass through the paramedian midbrain to reach the premotor saccade burst neurons in the contralateral pons, as corroborated by previous reports of unilateral midbrain lesions causing contralateral horizontal gaze palsy. Evidence for the precise anatomical level (midrain versus pons) for their decussation in humans is scarce.

Methods:
We report a case of bilateral horizontal conjugate palsy associated with right third nerve palsy and vertical gaze palsy in a patient with a strictly unilateral midbrain infarct. Video-oculography (VOG), video-head impulse test (vHIT) and brain MRI were performed.

Results:
A previously healthy 40-year-old woman presented with a 2-day history of binocular oblique diplopia. On exam, there was complete ptosis OD, right hypotropia (15D) and exotropia (30D) in mid gaze, and the right pupil was slightly larger than the left (4.5mm OD, 3.5mm OS) and less responsive to light. Passive ductions showed complete or near-complete restriction of both vertical and horizontal eye movements, with the exception of abduction OD (~30% restriction) and adduction OS, which was full. Albeit less restricted, rightward eye movements were markedly slow: on VOG, the average velocity of abducting saccades OD was 40°/s while average velocity of adducting saccades OS was 80°/s. Of note, pupil size remained unchanged during attempted abductions OU. Right torsional saccades were absent. Ocular pursuit on VOG, and vestibulo-ocular reflexes on vHIT displayed similar deficits to saccades. Brain MRI showed a right medial midbrain infarct, of which the cause remained undetected despite extensive investigation. Three months later, bilateral opthalmoparesis completely resolved.

Conclusions:
The occurrence of bilateral horizontal gaze palsy in association with a unilateral midbrain lesion, favours a midbrain level for the decussation of the descending pathways responsible for the execution of horizontal saccades, where crossed and uncrossed fibers may be simultaneously involved.

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Keywords: Adult strabismus with a focus on diplopia, Ocular Motility, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 122
Gaze-Position Dependent Opsoclonus in Post-Concussive Syndrome

Alexandra Lloyd-Smith Sequeira[1], Weiwei Dai[1], John-Ross Rizzo[1], Todd Hudson[1], Ivan Selesnick[1], David Zee[2], Steven Galetta[1], Laura Balcer[1], Janet Rucker[1]

[1]New York University School of Medicine, New York, New York, USA, [2]Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Introduction:
Opsoclonus is characterized by bursts of involuntary, back-to-back saccades without an intersaccadic interval at frequency of 10-25 Hz in horizontal vertical, and torsional planes. Opsoclonus with gaze-directional selectivity has been rarely described.

Methods:
We report a 50 year-old man who sustained a concussion three years prior followed by post-concussive headaches and disequilibrium. Exam revealed very small amplitude oscillations in left gaze that could not be further characterized on clinical exam. Different larger amplitude horizontal oscillations were present with convergence. There were no other posterior fossa signs. Brain MRI was unremarkable.

Results:
Video-oculography demonstrated opsoclonus predominantly in left gaze [median amplitude 5 deg (range <1-11 deg), frequency 24 Hz] and during leftward smooth pursuit, which improved as post-concussive symptoms improved.

Conclusions:
This case demonstrates opsoclonus with eye position selectivity in post-concussive syndrome. Various theories of opsoclonus exist, including lesions of saccade burst, omnipause, or cerebellar fastigial pause neurons which project to brainstem burst neurons. Ultimately, all of these lead to increased excitability in the inherently unstable saccade generators. Burst and omnipause neuron firing rates are not influenced by eye position. The leftward gaze-dependence in our case supports dysfunction of cerebellar dorsal vermis Purkinje cells leading to disinhibition of the fastigial ocular motor nucleus, as vermal pause neurons have gaze-directional selectivity. Vermal pause neurons exhibit a pause of discharge immediately before and during contralateral saccades. Thus, selective dysfunction, possibly related to concussion-related membrane instability, could create an imbalance in burst neuron excitability, resulting in triggering of unidirectional opsoclonus. Further, our patient's saccade system may be inherently prone to oscillations given the presence of larger amplitude horizontal oscillations consistent with 'voluntary flutter', which persisted when leftward opsoclonus improved.

References: None.

Keywords: Nystagmus, Ocular Motility

Financial Disclosures: The authors had no disclosures.

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Poster 123

Disabling Central Positioning Upbeat Nystagmus Associated With High Titers Of Anti-Glutamic Acid Decarboxylase (GAD) Antibodies

Ines Martins[1], Joao Carvalho[1], Argemiro Geraldo[1], Joao Lemos[1]

[1]*Coimbra University Hospital Center, Coimbra, Portugal*

Introduction:
Anti-glutamic acid decarboxylase (GAD) antibodies have been associated with cerebellitis and spontaneous vestibular syndromes. Positioning vestibulopathies on the other hand are usually related to semicircular canal lithiasis, and only rarely have been associated with cerebellitis. Similarly, hyperactive vestibulo-ocular reflexes (VOR) are a relatively rare finding in cerebellitis.

Methods:
We report a case of longstanding disabling positioning upbeat nystagmus associated with the presence of anti-GAD antibodies, markedly responding to immunotherapy.

Results:
A 68-year old female with type 1 diabetes and post-traumatic paraplegia presented with a 2-year history of disabling positioning vertigo in supine position. She also reported vertical diplopia in lateral gaze. Exam revealed upper limb ataxia and flaccid paraplegia. Oculomotor assessment showed spontaneous downbeat nystagmus (sDBN) (slow phase velocity [SPV], 4.3°/s) in light and dark, square wave pulses, alternate skew deviation (abducting eye hypertropic) and 1-minute intense positioning upbeat nystagmus (pUBN) (SPV, 25°/s) every time the patient laid supine. Video head impulse test (vHIT) revealed enhanced gain (up to 1.6) for the anterior and horizontal semicircular canals. Search for occult malignancy, serologies, anti-onconeural antigen panel and brain MRI were unrevealing. Initial treatment with baclofen 2.5mg tid transiently abated pUBN, but subsequent gastric intolerance led to its suspension. High titters of anti-GAD65 antibodies (239 U/mL) detected one month later, prompted treatment with intravenous immunoglobulin 30g/day over 5 days, leading to remarkable clinical improvement: pUBN and sDBN in dark disappeared and upper limb ataxia became milder. vHIT responses slightly decreased, while skew deviation and sDBN in light persisted.

Conclusions:
Anti-GAD-related ataxia may present with disabling positioning upbeat nystagmus. The existence of a hyperactive VOR may be a clue for the presence of a “deafferented” vestibular system lacking its normal cerebellar inhibitory input. Symptomatic and immunological therapies can help to regain cerebellar function.

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Keywords: Nystagmus, Ocular manifestations of vestibular disorders, Vestibular

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 124

Resolution of Downbeat Nystagmus Following Treatment with Topiramate in a Patient with Vestibular Migraine

Stacy Smith[1], Deborah Friedman[1], Shin Beh[1]

[1]UT Southwestern Medical Center, Dallas, Texas, USA

Introduction:

Vestibular migraine is a debilitating disorder associated with dizziness, migrainous features, and headache. Limited data suggest persistent interictal central vestibular dysfunction.(1) Expert opinion and small studies support the use of migraine preventive therapies for symptomatic relief; none have reported resolution of ocular motor abnormalities in these patients.(2,3,4) We report a case of vestibular migraine with downbeat nystagmus (DBN) whose symptoms and DBN improved with topiramate.

Methods:

A 66-year-old woman with chronic migraine headaches managed with topiramate 25 mg twice daily (BID) experienced three months of persistent dizziness (disequilibrium), motion sensitivity, and visual-vestibular mismatch. Vestibular evaluation including binocular infrared video-oculography showed DBN in eccentric horizontal and down gaze. Removal of fixation revealed right beating nystagmus in primary position. Various maneuvers provoked or amplified the DBN and horizontal nystagmus. Saccades, pursuit, fixation, and optokinetic responses were normal. Brain MRI and laboratory investigations were non-contributory.

Results:

Topiramate was increased to 50 mg BID, and her migraine headaches and dizziness improved by Month 2; exam revealed decreased DBN. Topiramate was increased to 75 mg BID and by Month 4, her dizziness resolved; DBN could only be elicited with hyperventilation and during positional testing. By Month 10, on topiramate 75 mg BID, DBN was observed only during positional testing. On follow-up one year later, her dizziness and DBN had resolved completely on topiramate 100 mg BID.

Conclusions:

The DBN and central positional nystagmus observed in our patient indicate a cerebellar localization. While infrequently reported in vestibular migraine, these findings are not surprising, as functional MRI studies have revealed abnormal cerebellar metabolism in vestibular migraine.(6) Our case is unique because we documented improvement in our patient's dizziness as well as DBN following treatment with topiramate. We hypothesize that topiramate therapy suppressed abnormal activity in the cerebellum, resulting in resolution of our patient's dizziness and ocular motor abnormalities.

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Keywords: Nystagmus, Ocular manifestations of vestibular disorders, Vestibular

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 125
Unusual presentation of Idiopathic Polycranial Neuropathy

Lindsey McDaniel[1], Bokkwan Jun[1]

[1]*University of Missouri- Department of Ophthalmology, Columbia, Missouri, USA*

Introduction:
To report and review a case of idiopathic polycranial neuropathy which is rarely reported in the literature.

Methods:
This is a descriptive case report based on clinical records, observation and analysis of diagnostic studies.

Results:
A 49-year old woman with past medical history of hypothyroidism, migraines, and osteoarthritis presented with 3-week history of blurry vision in the right eye with pain and 2-week history of double vision and right facial droop. The ocular pain was described as aching behind the eye and pain on eye movement. The double vision was described as binocular, oblique, worsening over time. The exam showed no signs of optic neuropathy in the right eye and extraocular motility test showed painful external ophthalmoplegia which was lower motor neuron type and incomplete with pupil sparing and with no ptosis in the right eye and showed mild orbital tenderness on palpation and decreased sensation of V1, V2 distribution of the right face and the exam of the left eye and face was unremarkable. CT head, orbit, CTA head and neck and MRI brain were unremarkable. Labs showed positive ACHr Binding Ab, GAD 65 Ab, Thyroperoxidase Ab, CRP, and FANA (1:1280) and negative ACE, GQ1b Ab, Lyme, syphilis. Systemic corticosteroid was administered with IV methylprednisolone followed by oral prednisone tapering and the double vision and external ophthalmoplegia resolved in two weeks.

Conclusions:
The patient had a polycranial neuropathy in the right eye including CN III, IV, V, VI, and VII. Idiopathic orbital inflammation, Tolosa Hunt syndrome, ocular myasthenia gravis were considered. The involvement of motor and sensory cranial nerves with no radiologic evidence of inflammation in the orbit and cavernous sinus and complete resolution after systemic corticosteroid lead us to consider idiopathic polycranial neuropathy.

References: None.

Keywords: Ocular Motility, Myasthenia, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 126
Head Trauma Unmasks Eye Movement Findings in Previously Asymptomatic Congenital Intracranial Malformations

Benjamin Whigham[1], Valerie Elmalem[1]

[1]SUNY Downstate, Brooklyn, New York, USA

Introduction:
Vertical gaze palsies can result from numerous insults to the central nervous system including obstructive hydrocephalus and trauma. Here we observe head trauma resulting in bilateral vertical gaze palsy and nystagmus. Workup revealed previously asymptomatic brain abnormalities and hydrocephalus. This report describes the patient's unique presentation and clinical course.

Methods:
Clinical case report.

Results:
A 54-year-old female had an unwitnessed fall with transient loss of consciousness. She remained oriented during the subsequent hospitalization. On exam, she had complete upgaze palsy, moderate downgaze palsy, and upbeat nystagmus. Neuroimaging revealed injuries consistent with recent head trauma including multiple facial fractures, contusions of the frontal and occipital lobes, and mild intraparenchymal and subarachnoid hemorrhages. Imaging also revealed multiple congenital brain anomalies including cerebellar tonsillar ectopia and rhombencephalosynapsis with severe ventriculomegaly. The ventriculomegaly was felt to be chronic in nature and neurosurgery elected to observe. The patient was discharged from the hospital after 1 week and was followed in ophthalmology clinic for five months. After 3 months, she had near total resolution of gaze deficits and nystagmus without intervention. During the 4th month the patient had placement of a ventriculoperitoneal shunt to minimize risk of future exacerbations. At the end of five months she had no recurrence, with near-full gazes and no significant nystagmus.

Conclusions:
Trauma can lead to acute gaze palsies and nystagmus in patients with chronic ventriculomegaly. The mechanism might be exacerbation of an already compromised ventricular outflow system. Spontaneous improvement of eye movements is possible, as seen in this case.

References: 1. Shallat, Pawl, Jerva, Significance of upward gaze palsy (Parinaud's syndrome) in hydrocephalus due to shunt malfunction, J Neurosurg.38(6), 717-21, 1973. 2. Sabates, Gonce, Farris, Neuro-ophthalmological findings in closed head trauma, J Clin Neuroophthalmol, 11(4), 273-7, 1991. 3. Suzuki, Matsubara, Kanamaru, Kojima, Chronic hydrocephalus presenting with bilateral ptosis after minor head injury: case report, Neurosurgery, 47(4), 977-9, 2000. 4. Halmagyi, Leigh, Upbeat about downbeat nystagmus, Neurology, 63(4), 606-7, 2004. 5. Ishak, Dempsey, Shaw, Tully, Adam et al, Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity, Brain, 135(Pt 5), 1370-86, 2012.

Keywords: Ocular Motility, Nystagmus

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 127
OCT Angiography: A Non-Invasive Method For Assessing Optic Nerve Head Vasculitis In Bartonella Neuroretinitis.

Aliaa Abdelhakim[1], Aakriti Garg[1], Jason Horowitz[1], Jeffrey Odel[1]

[1]Harkness Eye Institute, Columbia University Medical Center, New York, New York, USA

Introduction:
Bartonella henselae, an endotheliotropic pathogen, causes optic disc vasculitis with resulting neuroretinitis and peripapillary retinal exudation. We used OCT angiography (OCTA), fluorescein angiography (FA) and red-free photography to assess the disc vasculature in a rare case of bilateral Bartonella neuroretinitis.

Methods:
A 21-year-old woman presented with one week of painless, progressive vision loss OU. She adopted a kitten four months prior but denied fever or recent illness. Visual acuity was 20/40 OD and count fingers at three feet OS. She had a RAPD OS. There were 1+ anterior chamber cells, vitreous cells, severe disc edema more prominently nasally, and hard stellate exudates in the nasal macula OU. She had high titers of anti-Bartonella henselae IgM and IgG antibodies (1:256 and 1:1024, respectively), confirming a diagnosis of Bartonella neuroretinitis. OCTA demonstrated radial peripapillary capillary network attenuation and diminished perfusion of the temporal aspect of the left optic nerve compared to the right. This was corroborated by red-free photography and FA, which revealed pallor and decreased fluorescence respectively in the corresponding area of the left nerve. These findings supported our clinical exam and a poorer prognosis for recovery of the left eye.

Results:
N/A (Case report)

Conclusions:
Bartonella neuroretinitis, which only rarely presents bilaterally, can cause vasculitis of the optic disc and result in profound decrease in vision. We find that OCTA can be a useful adjunct to other established imaging modalities in assessing the extent of vasculitic involvement of the optic nerve as well as visual prognosis.

References: Purvin V, Sundaram S, Kawasaki A. Neuroretinitis: review of the literature and new observations. J Neuroophthalmol. 31, 58-68, 2011. Ghasemi Falavarjani K, Tian JJ, Akil H et al. Swept-source optical coherence tomography angiography of the optic disc in optic neuropathy. Retina (epub ahead of print) 2016.

Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 128

Post-Coronary Artery Bypass Grafting Non-Arteritic Ischemic Optic Neuropathy: Evaluation by Optical Coherence Tomography Angiography

Aakriti Garg[1], Dan Gong[1], Megan Ridley-Lane[1], Jason Horowitz[1], Jeffrey Odel[1]

[1]Columbia University Medical Center Edward S. Harkness Eye Institute, New York, New York, USA

Introduction:
Non-arteritic ischemic optic neuropathy (NAION) after coronary artery bypass grafting (CABG) is a rare and devastating complication typically associated with severe anemia (1). We report a case of post-CABG NAION with cotton-wool spots imaged with optical coherence tomography angiography (OCT-A).

Methods:
A 47-year-old man with hypertension, hyperlipidemia, and uncontrolled diabetes, was admitted for acute myocardial infarction and underwent CABG for 3-vessel disease. On post-operative day 4, he was seen for decreased vision OD. Examination revealed visual acuity of counting fingers OD and 20/30 OS, a right RAPD, disc edema OD, and prominent cotton-wool spots as well as neovascularization of the disc OS. Humphrey visual field testing demonstrated a large dense ceco-central scotoma OD with mean deviation of -24.82 dB, and was normal OS. Fluorescein angiography (FA) showed patchy capillary dropout OU. OCT-A demonstrated wipe-out of the radial peripapillary capillary network (RPCN) between 6 and 10 o'clock OD, while the RPCN OS was preserved. Additionally, OCT-A confirmed the preservation of perfusion of vascular structures deep to the cotton-wool spots, which were not visualized on FA due to signal blockage. Workup for infectious, inflammatory, neoplastic etiologies was negative. Of note, while his procedure was uncomplicated, his hematocrit fell from 40.6 to 21.9 in the post-operative period. He was diagnosed with post-CABG NAION OD and proliferative diabetic retinopathy OS.

Results:
Case report.

Conclusions:
This report supports the recent observation by Falavarjani et al showing defects in the RPCN in the setting of NAION (2). OCT-A is superior to FA in imaging the vascular damage incurred in NAION both because of its convenience as well as its ability to resolve the RPCN (2, 3).

References: 1. Mansour AM, Awwad ST, Najjar DM, Sibai AN, Sibai AM, Medawar WA, et al. Anterior ischaemic optic neuropathy after coronary artery bypass graft: the role of anaemia in diabetics. Eye (Lond). 2006;20(6):706-11. 2. Ghasemi Falavarjani K TJ, Akil H, Garcia GA, Sadda SR, Sadun AA. Swept Source Optical Coherence Tomography Angiography of the Optic Disc in Optic Neuropathy. Retina. 2016. 3. Spaide RF, Klancnik JM, Jr., Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015;133(1):45-50.

Keywords: Optic neuropathy, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 129
Utility of Optical Coherence Tomography in assessment of children with headache and swollen disc.

Su Ann Lim[1]

[1]*Tan Tock Seng Hospital, Singapore, Singapore*

Introduction:
Headache is a common symptom in the paediatric neuro-ophthalmolgy clinic. It can be the harbinger of serious neurological problems like increase intracranial pressure (ICP) or secondary to benign conditions like migraine. Patients with increase ICP can have papilloedema, However, many patients with headache can also have pseudopapilloedema. This paper aims to demonstrate the utility of optical coherence tomography (OCT) in the evaluation of such patients.

Methods:
A series of case studies to demonstrate how OCT, both the retinal nerve fibre layer (RNFL) as well as optic disc area (DA) can be used to differentiate papilloedema from pseudopapilloedema in children with headache.

Results:
OCT should be used with a meticulous history to decide if a brain scan and/or lumbar puncture in needed in children with headache and disc swelling. In addition, follow-up OCT as well as clinical evaluation is essential to ensure that life-threatening conditions are not overlooked.

Conclusions:
OCT is useful in evaluation of children with headache and optic disc swelling, when used with a good history, examination as well as follow-up.

References: Tariq YM, Li H, Burlutsky G, Mitchell P. Retinal nerve fibre layer and optic disc 70. measurements by spectral domain OCT: normative values and associations in young adults. Eye 2012; 26:1563.

Keywords: High intracranial pressure/headache, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy

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Grant Support: None.

Poster 130
The Strangled Bird's Neck Sign on OCT in CRAO Will this Replace ERG?

Jorge Mendoza-Valencia[1], Mohamed Al-Ameri[1], Nagham Al-Zubidi[2], Han Cheng[3], Rosa Tang[4], Jade Schiffman[5]

[1]Neuro-Ophthalmology of Texas, PLLC, Houston, Texas, USA, [2]Neuro-Ophthalmology of Texas, PLLC, Blanton Eye Clinic HMH, HOUSTON, Texas, USA, [3]University of Houston College of Optometry, Houston, Texas, USA, [4]Neuro-Ophthalmology of Texas, PLLC, Blanton Eye Clinic, UHC Optometry, Houston, Texas, USA, [5]Neuro-Ophthalmology of Texas, PLLC, UH college of Optometry, Houston, Texas, USA

Introduction:
ERG was traditionally used to differentiating optic atrophy secondary to retinal arterial occlusion from other optic neuropathy. We present a case to illustrate a signature sign on OCT (with a new eponym) that can assist in detecting inner retinal changes associated with retinal arteriole occlusion.

Methods:
Case report

Results:
A 63-year-old man with PMH of traumatic optic neuropathy OD, hypertension, hyperlipidemia, and cardiac catheterization presented with vision loss OS two weeks prior. The following day, his vision recovered some before it progressed to a total vision loss in the left eye. Two days later, his vision partially recovered and remained stable since. MRI of the brain and neck was unremarkable. Carotid Doppler revealed 30-40% stenosis in right ICA and < 25% in left ICA. Echocardiography revealed mild left atrial enlargement, mild to moderate left ventricular hypertrophy. Neuro-ophthalmological exam showed VA of 20/20 OD, 20/400 OS, 0.6-0.9-log unit RAPD, color vision loss and severe field loss in OS. Fundus exam revealed mild optic pallor OD and severe optic pallor OS. OCT showed RNFL thinning OD and in OS inner retinal layer thinning with an eye-catching characteristic pattern on the line scan through ONH and macula implying a retinal artery insult as the etiology.. Flash ERG showed normal responses in OD and attenuated b-wave OS. Retinal artery occlusion was diagnosed OS. Further investigation with TEE revealed a left sided clot in the heart. The patient was placed on anticoagulation.

Conclusions:
Our case demonstrates a characteristic "Strangled Bird's Neck" sign on peripapillary OCT resulting from inner nuclear layer loss in addition to RNFL and GCIPL loss in a retinal artery occlusion confirmed by ERG. This proved to be life saving for our patient, maximizing the embolic w/u with a TEE, uncovering the cardiac thrombus, and allowing timely anticoagulation to be initiated.

References: 1. Nolan R et al. Utility of optical coherence tomography in the evaluation of monocular visual loss related to retinal ischemia. J Clin Neurosci. 2016, 26: 116-21 2. Shinoda K et al. Changes in retinal thickness are correlated with alterations of electroretinogram in eyes with central retinal artery occlusion. Graefes Arch Clin Exp Ophthalmol.2008; 246(7):949-5

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Orbit/ocular pathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 131
A Case of Orbitocerebrovascular Zygomycosis Infection

Lucy Bailey[1], Eric Crowell[1], Magy Eskander[1], Emilio Supsupin[2], Meenakshi Bhattacharjee[3], Ore-ofe Adesina[1]

[1]McGovern Medical School, Ruiz Department of Ophthalmology and Visual Sciences, Houston, Texas, USA, [2]McGovern Medical School, Department of Diagnostic and Interventional Imaging, Houston, Texas, USA, [3]McGovern Medical School, Department of Pathology and Laboratory Medicine, Houston, Texas, USA

Introduction:
We present a case of orbitocerebrovascular zygomycosis in the setting of CNS lymphoma.

Methods:
A 61-year-old Hispanic man with PMH of DM 2, hepatitis C, cirrhosis, alcoholism, and portal hypertension developed painful vision loss and orbital swelling OS after removing a tick from his dog and scratching his head. His vision OS decreased to NLP after failing treatment with oral antibiotics. He was transferred to our facility. On exam, he had left periorbital swelling with ecchymosis and proptosis. EOM were limited in all directions OS. The left pupil was nonreactive with a RAPD. IOP and DFE were WNL OU. MRI brain/orbits with contrast showed heterogeneous intraorbital enhancement involving the left lacrimal gland, intraconal fat, and optic nerve sheath extending to the orbital apex and left cavernous sinus. Pachymeningeal enhancement was seen along the lateral convexity of the brain and left medial temporal lobe. Workup showed WBC 19,100, serum ACE level 121, and p-ANCA titer 1:80. LP showed elevated WBC, protein, and ACE, with cytology pending. He underwent lacrimal gland biopsy.

Results:
IV methylprednisolone was started for a presumed diagnosis of neurosarcoidosis. His mental status declined acutely. MRI brain with contrast showed acute hemorrhagic infarcts of the left left basal ganglia. CSF cytology and lacrimal gland biopsy showed B cell lymphoma, and granulomatous inflammation with zygomycosis respectively. Methylprednisolone was discontinued, and antifungals were started. He experienced further neurologic decline. Repeat neuroimaging showed extensive hemorrhagic transformation in the left temporal lobe and basal ganglia. His family subsequently withdrew care, and he passed away 29 days after symptom onset.

Conclusions:
Our patient experienced vision loss with diffuse orbital, perineural, and pachymeningeal inflammation. Neurosarcoidosis was initially diagnosed based on imaging and biochemical findings; however, CSF evaluation revealed CNS lymphoma, and lacrimal gland biopsy showed fungal organisms consistent with zygomycosis.

References: Angali RK, Jeshtadi A, et al. Fatal rhino-orbito-cerebral mucormycosis in a healthy individual. Journal of Oral and Maxillofacial Pathology. 18(3):460. 2014. Farooq AV, Patel RM, et al. Fungal Orbital Cellulitis: Presenting Features, Management and Outcomes at a Referral Center. Orbit. 34(3):152-159. 2015. Hassan EA, El-Rehim ASA, et al. Fungal infection in patients with end-stage liver disease: low frequency or low index of suspicion. International Journal of Infectious Diseases. 23:69-74. 2014. Herrera DA, Dublin AB, et al. Imaging findings of rhinocerebral mucormycosis. Skull Base. 19(02):117-125. 2009. Jiang N, Zhao G, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC ophthalmology. 16(1):1. 2016. Smirniotopoulos JG, Murphy FM, , et al. Patterns of Contrast Enhancement in the Brain and Meninges 1. Radiographics. 27(2):525-551. 2007.

Keywords: Orbit, Neuroimaging, Neuro-ophth & infectious disease (eg, AIDS, prion)

Financial Disclosures: The authors had no disclosures.

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Poster 132
Ocular Manifestation of the Contralateral Side in a Case with Dural Carotid-Cavernous Fistula

ADALGISA CORONA[1], LUIS SUAZO[2], JOHANNA AGUILERA[3]

[1]LASER CENTER, SANTO DOMINGO, Dominican Republic, [2]CENTRO GAMMA KNIFE DOMINICANO, SANTO DOMINGO, Dominican Republic, [3]HOSPITAL DR. ELIAS SANTANA, SANTO DOMINGO, Dominican Republic

Introduction:
Case presentation of a 60 y.o. female patient with an indirect low-flow dural carotid-cavernous fistula with contralateral signs and symptoms, treated by stereotaxic radiosurgery with Gamma Knife.

Methods:
Case report

Results:
This is a 60 y.o. female patient with blood hypertension and history of head trauma without loss of consciousness 2 years ago. Patient presented with mild pain, hyperemia, and foreign body sensation in the left eye. Symptoms also included diplopia in levoversion, 3 mm axial proptosis and elevation of 4 mm Hg of intraocular pressure in comparison with right eye. Angiography by CAT was performed with evidence of significant dilation of the left superior ophthalmic vein related to a carotid-cavernous fistula on same side. The conventional arteriography showed a low-flow dural fistula at the right carotid artery which drained through the coronary sinus to the contralateral cavernous sinus. Intra-arterial approach of the fistula for embolization purposes was not feasible due to the small lumen of the affected vessel. Treatment was performed successfully by means of stereotaxic radiosurgery with Gamma Knife.

Conclusions:
This is a case of dural carotid-cavernous fistula with exclusive manifestations at the contralateral side. We emphasize the importance of the bilateral conventional arteriography and present the stereotaxic radiosurgery with Gamma Knife as an alternative treatment for this condition.

References: None.

Keywords: Orbit, Ocular Motility, Vascular disorders, Neuroimaging, Interventional neuroradiology

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Poster 133
Trans-Sphenoidal Approach to an Orbital Apex Lesion

Jessica Chang[1], Adelita Vizcaino[2], Thomas Johnson[1], Timothy McCulley[1]

[1]Wilmer Eye Institute, Baltimore, Maryland, USA, [2]Johns Hopkins University Department of Pathology, Baltimore, Maryland, USA

Introduction:
Orbital apex lesions present diagnostic and therapeutic challenges. The following case exemplifies the risks and benefits of observation, steroid trial, and biopsy in the orbital apex. Furthermore, it illustrates the trans-sphenoidal endoscopic approach to the apex, which may sometimes be advantageous to the trans-orbital approach when tissue diagnosis is necessary.

Methods:
Case report and literature review. A 55-year-old man presented with acute onset right eye vision loss to no light perception, proptosis, and cranial nerve III and VI palsies. His past medical history was significant for poorly controlled diabetes and hypertension with recent myocardial infarction. His family history was notable for sarcoidosis. MRI brain/orbits revealed a right orbital apex lesion with hyperintense T1, T2 and FLAIR signal, measuring up to 1.9 cm, and with no significant contrast enhancement or adjacent sinusitis. CTA was unremarkable.

Results:
Extensive workup for infectious and inflammatory etiologies was undertaken. After three days, intravenous steroids were trialed with subsequent improvement in motility and vision. Follow up imaging showed no significant change in the lesion. Five months after original presentation, he again developed sudden vision loss. He underwent trans-sphenoidal endoscopic biopsy, revealing fibrovascular tissue with no malignancy but evidence of old and recent hemorrhage. After biopsy and decompression, vision returned to 20/70.

Conclusions:
Case series suggest carotid-cavernous fistula and neoplasia (mostly lymphoma) are the most common causes of orbital apex syndrome, although infections have been reported even in immune-competent hosts. In this patient, recurrent symptoms prompted biopsy, but initial observation allowed him several months to recover from his cardiac event so that he could undergo surgery more safely, although coincidental improvement with steroids led to diagnostic confusion. This case also illustrates that a trans-sphenoidal endoscopic approach allows for both biopsy and concurrent selective decompression of the apex, which may have therapeutic benefit.

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Keywords: Orbit

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Grant Support: None.

Poster 134
Systemic Amyloidosis Presenting as Orbital Apex Syndrome

Wimonwan Chokthaweesak[1], Anuchit Poonyathalang[1], Pattana Sornmayara[1], Panitha Jindahra[1], Supalak Ponguthai[1], Witoon Mitarnun[1]

[1]Ramathibodi hospital, Mahidol university, Bangkok, Thailand

Introduction:
An orbital apex syndrome is a rare presentation of systemic amyloidosis

Methods:
A single case summary.

Results:
A healthy 50-year-old man presented with acute binocular diplopia, progressive proptosis in the left eye, and left side headache for 10 days. On examination best corrected left visual acuity was 20/70 and left color vision was impaired. Ptosis, exophthalmos, and limited range of eye movement in all directions were detected in the left eye. Decreased left corneal reflex was demonstrated. Vision and eye movement in the right eye were unremarkable. MRI of the orbits showed infiltrative inhomogeneous enhancing lesions at the left orbital apex and anterior ethmoid sinus. Pathological examinations of the ethmoid tissues and abdominal subcutaneous fat revealed abnormal Congo red deposits, which showed an apple-green birefringence under polarized light. The findings were consistent with systemic amyloidosis.

Conclusions:
Amyloid involvement of the orbital apex can imitate Tolosa-Hunt syndrome, highlighting the necessity of the biopsy before steroid treatment in cases with orbital apex syndrome.

References: None.

Keywords: Adult strabismus with a focus on diplopia, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility, Neuroimaging

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Poster 135
What Lies Beneath

Ruchika Batra[1], Rasoul Amel-Kashipaz[2], Shahzada Ahmed[2], Swarupsinh Chavda[2], Timothy Matthews[1]

[1]Birmingham Neuro-ophthalmology Unit, Birmingham, Great Britain, [2]University Hospitals Birmingham, Birmingham, Great Britain

Introduction:
Marginal zone lymphoma of mucosal-associated lymphoid tissue (MALT) account for 7%-8% of all newly-diagnosed cases of non-Hodgkin lymphoma. Since MALT lymphomas are frequently localized and tend to stay localized, local treatment approaches such as moderate-dose radiotherapy are frequently successful. We describe a case of MALT lymphoma of the pterygopalatine fossa extending into the right orbital apex, in which the diagnosis and therefore treatment was delayed.

Methods:
A 30 year old previously well Caucasian male presented due to binocular horizontal and vertical diplopia and painful motility. The visual acuities were 20/20 OD and 20/16 OS. Limitation of elevation and adduction of the right eye was noted. 1.5mm of right axial proptosis was present. The optic nerve function was normal. Anterior and posterior segment examination was unremarkable. A CBC, serum ACE, serum Ca, ANA, ANCA, ESR, IgG4, HIV, hepatitis B and C serology and thyroid function tests were unremarkable. An enhanced MRI scan revealed a mass in the right pterygopalatine fossa extending into the orbital apex. An ENT opinion concluded that biopsy and tissue diagnosis would not be possible in view of the location of the lesion. Empirical treatment with oral prednisolone was commenced. Two weeks later there was an increase in the axial proptosis. A neuro-ophthalmology opinion prompted biopsy of the lesion.

Results:
The first biopsy was inconclusive, however, repeat biopsy achieved the diagnosis. Whole body PET scanning confirmed the absence of any other disease activity. The patient completed a course of radical radiotherapy to the right orbit and maxillary sinus. The optic nerve function remained normal bilaterally and the orbital signs have resolved.

Conclusions:
This case highlights the importance of repeated biopsy, despite an initial negative biopsy, in the presence of clinical suspicion. MALT lymphoma should be considered as a differential diagnosis in orbital cases presenting in this age group.

References: None.

Keywords: Orbit/ocular pathology

Financial Disclosures: The authors had no disclosures.

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Poster 136
Vision loss after endovascular treatment of arteriovenous malformation.

Alberto Distefano[1], Adeniyi Fisayo[1], Yanina Costina[1]

[1]Yale University School of Medicine, New Haven, Connecticut, USA

Introduction:
Vision loss is a serious risk associated with neurosurgical procedures. The mechanism is sometimes difficult to elucidate. Urgent intervention may be necessary. A proper evaluation and understanding of the anatomy aids in diagnosis.

Methods:
We present a single case report of vision loss in the right eye. Clinical and neuro-radiologic findings will be presented.

Results:
A 60-year-old female presented with six months of progressive, painless prominence of the right eye. Exam found right eye proptosis. Best corrected visual acuity on the right was 20/25 and 20/20 on the left. There was no relative afferent pupillary defect (rAPD). MRI found arteriovenous malformation in the right orbit, displacing the globe anteriorly and the optic nerve medially. The patient underwent selective embolization of an aneurysm off the ophthalmic artery. Upon awakening, the patient complained of having no vision in the right eye. Urgent CT scan found stable aneurysms at the orbital apex. Exam found vision of no light perception in the right eye with rAPD. The right eyelid was ptotic with decreased supra-, infra-, and adduction consistent with a third nerve palsy with onset noted during the procedure. Abduction was intact as was sensation along the trigeminal nerve. Intraocular pressure was within normal limits. Dilated fundus exam showed a mottled appearance on the right. Hours later, the patient was able to regain vision of counting fingers temporally. These findings were most consistent with a central retinal artery occlusion.

Conclusions:
This case highlights the importance of complete ophthalmic evaluation in post-operative vision loss. The differential after orbital procedures can include direct injury, compression, and vascular insults. Evaluation should quickly exclude compression as intervention may be necessary. However, complete evaluation should be performed that, along with an understanding of orbital anatomy, will aid in differentiation of the correct diagnosis.

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Keywords: Interventional neuroradiology, Orbit, Vascular disorders, Optic neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 137
A Case of Recurrent Malignant Hemangiopericytoma Presenting with Orbital Apex Syndrome and Proptosis

Amanda Henderson[1], M. Adelita Vizcaino[2], Lisa Rooper[2]

[1]Wilmer Eye Institute/Johns Hopkins University, Baltimore, Maryland, USA, [2]Department of Pathology, Johns Hopkins University, Baltimore, Maryland, USA

Introduction:
Hemangiopericytomas tend to recur and metastasize, and distinction between malignant and benign forms is not always clear. Continued surveillance is required in patients with hemangiopericytoma to prevent poor clinical outcomes.

Methods:
We present the clinical, neuro-radiologic, and histopathologic findings in a case of recurrent malignant hemangiopericytoma.

Results:
A 47-year-old female presented with left-sided blurry vision and proptosis. On examination, vision in the right eye was 20/20 and left eye 20/30 with a left afferent pupillary defect and proptosis. CT demonstrated a left extraconal mass. Biopsy revealed malignant hemangiopericytoma, with high cellularity, pleomorphism, and areas with brisk mitotic rate. One month postoperatively, vision was 20/20, right eye, and 20/50, left, with a left APD. There was a small adduction deficit in the left eye with a 4-mm enophthalmos. She underwent adjuvant external beam radiation and chemotherapy. 12 years later, she re-presented with two months of left eye pain and proptosis. Vision was 20/30, right eye, and no light perception, left eye, with an amaurotic left pupil. The left globe was frozen and proptotic. MRI showed a heterogeneously enhancing mass centered at the greater wing of the left sphenoid bone, extending to the middle cranial fossa and left orbit, maxillary sinus, and orbital apex, with involvement of the optic canal and superior and inferior orbital fissures. Endonasal biopsy demonstrated recurrent hemangiopericytoma. She was determined not to be a candidate for surgery, radiation, or chemotherapy, and was transitioned to hospice care.

Conclusions:
This case highlights the propensity for recurrence of malignant hemangiopericytoma, even after subtotal resection, chemotherapy, and radiation. Complete excision is the most important intervention to prevent recurrence and may include dural and bony excision. In the setting of subtotal excision, radiation therapy may provide limited benefit in some cases, but continued surveillance is required in these cases. The role of chemotherapy remains unclear.

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Keywords: Tumors, Orbit, Orbit/ocular pathology, Neuroimaging

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Poster 138
Bilateral Central Ptosis as a Presenting Manifestation of a Dorsal Midbrain Tumor

Gerard Hershewe[1], Alyssa Eckert[2], Josh Gratwohl[2], Micaela Koci[1], Jerad Hershewe[2], Joaquin Arista[2]

[1]University of Nevada Reno School of Medicine, Reno, Nevada, USA, [2]University of Nevada Reno, Reno, Nevada, USA

Introduction:
A 61-year-old female presents with a two-month history of sudden onset bilateral lid droop which was maximal at onset. The patient tilts her head backwards "in order to see". The lid droop was worse in the morning, and exacerbated by fatigue. The lid droop was unassociated with diplopia, dysphagia, neck weakness and proximal muscle weakness. There is no history of myasthenia gravis or family history of ptosis. The patient has a previous history of fibrocystic disease involving the right breast, without evidence of malignancy. She does not smoke and has history of hearing loss.

Methods:
Case report.

Results:
Best corrected visual acuity as 20/20 OD and 20/20-3 OS. Pupils measured 3.0 mm OD and 3.0 mm OS. Both pupils were briskly reactive to light without near-light dissociation. There was a small angle exotropia. There was no upgaze paralysis or convergence retraction nystagmus. Both optic nerves were normal.The patient maintained a chin-up position. There was marked ptosis OU. The palpebral fissures 4.5 mm OD 4.5 mm OS. There was a slight diminution of levator function bilaterally. There was a suggestion of fatigable ptosis following sustained upgaze.MRI of brain showed enhancing midbrain tumor with additional T2 and FLAIR hyperintensity surrounding the enhancing component, which may either represent infiltrative tumor or vasogenic edema.CSF cytology and flow cytometry showed no evidence of lymphoma.Chest CT was normal. The blood glucose level was elevated at 126 mg/dL, remaining laboratory studies were normal.

Conclusions:
This is a rare presentation of bilateral central ptosis secondary to a dorsal midbrain WHO grade II astrocytoma.The diagnosis was confirmed by a needle biopsy utilizing a left frontal approach. The abrupt onset of bilateral complete ptosis may be indicative of a structural lesion affecting the dorsal midbrain such as stroke, trauma or tumor.

References: None.

Keywords: Neuroimaging, Tumors

Financial Disclosures: The authors had no disclosures.

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Poster 139
Two Cases of Extraocular Muscle Enlargement Caused by Metastatic Cancer

JAEHO JUNG[1], Hee-Young Choi[2]

[1]PUSAN NATIONAL UNIVERSITY YANGSAN HOSPITAL, YANGSAN, Korea, Republic of, [2]Pusan national university hospital, Busan, Korea, Republic of

Introduction:
To report two cases of extraocular muscle enlargement due to malignant cancer metastasis

Methods:
A 56-year-old woman presented with horizontal diplopia first noted 1 month earlier. She had a history of smallcell lung cancer with brain and bone metastases. She had a -3 abduction deficit in the right eye and esotropia. The forced ductiontest showed no limitation in horizontal movement. Antibody tests for thyroid disease showed normal results. Brain magnetic resonanceimage showed multiple nodular enlargements of the right lateral and medial rectus muscles, al so multiple metastaticnodules in the brain. A 38-year-old woman presented with horizontal diplopia first noted 3 months previously. She had undergonebreast cancer surgery 6 months earlier. The patient had a -4 abduction deficit in the left eye and esotropia. The forced ductiontest showed no limitation in horizontal movement. Antibody tests for thyroid disease showed normal results. Orbital magneticresonance imaging showed nodular enlargement of left lateral rectus muscle including a tendon

Results:
Extraocular muscle metastasis cause extraocular enlargement and paralytic strabismus. In a patient with malignant cancer, the physician should consider the possibility of extraocular muscle metastasis and perform imaging for early diagnosis and treatment.

Conclusions:
Neverthelss, mean survival period of patient with extraocular muscle metastasis was only 14 months, ranging from two months to four years, prompt diagnosis and aggressive cancer treatment can be effective in the managing extraocular muscle metastasis and improving the quality of life of the patient.

References: None.

Keywords: Tumors, Ocular Motility, Adult strabismus with a focus on diplopia

Financial Disclosures: The authors had no disclosures.

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Poster 140
Allergic Fungal Sinusitis: Masquerade Syndrome and Delay in Diagnosis

Justin Karlin[1], Steven Newman[1], Jose Gurrola[1]

[1]*University of Virginia, Charlottesville, Virginia, USA*

Introduction:
Allergic fungal sinusitis is a chronic inflammatory upper respiratory disorder characterized by a type I immediate hypersensitivity reaction to fungal antigens. It may present with nasal polyps, sinus obstruction, and elevated serum IgE. Histopathology may demonstrate the presence of fungal hyphae and chronic inflammation. In its most severe forms, AFS may lead to orbital invasion, compressive optic neuropathy and intracranial extension.

Methods:
A 23 year old African American woman presented with complaints of blurred vision, diplopia and bulging eyes. She was found to have restrictive strabismus and optic neuropathy, and was presumptively diagnosed with thyroid eye disease. Corticosteroid therapy was initiated, and she showed improvements in vision and motility. A thyrotropin inhibitor binding assay was normal. The patient was then lost to follow up before orbit imaging could be completed. She returned 5 months later with worsening proptosis and vision loss. She was sent immediately for imaging of the orbits and sinuses, which demonstrated pansinusitis with invasion of the orbits, and laboratory workup showed elevated serum IgE. Findings were consistent with AFS and endoscopic sinus surgery was performed. Nasal polyps were identified intraoperatively and biopsy showed dense chronic inflammation. Sinus cultures grew mold, non-Aspergillus and non-Zygomycete. Postoperatively, she experienced improvement in her motility, proptosis and vision.

Results:
Relevant clinical, radiologic, laboratory and histopathologic findings are discussed.

Conclusions:
The aim of presenting this case is to highlight the potential of AFS to mimic the proptosis, restrictive strabismus and optic neuropathy seen in Graves' orbitopathy. We hope that in doing so clinicians may be able to recognize AFS sooner and initiate the appropriate treatment earlier, thus avoiding the potential complications.

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Keywords: Optic neuropathy, Skull Base, Neuro-ophth & infectious disease (eg, AIDS, prion), Orbit

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Poster 141
Acute right, pupil-sparing CN III palsy as first sign of metastatic breast cancer

Iulia Pana[1], Simon Quijada Angeli[2], Belen Gragera Soroa[1], Diego Urquia Perez[1], Javier Iturria Soler[1], Mónica Hijós Gastón[1]

[1]Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, [2]Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain

Introduction:
Orbital metastasis is an uncommon form of presentation of breast cancer given that the most common sites of spread of the metastatic breast cancer are bone, regional lymphatics, lung, liver and the brain, which normally have earlier symptoms.

Methods:
We present a single case report of acute right, pupil-sparing CN III palsy . Clinical and neuro-radiologic findings will be presented.

Results:
A 45-years old woman was seen in the Emergency Department presenting ptosis of the right upper lid and horizontal binocular diplopia for 4 days, with no clinical signs of an additional neuromuscular dysfunction of the eye. She had no systemic diseases or treatments and the neurological examination failed to reveal any other focal neurological deficit.She was diagnosed of acute right, superior divisional third nerve palsy. Non-contrast CT head showed an intraorbital lesion between the superior rectus muscle and the optic nerve. Brain MRI with contrast redemonstrated the lesion in the right orbit and several intracranial and bone lesions, suggestive of metastasis.A Physical exam revealed breast nodules with lymphadenopathy and a mammography was suggestive of breast cancer. Pathology showed a breast carcinoma .Body CT showed metastasis in the liver, bones,lymph nodes and retroperitoneal space.She was diagnosed of breast cancer stage four and for the moment she is being treated with holocraneal radiotherapy with good general condition .

Conclusions:
Neuro-ophthalmic emergencies can hide life threatening conditions and so a proper examination and imaging investigation it´s very important in these cases.Also in the case of a orbital lesion in a women without a medical history should be ruled out the breast cancer, being the most common malignant disease among women in western countries.

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Keywords: Orbit, Tumors, Orbit/ocular pathology, Neuroimaging

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Poster 142

Orbital apex syndrome and exudative retinal detachment due to metastatic esophageal adenocarcinoma.

Alexander Port[1], Ajay Jurangal[1], Gary Lelli[1], Marc Rosenblum[2], Cristiano Oliveira[1], Brian Marr[3]

[1]Department of Ophthalmology, Weill Cornell Medicine, New York, New York, USA, [2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [3]Ocular Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Introduction:

Orbital metastatic disease is a rare cause of the orbital apex syndrome. We present a case of metastatic esophageal adenocarcinoma causing an exudative retinal detachment and orbital apex syndrome.

Methods:

Descriptive case report.

Results:

A 76 year old man with a history of esophageal adenocarcinoma presented for evaluation of 4 months of progressive right eye pain, proptosis and vision loss, as well as worsening fatigue and weight loss. On examination, visual acuity was NLP in the right eye and 20/20 in the left eye. There was an afferent pupillary defect in the right eye and near-complete ophthalmoplegia of the right eye with limited ductions in all directions. IOP was 8 mmHg in the right eye and 12 mmHg in the left. Anterior examination demonstrated mild proptosis and chemosis of the right eye. Dilated fundus examination in the right eye was notable for optic disc edema, peripapillary hemorrhages, retinal pallor, venous engorgement and exudative retinal detachment. Fundus exam was normal in the left eye. B-scan ultrasound was performed and showed central retinal detachment as well as posterior scleral thickening. MRI brain and orbits demonstrated a heterogeneously enhancing mass affecting the posterior right orbit. Whole-body PET-CT demonstrated avid FDG uptake in the retrobulbar right orbit, but no other sites of metastatic disease. The patient underwent orbitotomy for tissue biopsy, but the tissue samples were non-diagnostic. The patient was referred to an ophthalmic oncologist. Fine-needle aspiration biopsy was performed and was positive for adenocarcinoma cells. The patient was referred to radiation oncology and completed a course of palliative radiation.

Conclusions:

Orbital metastases are associated with advanced disease and portend a poor prognosis. Esophageal adenocarcinoma is a rare cause of orbital metastatic disease. To the authors' knowledge, this is the first case of metastatic esophageal adenocarcinoma presenting with the orbital apex syndrome and exudative retinal detachment.

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Keywords: Tumors, Orbit, Orbit/ocular pathology

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Poster 143
Idiopathic Cyclic Alternating Anisocoria

Erin Conrad[1], Imran Jivraj[1], Randy Kardon[2], Grant Liu[1]

[1]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]University of Iowa and Veterans Administration, Iowa City, Iowa, USA

Introduction:
We present a rare case of idiopathic cyclic alternating anisocoria in an otherwise healthy patient and discuss potential localization.

Methods:
A 16 year old boy with a history of amplified localized pain of the abdomen and attention deficit disorder (ADD) presented with two years of alternating anisocoria. He was taking no medications. We recorded his pupil size as a function of time under dim lighting in three settings: 1) prior to topical medication administration, 2) after receiving brimonidine eye drops, and 3) after receiving tropicamide eye drops. We also reviewed MR-imaging of the brain, cervical spine, and chest, and MR-angiogram of the brain.

Results:
His right pupil demonstrated cyclic contraction and dilation with a periodicity of 55 seconds; his left pupil also varied in size over time, but without a periodicity. A review of old photographs demonstrated that the alternating anisocoria likely had been present for at least eight years. Brimonidine did not change the cyclic period of the right pupil. Tropicamide abolished cycling in both pupils. His neuroimaging was normal.

Conclusions:
This is a rare case of cyclic alternating anisocoria presenting as periodic dilation and contraction of the right pupil. The persistence of right pupil cycling after administering brimonidine and the cessation after administering tropicamide suggests that the cyclic generator either lies within the right parasympathetic pupil pathway or from pathways such as the locus coeruleus (sympathetic) projecting to the right Edinger Westphal nucleus. The locus coeruleus and its noradrenergic projections have been implicated in abnormal behavioral disorders, including attention deficit disorders and its neurons have also been shown to exhibit pacemaker rhythmicity. One hypothesis is that the unusual pupil cycling in this case may be a manifestation of abnormal rhythmic activity of the locus coeruleus associated with attention deficit disorder in our patient.

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Keywords: Pupils Retina, Neuroimaging, Pediatric neuro-ophthalmology

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Poster 144
Severe Congenital Ptosis Associated With Oculomotor Nerve Hypoplasia And Multiple CNS Anomalies

Tarek Shazly[1], S. Tonya Stefko[2]

[1]University of Pittsburgh, Department of ophthalmology, Pittsburgh, Pennsylvania, USA, [2]University of Pittsbrugh, Pittsburgh, Pennsylvania, USA

Introduction:
Congenital hypoplasia of the oculomotor nerve is a rare cause of congenital blepharoptosis.

Methods:
An 8 week old female presented for evaluation of bilateral congenital ptosis. Her parents noticed that she moves her head around to try to see. She was found to have severe congenital ptosis and abnormal extra-ocular motility with no nystagmus. She had severe limitation of upgaze and abduction, limited adduction with some preservation of infraduction. An MRI of her brain and orbits was obtained looking for the size of the extraocular muscles. MRI revealed thin, symmetric extra-ocular muscles suggesting congenital fibrosis of the extraocular muscles as well as very diminutive cranial nerves III and VI on each side. It also revealed bilateral small optic nerve colobomata, dysplastic posterior corpus callosum and small Rathke's cleft cyst in the sella.

Results:
At the age of 6 months, she underwent bilateral Silicon frontalis slings and bilateral inferior rectus recessions. Two revisions of the ptosis repair were required to optimize the lid position over the course of the first post-operative year with acceptable functional outcome, though the struggle to maintain visual acuity in the left eye continues.

Conclusions:
This case adds to the literature supporting aplasia/hypoplasia of the ocular motor nerves in cases of congenital extraocular muscle palsies.

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Keywords: Ocular Motility

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Poster 145
An atypical presentation of mucormycosis

Salina Teja[1], Duncan Anderson[1], jason barton[1], claire sheldon[1], sara simpson[1]

[1]*University of British Columbia, vancouver, Canada*

Introduction:
A 55 year-old male presented with a 10-day history of a right sided headache associated with facial pain and sudden-onset visual loss in the right eye 4 days prior.

Methods:
A CT scan showed mucosal thickening in all sinuses, and hypoattenuated areas in the frontal and occipital lobes with unremarkable orbits. He denied any past medical history but reported an 80 pack-year smoking history. On examination he had NLP vision in the right eye with a dense afferent pupillary defect. There was inferior segmental pallid edema of the right optic nerve. His ESR was 70 and CRP was 130. Endoscopic biopsy of the ethmoid sinus revealed nonspecific inflammation. He was placed on pulse IV steroids for presumed temporal arteritis. He subsequently developed thromboembolic occlusion of the right middle cerebral artery secondary to a right internal carotid artery dissection. Thrombectomy was attempted but unsuccessful. Over the next three days the patient developed cranial nerve V and VI palsies without any cavernous sinus abnormalities on CT or MRI. His MCA stroke continued to evolve eventually requiring hemicraniectomy for increasing cerebral edema and herniation. During his hospital stay he was diagnosed with uncontrolled diabetes type 2 and hypertension.

Results:
On autopsy, mucormycosis hyphae were present in the sphenoid sinus, permeating through the sphenoid bone with extension into the pituitary gland, cavernous sinus and associated cranial nerves. The wall of the carotid artery was infiltrated and the hyphae tracked downwards to cause total occlusion at the M1 level.

Conclusions:
Mucormycosis affects immunocompromised patients with diabetes or hematological malignancies (1). Rhinocerebral mucormycosis is the most common form of infection, and displays extension into adjacent tissues such as the palate, sphenoid sinus and cavernous sinus, and orbits (3). The fungus usually invades the cranium through the orbital apex, presenting with symptoms consistent with sinusitis and necrotizing periorbital cellulitis (4).

References: 1. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhinoorbito-cerebral mucormycosis: a retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol 2003; 51:231–6 2. Greenberg RN, Scott LJ, Vaughn HH, Ribes JA. Zygomycosis (mucormycosis): emerging clinical importance and new treatments. Curr Opin Infect Dis 2004; 17:517–25 3. Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Otorhinolaryngol 2005; 262:932–8 4. Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012 Feb;54:S23-34

Keywords: Orbit/ocular pathology, Neuro-ophth & infectious disease (eg, AIDS, prion), Neuroimaging

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Poster 146
Laughter-induced transient vision loss in a patient with silent sinus syndrome

Sara Reggie[1], Krishna Kalyam[2], Sophia Chung[1], John Holds[3]

[1]Saint Louis University Eye Institute, St. Louis, Missouri, USA, [2]Washington Unversity, St. Louis, Missouri, USA, [3]Saint Louis University Eye Institute Ophthalmic Plastic and Cosmetic Surgery, Inc., St. Louis, Missouri, USA

Introduction:
Silent sinus syndrome is a rare disease when the maxillary osteomeatal complex is blocked, resulting in negative maxillary sinus pressure and eventual atelectasis of the maxillary antrum.

Methods:
Case summary

Results:
We present a unique case report of a 32-year-old otherwise healthy female patient with untreated silent sinus syndrome who experienced transient ipsilateral monocular vision loss during intense laughter. The patient's transient vision loss resolved after maxillary sinus decompression.

Conclusions:
Silent sinus syndrome is the result of blockage of the maxillary osteomeatal complex, resulting in negative maxillary sinus pressure, with atelectasis and eventual collapse of the maxillary antrum. The authors hypothesize that this patient's transient blindness was likely due to compromised retinal blood flow from both the internal carotid artery and its external carotid artery collateral branches. Future cases of this phenomenon would benefit from angiographic studies to better understand its pathophysiology.

References: Soparkar, C.N., et al., The silent sinus syndrome. A cause of spontaneous enophthalmos. Ophthalmology, 1994. 101(4): p. 772-8. Numa, W.A., et al., Silent sinus syndrome: a case presentation and comprehensive review of all 84 reported cases. Ann Otol Rhinol Laryngol, 2005. 114(9): p. 688-94. Cox, S.V., A.C. Eisenhauer, and K. Hreib, "Seinfeld syncope". Cathet Cardiovasc Diagn, 1997. 42(2): p. 242. Macchi, C. and C. Catini, The anatomy and clinical significance of the collateral circulation between the internal and external carotid arteries through the ophthalmic artery. Ital J Anat Embryol, 1993. 98(1): p. 23-9.

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Financial Disclosures: The authors had no disclosures.

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North American Neuro-Ophthalmology Society

43rd Annual Meeting

April 1 – April 6, 2017
Washington Marriott Wardman Park • Washington, DC

Program Schedule

MONDAY, APRIL 3

6:00 am - 6:45 am	**Yoga Class**	**Washington Room 1**
6:30 am - 5:30 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
6:30 am - 7:30 am	**Breakfast**	**Exhibit Hall C**
6:30 am - 12:15 pm	**Exhibits**	**Exhibit Hall C**
7:00 am - 7:30 am	**NOVEL Editorial Board/Curriculum Committee Meeting**	**Washington 2**
7:30 am - 9:30 am	**Journal Club [2 CME]** *Moderators: Y. Joyce Liao, MD, PhD and Matthew J. Thurtell, MBBS, MSc, FRACP*	**Thurgood Marshall Ballroom**

The Journal Club symposium will cover updates on medical conditions of importance to Neuro-Ophthalmic practice, with review of recent important literature relating to masquerade retinopathies, pediatric optic neuritis, and myasthenia gravis.

Upon completion of this course, participants should be able to: 1) Describe the features, investigation, and management of retinopathies that can masquerade as optic neuropathy; 2) Discuss the investigation and management of pediatric optic neuritis; and 3) Discuss recent updates in the investigation and management of myasthenia gravis.

		PAGE
7:30 am - 7:55 am	**Masquerade Retinopathies (AZOOR, MEWDS, AIBSES, ARRON, AIR, Paraneoplastic CAR, MAR, PON),** *Y. Joyce Liao, MD, PhD*	**203**
7:55 am - 8:00 am	Q & A	
8:00 am - 8:25 am	**Clinical Trials of Neuro-Ophthalmic Interest**, *Neil R. Miller, MD*	**213**
8:25 am - 8:30 am	Q & A	
8:30 am - 8:55 am	**Pediatric Optic Neuritis**, *Grant T. Liu, MD*	**219**
8:55 am - 9:00 am	Q & A	
9:00 am - 9:25 am	**Myasthenia Gravis**, *Matthew J. Thurtell, MBBS, MSc, FRACP*	**223**
9:25 am - 9:30 am	Q & A	

9:30 am - 10:00 am	**Coffee Break**	**Exhibit Hall C**
10:00 am - 12:00 pm	**Hot Topics in OCT [2 CME]** *Moderators: Eric R. Eggenberger, DO and Victoria S. Pelak, MD*	**Thurgood Marshall Ballroom**

Optical Coherence Tomography (or OCT) is quickly advancing our understanding of disease pathology and becoming an important research tool for both discovery and outcomes. The use of OCT for the diagnosis of conditions that previously required more invasive techniques is quickly evolving.

Upon completion of this course, participants should be able to: 1) Employ OCT imaging to diagnose optic nerve head drusen; 2) Describe the imaging technique and potential applications of OCT angiography; 3) Describe current utility of OCT in tracking progression and effectiveness of treatment in multiple sclerosis; and 4) Explain current findings and potential utility of OCT in assessment of neurodegeneration in Alzheimer's disease and Parkinson's disease.

10:00 am - 10:15 am	**OCT and Optic Nerve Head Drusen,** *Fiona Costello, MD, FRCP*	**229**
10:15 am - 10:20 am	**Q & A**	
10:20 am - 10:35 am	**OCT Angiography,** *Guy V. Jirawuthiworavong, MD, MA*	**233**
10:35 am - 10:40 am	**Q & A**	
10:40 am - 10:55 am	**Optical Coherence Tomography (OCT) and Multiple Sclerosis (MS),** *Steven Galetta, MD*	**239**
10:55 am - 11:00 am	**Q & A**	
11:00 am -11:15 am	**OCT and Neurodegeneration of Alzheimer's Disease and Parkinson's Disease,** V*ictoria S. Pelak, MD*	**247**
11:15 am - 11:20 am	**Q & A**	
11:20 am - 11:35 am	**The Future of OCT: Merging Structure and Function,** *Robert C. Sergott, MD*	**261**
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1:30 pm - 3:00 pm **Applications of Advanced Retinal Vascular Imaging in Neuro-Ophthalmology [1.5 CME]** **Thurgood Marshall Ballroom**
Moderator: Hong Jiang, MD, PhD

The recent advances of ophthalmic imaging techniques, such as the Optic Coherence Tomography Angiography (OCTA) and the retinal function imager (RFI), enable vascular changes in the posterior segment of the eye to be qualitatively and quantitatively analyzed. This symposium will provide an overview of these fast growing, state of the art imaging techniques and their applications to the field of Neuro-Ophthalmology with clinical study outcomes.

Upon completion of this course, participants should be able to: 1) Recognize the vascular link between the eye and brain; 2) Describe currently available advanced ophthalmic imaging modalities for retinal vascular imaging and their applications in Neuro-Ophthalmology; and 3) Discuss possible changes of retinal microvasculature in optic neuropathy and central nervous system disorders, such as cerebral vascular diseases, multiple sclerosis, and dementia.

1:30 pm - 1:50 pm	**Update of Retinal Vascular Imaging Quantitative Analysis,** *Jianhua Wang, MD, PhD*
1:50 pm - 2:10 pm	**The Application of OCTA in Optic Neuropathy,** *Marie-Benedicte Rougier, MD, PhD*
2:10 pm - 2:30 pm	**Retinal Vascular Changes as a Biomarker for Cerebral Vascular Disease,** *Heather Moss, MD, PhD*
2:30 pm - 2:50 pm	**Retinal Microvascular Impairment in Multiple Sclerosis and Dementia,** *Hong Jiang, MD, PhD*
2:50 pm - 3:00 pm	**Q&A**

2:30 pm - 4:30 pm **Forum for New and Future Neuro-Ophthalmologists** **Washington Rooms 3-6**

All are welcome to attend. This gathering, however, is especially for students, residents, fellows, and Neuro-Ophthalmologists in the early years of their career. There will be small group discussions that provide an opportunity to ask questions, or listen to the questions and advice of others. Attendees can rotate between tables during the session. The first hour of discussions will be led by members of the Young Neuro-Ophthalmology (YONO) Committee who are recently out of fellowship, and is geared towards trainees, residents, and fellows. The second hour will be led by senior Neuro-Ophthalmologists, and is geared towards those in their first years of practice. Attendees can come for one or both hour-long sessions.

2:30 pm - 3:30 pm	**Session I: What Do You Want to Know About Becoming a Neuro-Ophthalmologist?** **Table 1:** Top 10 Financial Mistakes We Make (And How to Avoid Them), *Kaushal Kulkarni, MD* **Table 2:** Practice Models For Neuro-Ophthalmologists, *Kevin Lai, MD* **Table 3:** From an Ophthalmology Perspective, *Colin McClelland, MD* **Table 4:** What it's like to be a Neuro-Ophthalmologist, *Courtney E. Francis, MD*

3:30 pm - 4:30 pm **Session II: What Do You Want to Know About Your First Few Years of Practice?**
Table 1: Becoming a Clinician Scientist, *Alfredo Sadun, MD, PhD*
Table 2: Building Collaborations, Local and International, *Christian Lueck, MB BChir MA PhD FRCP(Ed) FRCP(UK) FRACP FAAN and Walter Jay, MD*
Table 3: Changing Jobs - Is This the Right Job for Me?, *Janet Rucker, MD*
Table 4: Work Life Balance, *Andrew Lee, MD*
At large: *Jorge Kattah, MD*

3:15 pm - 4:45 pm **Radiation Oncology for the Neuro-Ophthalmologist [1.5 CME]**
Facilitator: Scott L. Stafford, MD **Thurgood Marshall Ballroom**

This symposium is designed to introduce the basics of radiation oncology to the audience and will start with an introduction on the physical characteristics of photons and protons that are generated for medicinal use. Then, a case oriented approach to the tumors/conditions seen by Neuro-Ophthalmologists will be conducted including technique, toxicity, and outcomes.

Upon completion of this course, participants should be able to: 1) Describe the differences between protons and photons; 2) Define the role of radiation in orbital and optic nerve tumors; and 3) Evaluate the complexity of radiation as it applies to treating tumors of the orbit.

4:45 pm - 5:00 pm **Overview of the NANOS Practice & Compensation Survey**
Speaker: Meg Guerin-Calvert, President and Senior Managing Director, Center for Healthcare Economic and Policy, FTI Consulting, Inc. **Thurgood Marshall Ballroom**

NANOS leadership and the FTI Center for Healthcare Economics and Policy teamed together in an effort to obtain the most complete information on practices and compensation across the diverse practice settings of NANOS members. This was done to respond to members' requests for reliable benchmarks for Neuro-Ophthalmologic compensation and productivity. The collaboration resulted in the NANOS Practice & Compensation Survey launch in 2016; with the survey remaining open for member participation into 2017. The presentation will provide an overview and summary of survey results.

5:00 pm - 7:00 pm **Scientific Platform Presentations:**
Session I [2 CME] **Thurgood Marshall Ballroom**
Moderators: Matthew J. Thurtell, MBBS, MSc, FRACP & Michael S. Vaphiades, DO

8:30 pm - 9:30 pm **Medicare Reviews and Audits with Dr. Cheryl Ray** **Thurgood Marshall Ballroom**
Moderator: Larry Frohman, MD

8:30 pm- 9:15 pm *Medicare Reviews, Probes & Audits… Oh My!*

9:15 pm- 9:30 pm Q&A

This is a rare opportunity to hear from a Medical Official who genuinely understands our practice. Dr. Cheryl Ray is a VP of Medicare-Clinical and Lead Contractor Medical Director at WPS- Government Health Administrators.

MASQUERADE RETINOPATHIES

(AZOOR, MEWDS, AIBSES, ARRON, AIR, PARANEOPLASTIC CAR, MAR, PON)

Y. Joyce Liao, MD, PhD

Byers Eye Institute, Stanford University
Stanford, CA

LEARNING OBJECTIVES

1. Recognize the key similarities and difference in autoimmune/paraneoplastic retinopathies and optic neuropathies
2. Describe the diagnostic approaches in the setting of vision loss from suspected autoimmune/paraneoplastic etiologies
3. Explain that ERG abnormalities are common in autoimmune/paraneoplastic retinopathies and optic neuropathies and describe the most common OCT findings in early and late disease.

CME QUESTIONS

1. Which of the following is not a mechanism of autoantibody generation in autoimmune and paraneoplastic diseases?

    a. Epitope spreading
    b. Molecular mimicry
    c. Antigen presentation by major histocompatibility complex
    d. Antigenic mutation
    e. All of the above are mechanisms important in autoantibody generation

2. Which of the following is not an autoimmune retinopathy?

    a. AIBSES (acute idiopathic blind spot enlargement syndrome)
    b. MEWDS (multiple evanescent white dot syndrome)
    c. CAR (cancer-associated retinopathy)
    d. PON (paraneoplastic optic neuropathy)
    e. MAR (melanoma-associated retinopathy)

3. The immune system plays a positive role to regulate and prevent tumor growth, although some autoantibodies have been shown in vitro and in vivo to cause retinal neuronal apoptosis.

    a. True
    b. False

4. Which of the antibodies below is the most common autoantibody in cancer-associated retinopathy?

    a. Anti-recoverin antibody
    b. Anti-arrestin antibody
    c. Anti-rhodopsin antibody
    d. Anti-titin antibody

5. Which of the following autoantibody is associated with paraneoplastic optic neuropathy?

    a. Anti-arrestin antibody
    b. Anti-alpha-enolase antibody
    c. Anti-CV2/CRMP-5 antibody
    d. Anti-recoverin antibody
    e. Anti-titin antibody

KEYWORDS

1. Autoimmune Retinopathy
2. Autoantibodies
3. Paraneoplastic
4. Enlarged Blindspot

ABBREVIATIONS

AIBSES: acute idiopathic blind spot enlargement syndrome
AIR: autoimmune retinopathy
ARRON: autoimmune-related retinal and optic neuropathy
AZOOR: acute zonal occult outer retinopathy
CAR: cancer-associated retinopathy
CRMP5: collapsin response-mediator protein-5
ERG: electroretinography
GAPDH: glyceraldehyde 3-phosphate dehydrogenase
MAR: melanoma-associated retinopathy
MEWDS: multiple evanescent white dot syndrome
OCT: optical coherence tomography
PON: paraneoplastic optic neuropathy
SCLC: small cell lung cancer
VEP: visual evoked potential

ABSTRACT

Autoimmune paraneoplastic and non-paraneoplastic retinopathies are rare and can masquerade as optic neuropathies. These cases often present as diagnostic challenges and may require extensive and repeated testing over time to make the diagnosis. Although the retina is the more common target of such conditions, the optic nerve can also be involved (sometimes simultaneously), and there may be overlapping findings on clinical examination and ancillary testing (**Table 1,** see p. 209). This review summarizes the presentation, diagnosis, treatment, and prognosis of 3 groups of such heterogeneous conditions:

I. Autoimmune, non-paraneoplastic retinopathies associated with *enlarged blind spot* called acute zonal occult outer retinopathy (AZOOR), which is a spectrum of diseases that include multiple evanescent white dot syndrome (MEWDS), acute idiopathic blind spot enlargement syndrome (AIBSES), and others;
II. Autoimmune paraneoplastic and non-paraneoplastic *retinopathies* (AIR) associated with autoantibodies against retinal antigens, with special emphasis on cancer associated retinopathy (CAR) and melanoma-associated retinopathy (MAR);
III. Autoimmune non-paraneoplastic (ARRON) or paraneoplastic (PON) *optic neuropathies* associated with autoantibodies against optic nerve and retinal antigens.

INTRODUCTION: THE IMMUNE SYSTEM IN AUTOIMMUNE AND PARANEOPLASTIC DISEASES

Autoimmune and paraneoplastic diseases are complex conditions that can present as vision loss or visual disturbances.[1-4] Although these diseases are heterogeneous and may or may not be associated with cancer, they all involve the immune system, which provides surveillance to the entire body to identify and mount attack against foreign substances in the form of foreign antigens. Recognition of the foreign antigen in the form of a peptide presented by the major histocompatibility complex (MHC) leads to activation of T and B cells, CD8 and CD4 cytotoxic responses, with the goal of inducing apoptosis of the foreign cells. T cell, macrophage, natural killer cell infiltration of the tumor can occur in the *absence of an overt inflammatory response or tissue necrosis*. Unfortunately, an autoimmune process mounted against unintended targets—the self-antigens on the retina and optic nerve—leads to irreversible vision loss due to eventual apoptosis of retinal neurons and optic neuropathy.

In autoimmune diseases, immune activation occurs inappropriately through **molecular mimicry**.[2] Susceptible individuals mount an immune response to antigens with shared homology with endogenous proteins of the retina or optic nerve. The resultant antibodies then inappropriately cross-react with and localize to these tissue sites, where they disrupt normal cellular function, and ultimately cause visual dysfunction. This may also occur through **antigenic mutation** (conversion of normal self-protein to non-self protein) or **dysfunction of the immune system** (e.g. failure to mount regulatory T cell (T-regs) responses to turn off immune activation). Autoantibodies can also arise via a phenomenon called **epitope spreading**, in which a new antibody emerges during the course of the disease.[5] As the disease evolves (or as a tumor grows larger), additional antigens may be recognized by the immune system, and certain autoantibodies can be detected later in disease and even serve as good biomarkers of disease progression.

In cancer, it is well accepted that the immune system plays a positive role to regulate and prevent tumor growth. Immune infiltration of the tumor serves to detect altered self-antigens to initiate anti-tumor responses, which involve $CD4^+$ and $CD8^+$ cytotoxic T cells and natural killer cells. Some tumor antigens are recognized by antibodies and by cytotoxic T cells, and the presence of autoantibodies are often used as part of diagnostic workup given the association between certain autoantibodies and different cancer types. This process can keep the tumor growth at bay for months to years, making diagnosis and treatment very challenging. Because tumors can evade immune-mediate regulation by a variety of methods and eventually manifest themselves, the patients with suspected paraneoplastic diseases need to be monitored closely and worked up repeatedly as needed.

AUTOIMMUNE, NON-PARANEOPLASTIC *RETINOPATHIES* ASSOCIATED WITH *ENLARGED BLIND SPOT* (AZOOR, MEWDS, AIBSES)

Acute zonal occult outer retinopathy (AZOOR) is a spectrum of rare, autoimmune retinopathy due to chorioretinitis, vascular impairment, and outer retinal dysfunction that manifest as a unilaterally or asymmetrically *enlarged blind spot* and positive visual phenomena that occurs predominantly in younger women.[6] Historically, the spectrum of diseases that have been grouped under a single diagnosis AZOOR complex since 1993 include multiple evanescent white-dot syndrome (MEWDS), acute idiopathic blind-spot-enlargement syndrome (AIBSES), acute macular neuroretinopathy (AMN), multi-focal choroiditis, and the pseudo-presumed ocular histoplasmosis syndrome (P-POHS).[7-10] **Multiple evanescent white dot syndrome (MEWDS)** is characterized by the presence of multiple, faint, small, subretinal white dots at the posterior pole that may strongly fluoresce on autofluorescence fundus photography. **Acute idiopathic blind spot enlargement syndrome (AIBSES)** is first described in 1988 as a rare retinopathy characterized by unilateral, painless vision changes occurring predominantly in younger women in the setting of enlarged blindspot on visual field testing without presence of optic disc edema to explain the enlarged blindspot.[11] These conditions are all related to inflammation of the choroid, vascular impairment, and photoreceptor impairment.[6]

Clinical Features. Patients with AZOOR spectrum of diseases (MEWDS, AIBSES, AMN) typically present with acute onset of positive visual phenomena such as photopsias and scotomas affecting one or both eyes. Patients often have relatively good or mildly affected visual acuity and enlarged blind spot on visual field testing. Many can have color vision abnormality, delayed photostress recovery, or relative afferent pupillary defect (reflects asymmetry of disease). Enlarged blind spot on traditionally photopic visual field testing has been shown to normalize with dark-adaptation.[7,12]

Patient with AZOOR may report preceding flu-like symptoms or prior vaccination. It may be associated with other autoimmune diseases[13] but is not typically associated with presence of anti-retinal or optic nerve antibodies or increased risk of cancer. In one study of 51 primarily Caucasian patients, 28% of patients (14/51) had autoimmune diseases, including Hashimoto's thyroiditis in 6 patients and relapsing transverse myelopathy in 4 patients.[14] In another study of 38 Japanese patients, 34% of patients had systemic diseases, including Hashimoto disease, hyperthyroidism, cervical cancer, thyroid cancer, rheumatoid arthritis, suspected Sjögren's syndrome, atopic dermatitis, and chronic idiopathic pancreatitis.[15]

Fundus Findings and Testing. Within 2 weeks of onset, patients with AZOOR typically show signs of chorioretinal disease, such as optic disc congestion, disc staining on fluorescein angiography, peripapillary retinitis, and foveal changes.[16] Although optic disc edema is not described in the initial report of acute idiopathic blind spot enlargement syndrome (AIBSES), which help distinguish this condition from others, more common causes of enlarged blind spot,[11] a 2001 study of 27 patients with AIBSES demonstrates the presence of mild optic disc edema in patients with AIBSES.[17] In this study, 92% of fluorescein angiography (12 out of 13 patients) also show optic disc staining, and 38% (5 out of 13) have retinal pigment epithelial lesions with late staining.[17]

Peripheral retinal spots such as those typical of MEWDS may or may not be present. These spots are multiple, faint, small, subretinal white dots at the posterior pole to the mid-periphery. These spots strongly fluoresce on autofluorescence fundus photography, and there is typically a speckled pattern. Fluorescein angiography often shows optic disc staining, patchy hyperfluorescence of the whitish dots, and late-phase fluorescein angiography reveals leakages corresponding to presence of vascular sheathing. Indocyanine green angiography often shows diffuse, small, hypofluorescent spots scattering throughout the posterior pole.

Enhanced depth imaging (EDI) optical coherence tomography (OCT) imaging in the acute phase can reveal focal, multiple disruptions of the ellipsoid and interdigitation zones and external limiting membrane, hyperreflective dots in the inner choroid, full-thickness increase of the choroidal profile, and retinal pigment epithelium changes.[18] Disappearance of these findings is significantly associated with visual recovery, although atrophy is not typically reversible.

Electroretinopathy (ERG) is an important diagnostic test in AZOOR, and multi-focal ERG is more sensitive than full-field ERG.[17] On multi-focal ERG, abnormalities are typically bilateral, asymmetric, and patchy, even when the clinical presentation of findings is unilateral, indicating the damage is more widespread. Amplitude of cone ERG can be more reduced than that of rod ERG in the affected eye.

Treatment and Prognosis. Treatment may not be needed, and some cases may benefit from corticosteroid therapy. Prognosis is generally good, with improvement of the visual field defect but never to an unequivocally normal-sized blind spot.[16] The imaging findings typically resolve. OCT can show progressive and complete recovery of the outer retinal layer findings, which typically correlate with visual improvement. The electrophysiology changes are more often persistent, although the visual field and clinical features often improve. Choroidal neovascularization (CNV) can occur after recovery, which can be treated with anti-vascular endothelial growth factor (VEGF) injection.[19-21]

AUTOIMMUNE PARANEOPLASTIC AND NON-PARANEOPLASTIC *RETINOPATHIES* ASSOCIATED WITH AUTOANTIBODIES AGAINST RETINAL ANTIGENS (AIR, CAR, MAR)

Autoimmune retinopathy (AIR) refers to paraneoplastic or non-paraneoplastic conditions presenting as visual disturbances or visual loss, which are typically associated with autoantibodies against retinal antigens and there is absence of another cause of symptoms.[22,23] Although not well studied, AIR can sometimes be associated with autoantibodies against both retina and optic nerves. For the purpose of classification, AIR includes those conditions that present primarily as a retinopathy. Clinicians should have a high index of suspicion and clinical follow-up are paramount because these conditions are rare, difficult to diagnose, and may be associated with a bad outcome.

While paraneoplastic syndromes have been estimated to occur in as many as 10% of cancer patients, those presenting as visual disturbances or vision loss are very rare, occurring in about 0.01%.[2] **Cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR)** are rare conditions that are immunologically heterogeneous and associated with photoreceptor dysfunction or degeneration. There is progressive degeneration of the inner and outer segments of the photoreceptor layers along with the outer nuclear layer. Patients with MAR often have an established diagnosis of cutaneous melanoma, and then visual problems developing months to years later. There is typically no evidence of ocular or other metastasis at the time that visual symptoms begin.

Clinical Features. Patients present with unexplained visual loss, with or without photopsias, and typically none or subtle findings on ophthalmic examination. Visual complaints typically evolve over 0-6 months with photopsias, scotomas, dychromatopsia, nyctalopia, abnormal color vision, or photophobia. The visual symptoms can be attributed to rod (impaired dark adaptation and peripheral visual field loss) or cone dysfunction (decreased visual acuity, central scotomas, color dysfunction, photosensitivity, and glare after light exposure).[4] There may be a personal or family history of systemic autoimmune diseases. There may be concomitant bilateral progressive hearing loss and episodes of high-pitched tinnitus.

In 2016, there is a new consensus statement on the diagnostic criteria for non-paraneoplastic autoimmune retinopathy (AIR).[23] Essential diagnostic criteria (all should be satisfied) include: 1) no apparent cause responsible for visual function abnormality, 2) ERG abnormality (with or without visual field abnormality), 3) presence of serum anti-retinal antibodies, 4) absence of fundus lesions and retinal degeneration or dystrophy that may explain visual function loss, 4) absence of overt intraocular inflammation.[23]

Fundus Findings and Testing. Fundoscopy may show normal retina in the early stages. Mild uveitis or vitritis can be seen. In advanced cases, there may be retinal arterial narrowing, retinal pigment epithelial mottling, and optic disc pallor. Workup includes visual assessments including visual field testing, color vision assessment, and photostress recovery.

In patients with AIR, OCT may reveal significant thickening of the choroid, compatible with inflammation.[24] OCT study of patients with AIR may also show reduced central macular and foveal thickness as well as loss and disruption of photoreceptor layer outer retinal atrophy.[25] In one patient, disruption of the photoreceptor OS/IS junction corresponds to depressed central response on multifocal ERG (mfERG) testing.[25] When the photoreceptor nuclear layer is atrophic, the vision loss is more typically irreversible. OCT in CAR and MAR may show no significant findings initially and progressive thinning over time.

Important ophthalmic studies also include ERG, fluorescein angiogram, fundus autofluorescence, and OCT.[23,25] In AIR and CAR, ERG may show depressed or absent a-waves and b-waves in both scotopic and photopic conditions. The electrophysiologic dysfunction in MAR often involves the depolarizing bipolar cells or the signal transmission between photoreceptors and depolarizing bipolar cells, so there is typically a depression of the b wave.

A comprehensive malignancy evaluation to look for a tumor and serum anti-retinal antibody testing (see below) should be ordered because clinical presentation can be indistinguishable between paraneoplastic and non-paraneoplastic causes. The presence of autoantibodies can be helpful in diagnosis but is not always found. Antibody testing is not currently well standardized, and different antibodies can be found by different lab. Sometimes, anti-retinal antibodies can occur in the normal population or unrelated to vision loss, so the differential diagnoses should always include other causes of retinopathies.

Autoantibody testing. In AIR/CAR/MAR, western blot analysis may identify anti-retinal (and sometimes anti-optic nerve) autoantibodies such as anti-recoverin or anti-alpha-enolase antibodies in the serum or cerebrospinal fluid.[2-4,26] Many autoantibodies against retinal antigens have been associated with AIR, including, recoverin, alpha-enolase, heat-shock proteins, arrestin, transducin, neurofilament protein, and carbonic anhydrase II. The most frequently found autoantibodies include antibodies against retinal alpha-enolase (46 kDa), recoverin (23 kDa), and p35 (35 kDa), which predominantly affect photoreceptors but can also affect bipolar cells and retinal ganglion cells. The presence of multiple autoantibodies is likely related to polyclonal activation of the humoral immune system, and the number of positive anti-retinal antibody subtypes but not the specific subtypes is considered more consistent with the diagnosis of AIR.[23] In MAR, the antibodies are directed against the retinal bipolar cell antigens and other retinal layers, including a 35 kDa protein in the Muller glial cells, a 22 kDa neuronal antigen, and retinal transducin.[4,27]

Treatment and Prognosis. Prognosis is generally guarded and may be better in those with early diagnosis. Prognosis may be better in those with limited disruption of the photoreceptor OS/IS junction on OCT with no reduction in central macular thickness because photoreceptor outer segments are able to regenerate and reorganize.[28] Therapeutic approaches include treatment of underlying cancer or systemic disease, if any. There is agreement that corticosteroids and conventional immunosuppressive therapies are first- or second-line treatments, and biologics and intravenous immunoglobulin are appropriate considerations in the treatment of non-paraneoplastic AIR patients regardless of the stage of disease.[23] Unfortunately, treatment responses are highly variable and typically worse in those with paraneoplastic disease. More evidence is needed to treat non-paraneoplastic AIR patients with long-term immunomodulatory therapy.[29]

Monitoring. Time intervals for follow-up of AIR patients should be every 3 months and may differ depending on the patient, the treatment types, and clinical characteristics. Consensus was not reached for repeated serum anti-retinal antibody testing or dark-adapted testing, although this can be considered 2-4 weeks after treatment.[25]

AUTOIMMUNE PARANEOPLASTIC AND NON-PARANEOPLASTIC *OPTIC NEUROPATHIES* ASSOCIATED WITH AUTOANTIBODIES (ARRON, PON)

Autoimmune optic neuropathies associated with autoantibodies and distinct from optic neuritis are rare. They are characterized by painless, progressive or recurrent vision loss that are often associated with autoantibodies against optic nerve and retina. Autoimmune optic neuropathy is first described by Dutton et al. as recurrent episodes of optic neuropathy with autoantibodies but different from demyelinating optic neuritis.[30] In 2009, Keltner's group defines **autoimmune-related retinopathy and optic neuropathy (ARRON)** as a syndrome characterized by vision loss associated with autoantibodies against retinal or optic nerve antigens *in the absence of cancer*.[29] **Paraneoplastic optic neuropathy (PON)** is also rare and classically described as presenting with subacute vision loss along with other associated neurologic manifestations that can occur in isolation or associated with cerebellar degeneration, encephalitis, sensory neuropathy, Lambert– Eaton myasthenic syndrome (LEMS), and limbic encephalitis.[2,3,31] In workup of patients with cancer, it may be difficult to determine whether optic neuropathy is related to paraneoplastic disease or side effect of cancer therapies.

Clinical Features. Vision loss may be very mild or severe. It's typically painless, asymmetric, bilateral and progressive. One case of ARRON presented with bilateral blurry vision, worsening glare from fluorescent lights, and impaired night and color vision at the same time as decreased hearing. There was associated bilateral hearing loss. Patients with PON present with painless progressive bilateral visual loss over weeks to months and optic disc edema.[2-4] There may be other paraneoplastic symptoms including ophthalmoplegia, retinitis, subacute cerebellar syndrome, and others.[2-4]

ARRON is not associated with cancer by definition. PON is classically most commonly associated with SCLC and occasionally with thyroid, nasopharyngeal, renal, and thymus cancer in adults or neuroblastoma in children.[2-4]

Fundus Findings and Testing. Optic disc swelling can be seen in the acute stage, although patients may have normal optic nerves at presentation. A mild vitreous reaction may also be present. Similar to patients with autoimmune retinopathy, ERG abnormalities are often present in the majority of patients. The CSF may show lymphocytosis, increased protein content, and oligoclonal immunoglobulin bands on electrophoresis.

Autoantibodies. Serum (and CSF) should be sent to look for presence of autoantibodies against retinal and optic nerve antigens.[2-4] One case of ARRON had both anti-retinal and anti-optic nerve autoantibodies.[29] In the setting of SCLC, PON has been most associated with anti-CV2/CRPM-5 antibodies, which is directed against the 62 kDa collapsin response-mediator protein-5.[2-4] This antigen is widely expressed in the central and peripheral nervous system as well as in tumor tissue, and the neurological syndromes associated with CRMP5 antibodies are very diverse (similar to anti-Hu antibodies) and include peripheral neuropathy, limbic encephalitis, ataxia, as well as paraneoplastic chorea or optic neuritis.[32-35] Because anti-CRMP5 autoantibodies are found in almost 80% seropositive patients with lung cancer, CRMP5 has become an established biomarker for lung cancer-related paraneoplastic syndromes.[32]

Treatment and Prognosis. Prognosis is generally guarded and may be better in those with early diagnosis. Successful treatment of the underlying tumor is the mainstay for treating PON. Calcium-channel blockers and alemtuzumab have been found to improve visual function in cancer-associated retinopathy. Variable outcomes are reported among PON patients treated with steroids and IVIG.

SIGNIFICANCE OF AUTOANTIBODIES IN AUTOIMMUNE/PARANEOPLASTIC RETINAL AND OPTIC NERVE DISEASES

Autoantibodies are important diagnostic tools in some autoimmune and most paraneoplastic neurologic syndromes, and many autoantibodies are associated with particular types of cancers.[2-4] Some, such as anti-recoverin antibody in CAR, have been studied in detail and shown to be important in disease pathogenesis (see below). Many patients have both anti-retinal and anti-optic nerve antibodies,[34] but the significance of these antibodies remains unclear in most cases. Binding to optic nerve, glia, or retina may interfere with function, inhibit enzymes activities or promote apoptosis.[34] Different parts of the nervous system, including the retina, optic nerve, or eye movement control pathways, can be involved in isolation or in combination. The presence of multiple autoantibodies corresponds to polyclonal activation of the humoral immune system, and, in AIR, the number of positive anti-retinal antibody subtypes but not the specific subtypes is considered more diagnostic.[23]

Currently, autoantibody testing in patients with suspect autoimmune paraneoplastic or non-paraneoplastic vision loss can be slow and frustrating. Antibody testing is not well standardized, and different antibodies can be found by different lab. Sera from patients can be measured for presence of antibody through the use of Western blot reactions from pig or human retina and optic nerve extract, and the sensitivity and specificity are lab- and method-dependent. Ideally, the presence of autoantibodies detected as positive bands on Western blot is confirmed by binding to purified recombinant human proteins or staining pattern on confocal immunostaining of human retinas.[36] Currently, only one center in the United States provides anti-retinal antibody testing commercially, through a CLIA (clinical laboratory improvement amendments)-certified laboratory (Ocular Immunology Laboratory, Casey Eye

Institute, Oregon Health & Science University). Experts agreed that a standardized assay system is needed to detect serum anti-retinal antibodies and that ideally this should be a 2-tier design with different methods to maximize sensitivity and specificy.[23] For example, this can be Western blot (WB) or immunohistochemistry (IHC) initially and followed by a different diagnostic method, including WB, IHC, or enzyme-linked immunosorbent assay (ELISA).[23]

In one of the best labs, 56 normal sera using Western blotting shows that the vast majority of normal sera show no or low reactivity with optic nerve proteins, and only four out of 56 sera (7%) weakly reacted with optic nerve proteins (35, 46, 62 kDa).[34] However, autoantibodies are found in patients with different causes of vision loss, including age-related macular degeneration, uveitis, glaucoma, or systemic autoimmune diseases such as Behçet's disease, inflammatory bowel disease, systemic lupus erythematosus, and multiple sclerosis, and their roles in these disease of often unclear.[22,37-40] Anti-retinal and, to a lesser extent, anti-optic nerve antibodies, have also been found in those without vision loss.[41] Negative result in testing autoantibody against retinal or optic nerve antigens may be related to variability of disease, immunosuppressed state of the patient undergoing treatment, sampling variation, impaired detection, or other factors.

Many antigens have been reported to be associated with CAR and can be epitopes associated with photoreceptor (recoverin, arrestin) or metabolic, intracellular proteins. Recoverin is one of the earliest identified autoantigens in CAR and is the most common autoantibody (55%) found in patients with cancer-associated CAR. It is a calcium-binding protein that regulates rhodopsin phosphorylation in a calcium-dependent way. Recoverin is found in rods, cones, some bipolar cells, and a rare population of cells in the ganglion cell layer. The pathogenic role of anti-recoverin antibody has been shown by different groups in in vitro and in vivo studies. An epitope for anti-recoverin antibodies located within residues 64 to 70 and is uniquely pathogenic, causing photoreceptor degeneration upon immunization of Lewis rats with this peptide. About 50% of patients with anti-recoverin antibody have cancer, and those with anti-recoverin antibody are more likely to be older and present with sudden onset of symptoms and progressive course. Those with positive anti-recoverin antibody but no cancer are significantly more likely to have cancer than those with other autoantibodies and may be diagnosed years later.[36] Anti-recoverin antibody is associated with many types of cancer, including lung, gynecologic, breast, melanoma, bladder, and renal, and other cancers.

Although anti-carbonic anhydrase II antibodies are found in controls as well as patients with AIR or CAR, careful analysis of epitopes within each group reveals significant differences among the 3 groups.[42] The sera of 91% of patients with AIR react with the N-terminal epitope 85-90, which corresponds to the catalytic core of the enzyme. In 77% of patients with CAR, the antibodies react with peptide 218-222 within the alpha-helix, which is partially or fully exposed on the protein surface. In one patient, there was an epitope shift in antibody recognition from the N-terminal, AIR-like epitope to the peptide 218-222, CAR-like profile when patient developed cancer 2 years after initial symptoms of vision loss, consistent with intramolecular epitope spreading.[42] Sera from controls did not have either epitope pattern. While not currently clinically available, epitope mapping may help improve diagnostic sensitivity and specificity in the future. In the future, a protein array displaying thousands of human proteins or epitopes may be best able to assess autoantibodies in sera.[43]

SUMMARY

Autoimmune paraneoplastic and non-paraneoplastic retinopathies and optic neuropathies are rare causes of vision loss associated with abnormal fundus and electrophysiology findings and presence of autoantibodies against retinal or optic nerve antigens. Clinical evaluation, retinal imaging, and extensive testing, including cancer workup, electrophysiology, and autoantibody testing by Western blot and other methods, will help determine the correct diagnosis and treatment in a timely fashion. Classification of the different conditions and diagnostic testing (including autoantibody testing) will likely evolve as we better understand these conditions.

Table 1: Manifestations of autoimmune/paraneoplastic retinopathies (AZOOR, AIR, CAR, MAR) vs. optic neuropathies (ARRON, PON)

	Retinopathies (AZOOR, AIR, CAR, MAR)	Optic Neuropathies (ARRON, PON)
Presentation, Visual Symptoms and Signs	• Rare • **AZOOR:** acute onset of unilateral positive phenomena and enlarged blind spot in younger women; ± personal or family history of autoimmune disease • **AIR/CAR/MAR:** unilateral or bilateral central, painless, progressive vision loss over weeks to months; ± history of autoimmune disease, smoking or melanoma • **CAR:** reduced visual acuity to 20/70 to HM • **MAR:** visual acuity 20/60 or better • ± Color vision loss, photopsia, photophobia, nyctalopia, prolonged photostress recovery • **CAR:** typically present with vision loss *before* cancer diagnosis; ± other neurological paraneoplastic symptoms • **MAR:** typically present with vision loss *after* cancer diagnosis	• Rare • **ARRON/PON:** Painless progressive bilateral vision loss over weeks to months • **ARRON/PON:** range of visual acuities from 20/20 to no light perception • **ARRON:** vision loss can be reversible • **PON:** vision loss can be severe and irreversible • ± Color vision loss, photophobia; *less common*: photopsias, nyctalopia, prolonged photostress recovery • **PON:** ± other neurological paraneoplastic symptoms (ophthalmoplegia, retinitis, subacute cerebellar, and others)[4]
Exam Findings	• **AZOOR:** *early:* optic disc edema, retinitis; *chronic:* may be normal or subtle • **AIR/CAR/MAR:** *early:* may have normal optic nerve and retina; *chronic:* retinal pigment epithelial thinning and mottling, optic atrophy, arteriolar narrowing • ± Anterior chamber cells or vitritis • ± Other neurological symptoms[4]	• **ARRON:** *early:* normal or optic disc edema; *chronic:* optic atrophy • **PON:** *early:* normal or optic disc edema; *chronic:* optic atrophy • ± Anterior chamber cells, vitritis, retinitis • ± Other neurological symptoms[4]
Electrophysiology Findings	• **AZOOR/AIR/CAR: ERG abnormality in majority.** Loss of rod and/or cone responses on ERG, affecting a and b waves • **MAR:** reduced b-waves, may have normal dark adapted a-waves • **AIR:** Loss of central multi-focal ERG signal corresponds to disruption of IS-OS junction (may be reversible)	• **ARRON/PON: ERG abnormality in majority.** Loss of rod and/or cone responses on ERG, affecting a and b waves • VEP abnormalities
OCT Findings	• **AZOOR/AIR:** Disruption or loss of IS-OS junction (may be reversible) • **AZOOR/AIR:** markedly thickened choroid in both eyes, consistent with inflammation • **CAR/MAR:** *early:* can be normal; *chronic:* thinning of the foveal, outer retinal, or total retinal thickness	• **ARRON:** *acute:* thickening of the retinal nerve fiber layer (RNFL) complex; *chronic:* thinning of the ganglion cell complex (GCC); presence of CME • **PON:** *early:* can be normal or show RNFL thickening; *chronic:* progressive thinning of RNFL and GCC

CSF Findings	• Can be normal • May have mild lymphocytic pleocytosis and elevated protein • May have autoantibodies	• Can be normal • May have mild lymphocytic pleocytosis and elevated protein • May have autoantibodies
Most Common Cancers	• **AZOOR:** not associated with cancer • **CAR:** SCLC, breast cacer, lymphoma, non-small cell lung, ovarian, cervical, and endometrial cancers • **MAR**: melanoma	• **ARRON:** not associated with cancer • **PON:** most commonly associated with SCLC[2-4]
Most Common Autoantibodies	• **AZOOR:** no autoantibody • **CAR:** most common anti-recoverin, alpha-enolase antibodies • **MAR:** most common antibody against bipolar cells	• **PON:** Anti-CRMP5 antibody in SCLC.[2-4]

CME ANSWERS

1. e
2. d
3. True
4. a
5. c

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CLINICAL TRIALS OF NEURO-OPHTHALMIC INTEREST

Neil R. Miller, MD

Johns Hopkins University School of Medicine
Baltimore, MD

LEARNING OBJECTIVES

1. Describe the results of a randomized clinical trial of treatment for mild/moderate primary pseudotumor cerebri syndrome
2. Recognize the potential for an adjunctive treatment for patients with giant cell arteritis
3. Explain the status of two gene therapy trials for patients with Leber hereditary optic neuropathy
4. Tell about a new treatment for children with optic pathway gliomas

CME QUESTIONS

1. Patients with primary pseudotumor cerebri syndrome can often tolerate up to what daily dose of acetazolamide?

   a. 1 gram
   b. 2 grams
   c. 4 grams
   d. 6 grams

2. A new add-on drug for patients with giant cell arteritis is:

   a. Rituximab
   b. Tocilizumab
   c Infliximab
   d. Methotrexate

3. A new potential treatment for children with an optic pathway glioma is:

   a. Murine nerve growth factor
   b. Adalimumab
   c. Human growth hormone
   d. Bone marrow transplant

KEYWORDS

1. Pseudotumor Cerebri Syndrome
2. Leber Hereditary Optic Neuropathy
3. Optic Pathway Glioma
4. Giant Cell Arteritis
5. Tocilizumab

INTRODUCTION

2016 was a good year for clinical trials of interest to neuro-ophthalmologists. In this syllabus, I will discuss final or preliminary results from five treatment trials dealing with four disorders: primary pseudotumor cerebri syndrome (n=1), leber hereditary optic neuropathy (n=2), giant cell (temporal) arteritis (n=1), and optic pathway gliomas (n=1). It also is possible that preliminary or final results from one other trial for patients with leber hereditary optic neuropathy and one other trial for patients with giant cell arteritis will be published before the NANOS meeting, in which case these will be discussed in addition to what is presented in this syllabus.

PRIMARY PSEUDOTUMOR CEREBRI SYNDROME (AKA, IDIOPATHIC INTRACRANIAL HYPERTENSION)

The idiopathic intracranial hypertension treatment trial (IIHTT) run by NORDIC and funded by the NEI (NCT01003639) continues to generate important information. This treatment trial was designed to determine if weight loss alone was as effective as weight loss combined with acetazolamide for subjects with mild/moderate primary pseudotumor cerebri characterized by papilledema and mean deviation on automated perimetry of -2 to -5 dB in the worse eye. Participants were randomized into one of two groups: a weight loss program + acetazolamide beginning at 500 mg bid or a weight loss program + placebo. The weight loss part of the trial was run by the New York Obesity Research Center (NYORC). Weight loss was monitored by counselors who interacted with the participants by telephone. The primary outcome measure was visual status at 6 months. The results of the study, published in 2014[1] were: 1) average weight loss of the participants who completed the study was about 6%, 2) participants in the weight loss + acetazolamide group had a better visual outcome than participants treated with weight loss alone, and 3) the effects of acetazolamide are not due solely to its effect on weight. Several papers subsequently were published in 2015, dealing with photographic methods and baseline results,[2] quality of life,[3] retinal and choroidal folds in the participants,[4] and risk factors for poor outcome in the trial.[5] In 2016, five further papers were published in peer-reviewed journals.

Wall et al.[6] reported the results of an in-depth assessment of the visual field findings in the two groups of participants enrolled in the IIHTT. They found using pointwise linear regression that the average study eye had 36 of 52 test

locations with improving sensitivity and that differences between the acetazolamide and placebo groups were not significant. Pointwise results mostly improved in both treatment groups, with the magnitude of the mean change within groups greatest and statistically significant around the blind spot and the nasal area, especially in the acetazolamide group. The consensus classification of visual field change from baseline to 6 months in the study eye yielded percentages (acetazolamide, placebo) of 7.2% and 17.5% worse, 35.1% and 31.7% with no change, and 56.1% and 50.8% improved; group differences were not statistically significant. Thus, the only real difference between the groups was a reduction in blind spot size related to improvement in papilledema.

Cello et al.[7] reported the prevalence of visual field treatment failures (TFs) and performance failures (PFs), and discussed the factors associated with PFs in the IIHTT. The IIHTT Visual Field Reading Center evaluated 2950 fields from the participants in the study. They diagnosed a TF when the participant's mean deviation (MD) worsened ≥2-3 dB from the average baseline MD (with a second retest confirming the deterioration). They considered a PF to have occurred when the participant's: 1) visual field results met TF criteria but were not confirmed on retest, 2) deterioration was confirmed on retest but the IIHTT Adjudication Committee concluded a TF was clinically unlikely. Using these criteria, the authors identified a TF in 7/165 (4%) of the participants and a PF in 35/165 (21%) of the participants on at least one examination. Four of the 35 PFs were adjudicated for a TF; however, based on clinical review by the Adjudication Committee and a third retest, these were judged instead to be PFs. Thus, of the 2,950 total IIHTT field examinations, 2.7% met the criteria for a PF. Thus, a PF was identified in 21% of participants and in 2.7% of the total number of VF examinations and was reversible on repeat testing. The bottom line was that in this cohort of participants, when perimetric worsening appears to have occurred in someone with papilledema who otherwise is clinically stable or improving, retesting is likely to reveal that the apparent worsening is due to poor performance rather than true worsening of the condition. This phenomenon applies to other settings as well, particularly subjects with glaucoma and ocular hypertension.

The protocol for the IIHTT allowed participants to have their oral treatment (acetazolamide or placebo) increased to a dose of (in the case of acetazolamide) 4 gm per day if, in the opinion of the investigator, the participants were failing therapy. Ten Hove et al.[8] reported that during the course of the trial, 38 of 86 participants randomized to the acetazolamide group (44.1%) tolerated the maximum allowed dosage of 4 g/d. The percentages of participants reporting at least one adverse event in the nervous, gastrointestinal, metabolic, and renal organ systems were significantly higher in the acetazolamide group ($P < 0.05$). The odds of paresthesia (OR 9.82; 95% CI 3.87-27.82), dysgeusia (OR ∞; 95% CI 3.99-∞), vomiting and diarrhea (OR 4.11; 95% CI 1.04-23.41), nausea (OR 2.99; 95% CI 1.26-7.49) and fatigue (OR 16.48; 95% CI 2.39-702.40) also were higher in the acetazolamide group than in the placebo group. Nevertheless, the authors concluded that acetazolamide is likely to be tolerated and appears to have an acceptable safety profile at dosages up to 4 g/d in the treatment of subjects with primary pseudotumor cerebri.

As noted above, all participants in the IIHTT were enrolled in a weight loss program that was run by the NYORC and monitored via telephone by counselors. Weil et al.[9] compared the results in both the acetazolamide and placebo groups and concluded that a telephone-based weight loss program achieves results similar to those of a personal-interaction program in subjects who presumably do not have primary pseudotumor cerebri. This presumption is reasonable if one considers that Krispel et al.[10] performed a photographic assessment of the fundi in 606 subjects with an average body mass index of 47 kg/m^2 who attended the UC Davis Bariatric Surgery Clinic over a 3-year period. These investigators found that 17 of these individuals (2.8%) had photographic optic disc findings or symptoms suspicious for papilledema; however, of the 11 who subsequently were evaluated clinically, seven did not have disc swelling. Of the four subjects in whom disc swelling was confirmed on clinical examination, all had "subtle" swelling only. These four subjects all had normal neuroimaging and the three who subsequently underwent lumbar puncture had only borderline high opening pressure. Thus, even if one assumes that the six subjects who had photographic findings suggesting optic disc swelling, 10/600 subjects (1.7%) may have had increased intracranial pressure (ICP). Thus, if one accepts the findings of these investigators that fewer than 2% of neurologically asymptomatic individuals who are morbidly obese are likely to have increased ICP, the findings in the IIHTT regarding weight loss indicate that there is no reason that with the proper regimen, subjects with primary pseudotumor cerebri should be able to lose weight to the same degree (ie, about 6% over 6 months) as individuals who do not have primary pseudotumor cerebri.

Finally, Bruce et al.[11] assessed the quality of life (QOL) in participants in the IIHTT using three measures: the NEI-VFQ-25, the 10-item NEI-VFQ-25 Neuro-Ophthalmic Supplement, and the 36-item Short form Health Survey. These authors found marked reductions in baseline QOL that were improved in the subjects treated with acetazolamide. Their findings would appear to support the use of acetazolamide in addition to dietary intervention in this group of patients.

LEBER HEREDITARY OPTIC NEUROPATHY

The quest for a method of preventing vision loss and restoring vision once it has been lost in patients with Leber hereditary optic neuropathy (LHON) continues following the failure of idebenone,[12] brimonidine,[13] and other agents[14]. In

recent years, gene therapy using an adeno-associated viral (AAV) vector carrying ND4 genetic material has emerged as the next great hope. This has led to three prospective clinical trials, one in China, one in Europe (with sites in the US as well), and one in the United States. To date, only the Japanese trial has published final results, whereas the US trial has published some preliminary data. The trial in France (and the US) has yet to publish anything in the peer-reviewed literature; however, there are some data that are discussed below.

Investigators in China[15, 16] performed a prospective, open-label trial (NCT01267422) involving nine subjects with LHON associated with the G11778A mitochondrial mutation at Tongji Hospital, Wuhan, China, from August 2011 to December 2015. All nine subjects, whose symptoms and signs had begun between 1 and 17 years previously, received a single intravitreal injection of rAAV2-ND4. Systemic examinations and visual function tests were performed during the 36-month follow-up period to determine the safety and efficacy of this gene therapy. Based on successful experiments in an animal model of LHON, 1 subject also received a rAAV2-ND4 injection in the second eye 12 months after gene therapy was administered in the first eye. The primary outcome of this trial was recovery of visual acuity. Secondary endpoints were changes in the visual field, visual evoked potential (VEP), optical coherence tomography (OCT) findings, liver and kidney function, and antibodies against AAV2. Eight subjects received unilateral gene therapy, following which improvement in visual function was observed in both treated (Subjects 4, 6, 7, and 8) and untreated eyes (Subjects 2, 3, 4, 6 and 8). Visual regression fluctuations, defined as changes in visual acuity greater than or equal to 0.3 logMAR, were observed in two subjects. Age at disease onset, disease duration, and the amount of remaining optic nerve fibers by OCT did not have a significant effect on the visual function improvement. The visual field improved in all subjects, with both eyes improving in five, two of whom subsequently had worsening. There was a statistically significant decrease in the P100 latency on the pattern-reversal VEP in these subjects, and the P100 amplitude also increased although the increase was not significant. The one subject (Subject 1) who received gene therapy in both eyes had improved visual acuity in the injected eye after the first treatment; however, visual acuity in this eye decreased 3 months after he received gene therapy in the second eye. No serious adverse events occurred during the 3-year follow-up in any of the nine participants.

Feuer et al.[17] reported preliminary results of a phase 1 prospective open-label trial (NCT02161380) of intravitreal gene therapy for LHON associated with the G11778A mutation being conducted at the Bascom Palmer Eye Institute in Miami, Florida. There are three groups of subjects in this trial. ***Group I*****:** Patients with ≥12 months since onset in one eye and at least 6 months onset in the more recently affected eye. Both eyes must have acuity reduced to ≤ 35 letters. If both eyes have ≥12 months since onset, the eye with worse visual acuity is injected. If both eyes have the same acuity, the eye with longest onset is injected. If one eye has <12 months and >6 months since onset and the difference in acuity between the eyes is ≤10 letters, the eye with ≥12 months is injected. If eyes have an acuity difference >10 letters, the eye with worse acuity is injected. ***Group II:*** Acute and bilateral loss of visual acuity to < 35 ETDRS letters (Snellen = 20/200) in both eyes for less than 12 months. ***Group III.*** Unilateral loss of acuity to < 35 ETDRS letters in one eye, but with mildly impaired but good acuity ≥ 70 letters (Snellen = 20/40) in the contralateral eye. For each group, administration of study drug follows an adaptive plan to identify the maximum tolerated dose. If none of three subjects at a given dose level develops a Safety Endpoint, the next cohort of patients receives the next higher dose. The investigators wait a minimum of 6 weeks between patient injections of the same dose and 3 months before moving to the next higher dose. They test the low dose first in 3 patients of group I, before moving on to testing this low dose in group 2, then last in group 3. Even in the absence of Safety Endpoints in groups I and II, there will be a delay of 12 months before the first injection in group III. In this trial, the study drug is self-complementary AAV-P1ND4v2. The preliminary results reported by the investigators indicate that they injected the drug unilaterally into the eyes of five participants with G11778A LHON. Four participants with bilateral visual loss for more than 12 months (Group I) were treated. The fifth participant had bilateral visual loss for less than 12 months (Group II). The first 3 participants (Group I) were treated with the low dose of vector (5 × 10(9) vg), the fourth participant (also in Group I) was treated with the medium dose (2.46 × 10(10) vg). The fifth participant with visual loss for less than 12 months (Group II) received the low dose. Treated participants were followed for 90 to 180 days and underwent ocular and systemic safety assessments along with visual structure and function examinations. Among these five participants, no one lost vision, and no serious adverse events were observed. Minor adverse events included a transient increase of intraocular pressure, exposure keratitis, subconjunctival hemorrhage, a sore throat, and a transient increase in neutralizing antibodies (NAbs) against AAV2 in 1 participant. All blood samples were negative for vector DNA. Visual acuity as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart remained unchanged from baseline to 3 months in the first three participants. For two participants with 90-day follow-up, acuity increased from hand movements to seven letters in 1 and by 15 letters in 1, representing an improvement equivalent to 3 lines. Additional study follow-up of these and additional participants is planned for the next 4 years.

The European trial (NCT02064569) was sponsored by Gensight. Each subject (G11778A mutation) in this phase 1/2 trial had one eye randomly selected to receive a single injection of GS010, a recombinant AAV vector serotype 2

(rAAV2/2) containing the wild-type ND4 gene (rAAV2/2-ND4); the other eye received a sham injection. Although the investigators have not published the results of this trial in a peer-reviewed journal at the time this syllabus was written, they gave a press release recently that indicated that they had treated 15 subjects who were divided into groups of three in a dose-escalation fashion similar to that in the trial reported by Feuer et al. described above. At 48 weeks after treatment, there were no significant adverse effects. In addition, LHON patients who had lost vision within 2 years of treatment showed a gain of 30 letters in the treated eye and a gain of 13 letters in the untreated eye. No significant change in visual acuity, however, was reported in those with disease onset of more than 2 years (on average, trial participants had been symptomatic for 6 years). The company also reported that the vision in those subjects whose vision improved remained stable beyond 48 weeks. These results were sufficient for the company to begin two new phase 3 trials, one (NCT02652767) assessing treatment effects of GS010 in subjects with vision loss that began less than 6 months earlier (PI: Nancy Newman) and the other (NCT02652780) assessing treatment effects in subjects with visual loss between 7 and 12 months earlier (PI: Patrick Yu-Wai Man).

GIANT CELL (TEMPORAL) ARTERITIS

At this time, the only accepted treatment for patients with giant cell arteritis (GCA) is systemic steroids. Unfortunately, steroids produce significant side effects that increase in frequency and severity the longer they are used. Thus, investigators have attempted to identify other drugs that either might be used instead of systemic steroids or might reduce the length of time that steroids are required. Until recently, the only randomized prospective clinical treatment trials were those in which the efficacy of methotrexate as an adjunctive agent was assessed.[18, 19] These studies showed no efficacy. Recently, however, the results of a single-center, randomized, placebo-controlled, phase 2 trial in Switzerland using tocilizumab (TCZ) as add-on therapy, were published.[20] Tocilizumab is a humanized monoclonal anti-IL-6 receptor antibody that binds both soluble and membrane-bound IL-6 receptors and, thus, inhibits Il-6 signal transduction. It has been approved for treatment of patients with rheumatoid and juvenile rheumatoid arthritis and is administered as a monthly infusion of 4 or 8 mg/kg. In this trial, participants satisfying 1990 ACR criteria were randomly assigned in a 2:1 ratio to receive either prednisone + TCZ (8 mg/kg IV of body weight) or prednisone + intravenous placebo. The dose of prednisone was started at 1mg/kg/d and tapered by 0.1mg/kg/d weekly until week 8, then by 0.05mg/kg/d weekly until week 12 (0.1mg/kg/d). Thereafter, the dosage was decreased by 1mg/d monthly to 0mg. The dosage of TCZ was 8mg/kg of body weight, with infusions given every 4 weeks. The primary outcome was the number of subjects in complete remission at week 12 (steroid dose of 0.1mg/kg/d). The secondary outcome was the number of subjects who remained relapse-free at week 52 while the steroids were being tapered. After 12 weeks, 17 participants (85%) in the TCZ group versus four (40%) in the placebo group were in complete remission ($P = 0.030$). At end of trial, 17 subjects (85%) in the TCZ group versus two (20%) in the placebo group had experienced no relapse ($P = 0.008$) (Figure below).

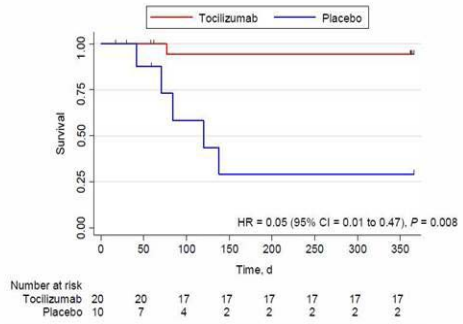

Figure: Kaplan Meier estimate of the time to first relapse after induction of remission.

In terms of safety, 75% of subjects in the TCZ group had side effects vs 70% in the placebo group. Most of the side effects were gastrointestinal and minor; however, nine of the subjects in the TCZ group developed neutropenia. The conclusion of this study was that TCZ is efficacious for induction and maintenance therapy in patients with newly diagnosed or relapsed GCA in the context of rapidly tapered corticosteroids. However, both the investigators and the writer of an accompanying editorial[21] emphasized that the long-term efficacy of TCZ remains unknown as does whether or not the drug should be used instead of steroids as first-line therapy for GCA.

A second trial, the GiACTA Trial, designed to assess the efficacy of TCZ as an add-on drug for GCA finished recruiting in April of 2016. This was a multicenter, placebo-controlled trial in which, like the previous study, patients were randomized to receive either systemic corticosteroids + TCZ or corticosteroids + placebo. The primary outcome was sustained remission at 52 weeks.[22] As of the writing of this syllabus, the results of this study have not been reported; however, the "word on the street" is that the results were similar to those of the Swiss trial (see a NANOS 2017 poster by S Mollan).

OPTIC PATHWAY GLIOMAS

Most optic pathway gliomas occur in children, are extremely slow growing, and do not damage vision sufficiently to require treatment. Nevertheless, treatment may be appropriate in some patients with gliomas confined to one optic nerve as well as patients with chiasmal gliomas. Falsini et al.[23] treated five children with optic nerve gliomas and severe optic disc pallor with a 10-day course of

topical murine nerve growth factor. After treatment, all five showed an increase in VEP amplitudes that persisted for 90 days. The amplitudes declined by 180 days but remained above baseline. During this period, MR imaging showed no change in tumor size. Falsini et al.[24] also performed a randomized, double-masked, phase 2 clinical trial in 17 patients with optic pathway gliomas who had stable visual function and imaging. Patients were treated with either a 10-day course of 0.5 mg of murine nerve growth factor (n=10) or placebo (n=8). All were evaluated at baseline and at 15, 30, 90 and 180 days. The evaluation included assessment of visual acuity and visual field as well as VEP amplitudes, OCT of the peripapillary retinal nerve fiber layer, and MR imaging. These investigators noted no adverse effects from treatment and statistically significant improvement in all parameters in subjects receiving nerve growth factor. Visual field worsening occurred only in subjects who had received placebo. These trials suggest that the use of murine nerve growth factor may be a safe and effective way to stabilize or restore vision in eyes with reduced function in the setting of optic pathway gliomas.

CME ANSWERS

1. c
2. b
3. a

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PEDIATRIC OPTIC NEURITIS

Grant T. Liu, MD

University of Pennsylvania/Children's Hospital of Philadelphia
Philadelphia, PA

LEARNING OBJECTIVES

1. Demonstrate articles regarding pediatric optic neuritis published from 2014-2016
2. Explain the emerging role of anti-MOG antibodies in pediatric demyelinating diseases
3. Describe the Pediatric Eye Disease Investigator Group (PEDIG)/Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) co-sponsored pediatric optic neuritis prospective study

CME QUESTIONS

1. As in adults, white matter lesions on MRI are predictive of conversion to MS in pediatric optic neuritis.
   a. True
   b. False
2. Anti-MOG antibodies in pediatric optic neuritis predict a poorer prognosis for visual outcome and speed of recovery.
   a. True
   b. False
3. The ONTT found that steroids hasten visual recovery in children with optic neuritis.
   a. True
   b. False

KEYWORDS

1. Pediatric Optic Neuritis
2. Multiple Sclerosis
3. Anti-MOG Antibodies
4. Acute Disseminated Encephalomyelitis (ADEM)
5. NMO Spectrum Disorder

INTRODUCTION

Pediatric optic neuritis differs from adult optic neuritis because the condition in children is commonly bilateral, associated with optic disc swelling, and characterized by severe vision loss.[1] The risk of developing multiple sclerosis (MS) is related to the presence of white matter lesions in the brain at presentation, like in adults, but is also associated with older age at presentation.[2]

Several articles have been published from 2014-2016 which have further characterized the clinical and laboratory features of pediatric optic neuritis. The importance of anti-MOG antibodies in pediatic optic neuritis and demyelinating disorders has emerged. Finally, a description of the Pediatric Eye Disease Investigator Group (PEDIG)/ Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) sponsored Pediatric Optic Neuritis Prospective Outcomes Study was published in 2016.

I will restrict the discussion to articles in English published on the subject 2014-16. I will not be discussing case reports describing small numbers of children with optic neuritis purportedly associated with another medical condition.

VISUAL OUTCOME

Wan et al.[3] retrospectively analyzed 59 pediatric patients with first-episode optic neuritis seen at the Children's Hospital of Boston. Fifty-two percent had or developed an underlying diagnosis (39% multiple sclerosis (MS), 7% acute disseminated encephalomyelitis (ADEM), 7% neuromyelitis optica (NMO)), and 91% received some treatment (85% corticosteroids, 7% multimodal). At 1 year, 81% had visual acuity of at least 20/20 and 89% saw at least 20/40. A poor visual outcome at one year (<20/40) was associated with vision of <20/20 at 3 months. Visual acuity at presentation, sex, bilateral involvement, optic nerve edema, and underlying diagnoses were not associated with poor visual outcomes. They concluded that the majority of patients regained normal visual acuity at one year, regardless of baseline clinical characteristics.

Wan et al.[3] also included data on speed of recovery. Patients who regained normal visual acuity took an average of 61 days to do so, but the time to recovery depended on the presenting visual acuity. Those who presented with a mean of counting fingers or worse took a mean of 97 days to recover normal vision, while those who presented with visual acuity better than counting fingers took a mean of 35 days.

ELEVATED CSF OPENING PRESSURE

Narula et al.[4] reviewed the lumbar puncture (LP) results of pediatric patients with ADEM, MS or a clinical isolated syndrome (including optic neuritis and transverse myelitis). Only those patients who had an LP within one month of presentation were eligible for inclusion, and these were compared to a reference cohort of healthy children from the same institution.[5] Opening pressure was elevated in 15 of 53 (28%) children, which was significantly higher than in the reference cohort (10%) (p=.0001). There was no relationship between elevated opening pressure and any patient clinical or radiologic variables. They concluded that almost one third of children with inflammatory demyelinating disease may have an elevated CSF opening pressure. Therefore the CSF opening pressure alone can not be used to differentiate bilateral disc swelling in a child due to pseudotumor cerebri syndrome from that due to bilateral optic neuritis.

OCT FEATURES

Graves et al.[6] reviewed the SD-OCT findings in MS patients with and without a history of optic neuritis. They found that eyes with a history of optic neuritis showed reduced retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) volumes than control eyes, and those without a history of optic neuritis had lower temporal RNFL and GCL volumes than control eyes. Eyes with optic neuritis were more affected than non-optic neuritis eyes. Greater axonal injury occurred in boys compared to girls. Yeh et al.[7] also found that mean RNFL thickness and GCL thickness was lower in patients with demyelination compared to controls, but only GCL thickness was decreased regardless of history of optic neuritis.

On the other hand Avery et al.[8] reviewed TD-OCT evidence that RFNL thickness may be preserved in children with MS who did not have a history of optic neuritis in either eye.

RISK OF CONVERSION TO MS

Heussinger et al.[9] reviewed the records of 357 children with optic neuritis as a first demyelinating event. Abnormal MRI, the presence of oligoclonal bands and age predicted conversion to MS, while sex and laterality (uni- or bilaterality) had no influence. Patients with a combined abnormal MRI and presence of oligoclonal bands had a 27x's greater risk of converting to MS compared to those without either. Forty-one percent converted to MS after a mean follow-up of 4.0 years.

Kim et al.[10] found a 7.7% conversion rate to MS in a series of Korean patients, but the mean follow-up was 16 months in prepubertal patients and 8 months in postpubertal ones.

NEUROMYELITIS OPTICA (NMO)

With only a few exceptions, for instance the presence of aquaporin-4 immunoglobulin G (AQP4IgG) in a patient with ADEM, most clinical scenarios described in the adult diagnostic criteria for NMOSD apply to children.[11]

In one series of twenty cases of pediatric NMO,[12] AQP4IgG positivity was associated with early recurrence and visual impairment, while AQP4IgG negativity was associated with physical disability. Because of cumulative attack-related disability,[13] rituximab has been advocated as a first-line therapy.[14]

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY (ANTI-MOG) ASSOCIATION

Antibodies to myelin oligodendrocyte glycoprotein (anti-MOG antibodies) have been associated with acquired demyelinating diseases. The glycoprotein is located on the external surface of the myelin sheath. Antibodies have been found in pediatric patients with ADEM but only infrequently in those children with MS.

Thulasirajah et al.[15] described five children with anti-MOG syndrome. Two patients had optic neuritis as part of their clinical course, but other presentations included polyfocal demyelination, longitudinally extensive tranverse myelitis (LETM), NMO spectrum disorder, and ADEM. The concluded that children with anti-MOG antibody syndrome had more favorable outcomes (ie more rapid recovery and fewer relapses) compared with other demyelinating conditions. Hino-fukuo et al.[16] also found a favorable prognosis in patients with demyelination associated with anti-MOG antibodies. Anti-MOG antibodies predicted a non-MS course in one other study[17]

Fernandez-Carbonell et al.[18] found that 12 of 74 of pediatric patients with demyelinating disease were positive for anti-MOG antibodies. Younger patients had a high prevalence of encephalopathy, while some of the older group presented almost exclusively with optic neuritis.

Baumann et al.[19] found that 19 of 33 children with ADEM were positive for anti-MOG antibodies. The 19 patients had a uniform MRI pattern characterized by large, hazy, and bilateral lesions and the absence of small, well-defined lesions. Those with anti-MOG antibodies had involvement of more anatomical areas including LETM, more complete resolution of lesions, and better outcome.

Miyauchi et al.[20] reported a patient with the phenotype of ADEM followed by optic neuritis who was positive for anti-MOG antibody. Tsuburaya et al.[21] reported a child with anti-MOG antibodies and recurrent optic neuritis.

Ramanathan et al.[22] review the evidence whether anti-MOG is indeed pathogenetic. They also provide a diagnostic algorithm, highlighting that serum anti-MOG should be tested for in cases not typical for MS, ADEM, or NMOSD, particularly when AQP4IgG testing is negative.

TREATMENT

Yeh et al.[23] stated that treatment of pediatric optic neuritis consists of IV methyprednisolone for 3-5 days although they did state that there have been no clinical trials to establish the efficacy of this treatment modality. Children were not included in the Optic Neuritis Treatment Trial (ONTT). The optimal duration of oral steroids following IV is also not clear. One study[24] found no difference in outcome between a shorter (2 weeks) and longer (>2 weeks) course of steroids in children with pediatric optic neuritis. Case reports and small series have described the success of intravenous immunoglobulin and plasmapheresis in patients with optic neuritis not responsive to corticosteroids.[25, 26]

PEDIATRIC OPTIC NEURITIS PROSPECTIVE OUTCOMES STUDY (IN JNO 2016)

Pineles et al.[27] described the PEDIG/NORDIC co-sponsored study which has two aims: to determine the feasibility of sufficient enrollment for a pediatric optic neuritis treatment trial, and to measure clinically important outcomes in a prospectively studied cohort of children with pediatric optic neuritis. This study will provide sorely needed prospective data regarding this condition.

CME ANSWERS

1. True
2. False
3. False

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MYASTHENIA GRAVIS

Matthew J. Thurtell, MBBS, MSc, FRACP

University of Iowa
Iowa City, IA

LEARNING OBJECTIVES

1. Review recent studies investigating autoantibodies implicated in the pathogenesis of seronegative myasthenia gravis
2. Review a recent prospective study investigating the role of thymectomy in the treatment of myasthenia gravis
3. Review recent prospective studies investigating the role of steroids and steroid-sparing agents in the treatment of myasthenia gravis

CME QUESTIONS

1. Which of the following autoantibodies is most likely to be a marker for myasthenia gravis rather than pathogenic?

    a. Titin antibody
    b. Acetylcholine receptor antibody
    c. Muscle-specific kinase (MuSK) antibody
    d. Lipoprotein-related receptor protein 4 (LRP4) antibody

2. Thymectomy in patients with seropositive generalized myasthenia gravis without thymoma results in which of the following:

    a. Decreased clinical activity of myasthenia
    b. Decreased requirement for immunosuppressive therapy
    c. Decreased number of side-effects related to immunosuppressive therapy
    d. All of the above

3. Which of the following immunomodulatory agents is least likely to be effective for treatment of generalized myasthenia gravis?

    a. Azathioprine
    b. Methotrexate
    c. Cyclosporine
    d. Intravenous immunoglobulin

KEYWORDS

1. Myasthenia Gravis
2. Autoantibodies
3. Thymectomy
4. Immunosuppression

INTRODUCTION

Myasthenia gravis is a disorder of neuromuscular transmission resulting from binding of autoantibodies to various components of the neuromuscular junction. In this journal club session, I will review recent studies evaluating potentially pathogenic autoantibodies in patients with seronegative myasthenia gravis (i.e., those without acetylcholine receptor or muscle-specific kinase autoantibodies). I will also review several recent prospective randomized trials evaluating the role of thymectomy and immunosuppressant therapies in the treatment of myasthenia gravis.

PATHOGENESIS OF MYASTHENIA GRAVIS

Antibodies to the post-synaptic acetylcholine receptor are the most commonly identified autoantibodies in myasthenia gravis.[1] Muscle-specific kinase (MuSK) antibodies can be detected in a subgroup of patients who do not have acetylcholine receptor antibodies.[1] However, some patients are double seronegative. Several recent studies have identified new autoimmune targets in double seronegative myasthenia gravis patients.[2] However, to establish if an antibody is pathogenic, strict criteria must be met: (1) antibodies must be identified at the site of pathology; (2) antibodies from patients must induce pathology consistent with the disease; (3) immunization with antigen must reproduce the disease; and (4) removal of antibodies must improve symptoms and signs.[3] Thus, the pathogenic nature of several of these antibodies has not yet been confirmed.

ANTIBODIES TO LIPOPROTEIN-RELATED RECEPTOR PROTEIN 4

Marino M, Scuderi F, Samengo D, et al. Flow cytofluorimetric analysis of anti-LRP4 (LDL receptor-related protein 4) autoantibodies in Italian patients with myasthenia gravis. *PLoS One* 2015; 10(8): e0135378.[4]

Background: Myasthenia gravis (MG) is an autoimmune disease in which 90% of patients have autoantibodies against the muscle nicotinic acetylcholine receptor (AChR), while autoantibodies to muscle-specific tyrosine kinase (MuSK) have been detected in half (5%) of the remaining 10%. Recently, the low-density lipoprotein receptor-related protein 4 (LRP4), identified as the agrin receptor, has been recognized as a third autoimmune target in a significant portion of the double sero-negative (dSN) myasthenic individuals, with variable frequency depending on different methods and origin countries of the tested population. There is also convincing experimental evidence that anti-LRP4 autoantibodies may cause MG.

Methods: The aim of this study was to test the presence and diagnostic significance of anti-LRP4 autoantibodies in an Italian population of 101 myasthenic patients (55 dSN, 23 AChR positive and 23 MuSK positive), 45 healthy blood donors and 40 patients with other neurological diseases as controls. All sera were analyzed by a cell-based antigen assay employing LRP4-transfected HEK293T cells, along with a flow cytofluorimetric detection system.

Results: We found a 14.5% (8/55) frequency of positivity in the dSN-MG group and a 13% frequency of co-occurrence (3/23) in both AChR and MuSK positive patients; moreover, we report a younger female prevalence with a mild form of disease in LRP4-positive dSN-MG individuals.

Conclusion: Our data confirm LRP4 as a new autoimmune target, supporting the value of including anti-LRP4 antibodies in further studies on Myasthenia gravis.

Overall, this study supports several other recent studies[5,6] suggesting a role for LRP4 antibodies in causing myasthenia gravis.

ANTIBODIES TO CORTACTIN

Cortes-Vincente E, Gallardo E, Martinez MA, et al. Clinical characteristics of patients with double-seronegative myasthenia gravis and antibodies to cortactin. *JAMA Neurol* 2016; 73: 1099-1104.[7]

Importance: Double-seronegative myasthenia gravis (dSNMG) includes patients with myasthenia gravis (MG) without detectable antibodies to the nicotinic acetylcholine receptor (AChR) or to muscle-specific tyrosine kinase (MuSK). The lack of a biomarker hinders the diagnosis and clinical management in these patients. Cortactin, a protein acting downstream from agrin/low-density lipoprotein receptor-related protein 4 (LRP4)/MuSK, has been described as an antigen in dSNMG.

Objective: To describe the frequency and clinical features of patients with dSNMG who have cortactin antibodies.

Design, setting, and participants: A retrospective cross-sectional study was conducted at Hospital de la Santa Creu i Sant Pau, an institutional practice referral center in Barcelona, Spain, between May 1, 2015, and November 30, 2015. We included 250 patients with a definitive diagnosis of MG with available serum samples at the time of diagnosis. Descriptive and comparative data analyses were performed.

Exposures: Cortactin antibodies were measured by enzyme-linked immunosorbent assay and Western blot; AChR, MuSK, and anti-striated muscle antibodies were detected using a standard method; and LRP4 antibodies were tested using a cell-based assay.

Main outcomes and measures: The primary outcome was the frequency of patients with dSNMG who have cortactin antibodies. Secondary outcomes were demographic, clinical, neurophysiological, and laboratory data.

Results: Of 250 patients (mean [SD] age at onset, 49.7 [21.2] years; 56% female), 38 (15.2%) had dSNMG, 201 (80.4%) had MG with AChR antibodies, and 11 (4.4%) had MG with MuSK antibodies. Cortactin antibodies were identified in 28 patients with MG: 9 of 38 (23.7%) who had dSNMG, 19 of 201 (9.5%) who had MG with AChR antibodies (significantly lower than those with dSNMG: 9.5% vs 23.7%; P = .02), and 0 of 11 who had MG with MuSK antibodies; 0 of 29 controls had cortactin antibodies. At onset, among the 9 patients with dSNMG and cortactin antibodies, 6 had ocular MG and 3 had Myasthenia Gravis Foundation of America clinical classification IIA. Two patients with ocular MG developed generalized MG. The group with dSNMG and cortactin antibodies, compared with those who had MG with AChR antibodies, more frequently had mild forms at onset (100.0% vs 62.7%; P = .03), had fewer bulbar signs at maximal worsening (0% vs 41.3%; P = .01), and were younger at onset (median [interquartile range], 34.9 [9.5] vs 53.9 [38.5] years; P = .03); the group with dSNMG and cortactin antibodies also more frequently had ocular MG at onset than those with MG and AChR antibodies, although the difference was not statistically significant (66.7% vs 40.8%; P = .17). Of 17 patients with ocular dSNMG, 4 (23.5%) had antibodies to cortactin.

Conclusions and relevance: In this study, patients with cortactin antibodies and dSNMG had an ocular or mild generalized phenotype of MG. Including the detection of cortactin antibodies in the routine diagnosis of dSNMG may be helpful in ocular MG.

Overall, this study suggests a role for cortactin antibodies in causing myasthenia gravis. Double seronegative patients with cortactin antibodies tended to have either ocular myasthenia or mild generalized myasthenia.

ANTIBODIES TO TITIN

Stergiou C, Lazaridis K, Zouvelou V, et al. Titin antibodies in "seronegative" myasthenia gravis – a new role for an old antigen. *J Neuroimmunol* 2016; 292: 108-115.[8]

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies targeting the neuromuscular junction of skeletal muscles. Triple-seronegative MG (tSN-MG,

without detectable AChR, MuSK and LRP4 antibodies), which accounts for ~10% of MG patients, presents a serious gap in MG diagnosis and complicates differential diagnosis of similar disorders. Several AChR antibody positive patients (AChR-MG) also have antibodies against titin, usually detected by ELISA. We have developed a very sensitive radioimmunoprecipitation assay (RIPA) for titin antibodies, by which many previously negative samples were found positive, including several from tSN-MG patients. The validity of the RIPA results was confirmed by western blots. Using this RIPA we screened 667 MG sera from 13 countries; as expected, AChR-MG patients had the highest frequency of titin antibodies (40.9%), while MuSK-MG and LRP4-MG patients were positive in 14.6% and 16.4% respectively. Most importantly, 13.4% (50/372) of the tSN-MG patients were also titin antibody positive. None of the 121 healthy controls or the 90 myopathy patients, and only 3.6% (7/193) of other neurological disease patients were positive. We thus propose that the present titin antibody RIPA is a useful tool for serological MG diagnosis of tSN patients.

Overall, this study suggests that titin antibodies may be a useful marker for myasthenia gravis, especially in patients who are triple-seronegative (i.e., no acetylcholine receptor, MuSK, or LRP4 antibodies).

TREATMENT OF MYASTHENIA GRAVIS

The treatment for myasthenia gravis aims to alleviate symptoms and, ideally, induce disease remission. Symptoms and signs frequently improve with acetylcholinesterase inhibitors, such as pyridostigmine. However, many patients require immunomodulatory therapy to alleviate symptoms and induce disease remission. Corticosteroids remain the mainstay of immunomodulatory therapy for myasthenia gravis, although steroid-sparing agents, such as azathioprine and cyclosporine, can be effective in patients who require larger maintenance doses of corticosteroids or who develop significant corticosteroid complications. Several recent prospective randomized studies have evaluated medical and surgical treatments for myasthenia gravis.

THYMECTOMY

The thymus is thought to have a central role in the pathogenesis of myasthenia gravis.[9] Thus, thymectomy has been proposed as a treatment for non-thymomatous myasthenia gravis; the first study reporting a potential benefit was published 75 years ago.[10] The role of thymectomy in the treatment of myasthenia gravis has remained uncertain, due to a lack of randomized trial data.

Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016; 375: 511-522.[11]

Background: Thymectomy has been a mainstay in the treatment of myasthenia gravis, but there is no conclusive evidence of its benefit. We conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.

Methods: We compared extended trans-sternal thymectomy plus alternate-day prednisone with alternate-day prednisone alone. Patients 18 to 65 years of age who had generalized non-thymomatous myasthenia gravis with a disease duration of less than 5 years were included if they had Myasthenia Gravis Foundation of America clinical class II to IV disease (on a scale from I to V, with higher classes indicating more severe disease) and elevated circulating concentrations of acetylcholine-receptor antibody. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score (on a scale from 0 to 39, with higher scores indicating more severe disease) over a 3-year period, as assessed by means of blinded rating, and the time-weighted average required dose of prednisone over a 3-year period.

Results: A total of 126 patients underwent randomization between 2006 and 2012 at 36 sites. Patients who underwent thymectomy had a lower time-weighted average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone (6.15 vs. 8.99, $P<0.001$); patients in the thymectomy group also had a lower average requirement for alternate-day prednisone (44 mg vs. 60 mg, $P<0.001$). Fewer patients in the thymectomy group than in the prednisone-only group required immunosuppression with azathioprine (17% vs. 48%, $P<0.001$) or were hospitalized for exacerbations (9% vs. 37%, $P<0.001$). The number of patients with treatment-associated complications did not differ significantly between groups ($P=0.73$), but patients in the thymectomy group had fewer treatment-associated symptoms related to immunosuppressive medications ($P<0.001$) and lower distress levels related to symptoms ($P=0.003$).

Conclusions: Thymectomy improved clinical outcomes over a 3-year period in patients with non-thymomatous myasthenia gravis.

Overall, this randomized rater-masked trial showed a benefit of thymectomy in patients with seropositive generalized myasthenia gravis without thymoma over a period of three years with respect to: clinical outcomes; requirements for immunosuppressive therapy; number of symptoms and distress level related to immunosuppressive therapy; and need for hospitalization to manage disease exacerbations. The role of thymectomy in the treatment of patients with seronegative generalized myasthenia gravis and ocular myasthenia gravis (seropositive or seronegative) remains unclear.

CORTICOSTEROIDS

While corticosteroids remain the mainstay of immunomodulatory therapy for myasthenia gravis, the role of corticosteroids in the treatment of ocular myasthenia gravis remains unclear.

Benatar M, McDermott MP, Sanders DB, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): a randomized, controlled trial. *Muscle Nerve* 2016; 53: 363-39.[12]

Introduction: In this study we evaluated the safety, tolerability, and efficacy of prednisone in patients with ocular myasthenia gravis (OMG) concurrently treated with pyridostigmine.

Methods: This investigation was a randomized, double-blind, placebo-controlled trial. Participants whose symptoms failed to remit on pyridostigmine were randomized to receive placebo or prednisone, initiated at 10 mg every other day, and titrated to a maximum of 40 mg/day over 16 weeks. The primary outcome measure was treatment failure.

Results: Fewer subjects were randomized than the 88 planned. Of the 11 randomized, 9 completed 16 weeks of double-blind therapy. Treatment failure incidence was 100% (95% CI 48%-100%) in the placebo group (n = 5) vs. 17% (95% CI 0%-64%) in the prednisone group, P = 0.02 (n = 6). Median time to sustained minimal manifestation status (MMS) was 14 weeks, requiring an average prednisone dose of 15 mg/day. Adverse events were infrequent and generally mild in both groups.

Conclusions: A strategy of low-dose prednisone with gradual escalation appears to be safe, well-tolerated, and effective in treating OMG.

Overall, this randomized, double-masked, and placebo-controlled trial demonstrated that corticosteroids are effective and safe for treatment of ocular myasthenia. Since the follow-up period was short, it remains unclear if corticosteroid treatment might decrease the risk of generalization as has been suggested by retrospective studies.[13]

METHOTREXATE

The role of several steroid-sparing agents for treatment of myasthenia gravis remains unclear. Azathioprine and cyclosporine have been shown to be effective in randomized placebo-controlled studies,[14,15] but an effect from azathioprine was not discernable until after 15 months of treatment and use of cyclosporine is limited by complications (e.g., renal toxicity). Mycophenolate did not show a beneficial effect in two studies.[16,17] Thus, there is an ongoing need to identify steroid-sparing agents that are effective for treating myasthenia gravis.

Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology* 2016; 87: 57-64.[18]

Objective: To determine the steroid-sparing effect of methotrexate (MTX) in patients with symptomatic generalized myasthenia gravis (MG).

Methods: We performed a 12-month multicenter, randomized, double-blind, placebo-controlled trial of MTX 20 mg orally every week vs placebo in 50 acetylcholine receptor antibody-positive patients with MG between April 2009 and August 2014. The primary outcome measure was the prednisone area under the dose-time curve (AUDTC) from months 4 to 12. Secondary outcome measures included 12-month changes of the Quantitative Myasthenia Gravis Score, the Myasthenia Gravis Composite Score, Manual Muscle Testing, the Myasthenia Gravis Quality of Life, and the Myasthenia Gravis Activities of Daily Living.

Results: Fifty-eight patients were screened and 50 enrolled. MTX did not reduce the month 4-12 prednisone AUDTC when compared to placebo (difference MTX - placebo: -488.0 mg, 95% confidence interval -2,443.4 to 1,467.3, p = 0.26); however, the average daily prednisone dose decreased in both groups. MTX did not improve secondary measures of MG compared to placebo over 12 months. Eight participants withdrew during the course of the study (1 MTX, 7 placebo). There were no serious MTX-related adverse events. The most common adverse event was nonspecific pain (19%).

Conclusions: We found no steroid-sparing benefit of MTX in MG over 12 months of treatment, despite being well-tolerated. This study demonstrates the challenges of conducting clinical trials in MG, including difficulties with recruitment, participants improving on prednisone alone, and the need for a better understanding of outcome measure variability for future clinical trials.

Classification of evidence: This study provides Class I evidence that for patients with generalized MG MTX does not significantly reduce the prednisone AUDTC over 12 months of therapy.

Overall, this randomized, double-masked, and placebo-controlled trial suggests that methotrexate is ineffective as a steroid-sparing agent for myasthenia gravis.

CONSENSUS GUIDELINES FOR TREATMENT

While there is agreement about the use of many treatments for myasthenia gravis, there is no internationally accepted standard of care. Due to the heterogeneity of the disease, no one treatment approach is suitable for all patients.[1,19] Therefore, an effort to develop a consensus among international experts has been undertaken to help guide clinicians in the multifaceted approach to managing myasthenia gravis.

Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology* 2016; 87: 419-425.[20]

Objective: To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methods: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness methodology was used to develop consensus guidance statements. Definitions were developed for goals of treatment, minimal manifestations, remission, ocular MG, impending crisis, crisis, and refractory MG. An in-person panel meeting then determined 7 treatment topics to be addressed. Initial guidance statements were developed from literature summaries. Three rounds of anonymous e-mail votes were used to attain consensus on guidance statements modified on the basis of panel input.

Results: Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy.

Conclusion: This is an international formal consensus of MG experts intended to be a guide for clinicians caring for patients with MG worldwide.

Guidance statements were developed for seven categories. A summary of the guidance statements for each category is given below.

Symptomatic and immunosuppressive treatment: Pyridostigmine should be part of the initial treatment in most patients, with doses adjusted as needed based on symptoms. Immunosuppressive therapies should be used in patients who have not met treatment goals after an adequate trial of pyridostigmine. A steroid-sparing agents should be used when there are significant steroid side-effects, no response to a trial of steroids, or there is difficulty reducing steroid dose due to symptom relapse. The choice of initial steroid-sparing agent is unclear due to little literature comparing agents. However, the expert consensus suggests azathioprine over cyclosporine, mycophenolate, and tacrolimus. Patients with refractory myasthenia gravis may respond to intravenous immunoglobulin, plasma exchange, cyclophosphamide, and rituximab. The duration of therapy is unclear, although expert consensus was that it is necessary to maintain immunosuppression for many years in most patients. In the case of steroid-sparing agents, expert consensus suggested not tapering until treatment goals had been maintained for at least 6 months with dose adjustments being made no more frequently than once every 3-6 months.

Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX): Expert consensus was that both of these therapies are effective as short-term treatments for myasthenic crisis. The treatments are probably equally effective for generalized myasthenia (with PLEX being more effective for MuSK myasthenia. IVIg can be effective maintenance therapy for patients with refractory myasthenia or contraindications to other therapies.

Impending and manifest myasthenic crisis: Impending and manifest crisis requires hospital admission (often intensive care or step-down unit). Expert consensus was that IVIg and PLEX constitute the mainstay of treatment, but that PLEX tends to be more effective with a more rapid onset of effect. Steroid or steroid-sparing agents can also be started for ongoing (long-term) treatment.

Thymectomy: All patients with thymoma should undergo thymectomy, although radiation could be an alternative treatment for elderly or severely ill patients. Thymectomy may be beneficial in patients with seropositive generalized non-thymomatous myasthenia gravis (see above).

Juvenile myasthenia gravis: Children with ocular myasthenia gravis are more likely to go into spontaneous remission and should be treated solely with pyridostigmine if possible. Due to the high risk of steroid side-effects, steroids should be used only when treatment goals are not met with the lowest effective dose.

MuSK myasthenia gravis: Patients with MuSK myasthenia gravis tend to respond poorly to pyridostigmine, but respond well to steroids, steroid-sparing agents, and PLEX. IVIg is often less effective. Rituximab can be used in those who do not respond well to other immunosuppressive agents.

Myasthenia gravis in pregnancy: Pyridostigmine is first-line treatment during pregnancy and steroids are the immunosuppressive agent of choice. While both azathioprine and cyclosporine are relatively safe when disease is not controlled with pyridostigmine and steroids, mycophenolate and methotrexate increase the risk of teratogenicity. IVIg and PLEX can be helpful in the case of myasthenic crisis, but the benefits of their use must be weighed against risk to both mother and fetus.

CME ANSWERS

1. a
2. d
3. b

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OPTICAL COHERENCE TOMOGRAPHY AND OPTIC NERVE HEAD DRUSEN

Fiona Costello, MD, FRCP

Associate Professor, Departments of Clinical Neurosciences and Surgery, University of Calgary
Calgary, Alberta, Canada

LEARNING OBJECTIVES

1. Identify spectral domain optical coherence tomography (SD-OCT) features of optic nerve head drusen (ONHD)
2. Determine what potential advantages SD-OCT may offer relative to other ancillary tests to facilitate the detection of ONHD
3. Compare SD-OCT findings that differentiate papilledema from pseudo-papilledema secondary to ONHD
4. Highlight advancements in OCT that might improve upon our current understanding of how this technology can be used in the diagnosis and management of ONHD

CME QUESTIONS

1. Name one potential advantage of SD-OCT over standard ancillary tests in the diagnosis of ONHD:
    a. SD-OCT can help localize non-calcified drusen
    b. SD-OCT has been reported to demonstrate correlations between ONHD, RNFL thickness, and visual field defects
    c. SD-OCT is a non-invasive, high resolution ocular imaging technique
    d. All of the above
2. OCT features that may help distinguish ONDH from papilledema include:
    a. Thicker nasal RNFL values in cases of ONHD
    b. Thinner temporal RNFL values in cases of ONHD
    c. Thicker subretinal hyporeflective space values in cases of ONHD compared to eyes with optic disc edema
    d. The angling of Bruch's membrane towards the vitreous in cases of papilledema
3. EDI-OCT provides what advantage over conventional OCT methods in the detection of ONHD:
    a. EDI-OCT has made it possible to visualize structures, including ONHD, 500–800µm deeper than with SD-OCT
    b. Reduced optic disc drusen diameter correlates with increased sectors of thinned RNFL with EDI-OCT
    c. EDI-OCT has shown that reduced drusen within the optic canal has been associated with thinner RNFL values
    d. EDI-OCT provides more patient comfort than SD-OCT

KEYWORDS

1. Spectral-Domain OCT
2. Superficial ONHD
3. Buried ONHD
4. Enhanced Depth Imaging OCT
5. Swept Source OCT
6. Papilledema
7. Pseudopapilledema

INTRODUCTION

Optic nerve head drusen (ONHD) are deposits of calcium, amino and nucleic acids, and mucopolysaccharides, which may be buried within the optic nerve or lie at the surface of the optic disc.[1] These deposits often become calcified over time. Clinically apparent ONHD are estimated to occur in 0.3% of the population; in approximately 75% of cases, ONHD are bilateral.[1] While ONHD may occur in association with several clinical conditions including: retinitis pigmentosa, pseudoxanthoma elasticum, and Alagille syndrome, the majority of affected individuals have no underlying ocular or systemic abnormalities.[1] Associated visual field abnormalities are observed in 24%–87% of ONHD cases, and these deficits may progress at variable rates over time.[1] Previously, Lee and Zimmerman[3] reported a 1.6% per year increase in severity of ONHD-related visual field loss during a 36-month follow up period. While the mechanism(s) of vision loss in ONHD has not been fully elucidated, it has been postulated that mechanical stress

on structures within the prelaminar scleral canal may lead to retrograde axonal degradation and ganglion cell death.[1] Currently there are no treatments available to prevent or ameliorate vision loss caused by ONHD.

IDENTIFYING OPTIC NERVE HEAD DRUSEN: THE ROLE OF ANCILLARY TESTING

When ONHD are superficial, the diagnosis can readily be made with careful ophthalmoscopic observation. In this setting, the examination will typically reveal optic disc elevation, blurred optic disc margins without obscuration of peripapillary retinal vessels, and a nodular appearance of the optic disc border.[4] In clinical practice, these fundus findings have conventionally been relied upon to help distinguish ONHD from papilledema, which, in contrast, is characterized by: opacification with obscuration of retinal vessels, capillary dilation over the optic disc surface, and retinal hemorrhages.[4] It has been posited that superficial ONHD become visible in an age-dependent fashion because of drusen-related growth, or alternatively, loss of overlying neural tissue which may have initially obscured visualization.[1] In contrast, when ONHD are "buried" and lie relatively to the lamina cribrosa, they can be difficult to detect and differentiate from papilledema by ophthalmoscopy alone.[1] In this setting, ancillary testing may be needed to confirm the diagnosis. To this end, B-scan ultrasonography, has been used to identify calcified ONHD, which appear as highly reflective round structures that can also be identified by their acoustic shadowing.[1] Ultrasonography also provides some detail regarding the posterior limits and dimensions of ONHD,[1] however this testing modality offers relatively poor resolution and provides no information regarding the neuroaxonal integrity of the optic nerve and retinal structures. Fundus auto-fluorescence exploits the auto-fluorescent properties of ONHD, and can be useful for differentiating ONHD from optic disc edema. Yet this technique is relatively insensitive in the detecting deeper, buried drusen.[1] Fluorescein angiography uses a fluorescent dye and camera to provide information regarding retinal and choroidal circulation. Pineles and Arnold [4] reported that fluorescein angiography can be effective in differentiating between ONHD and optic disc edema, even in cases of buried optic disc drusen. According to their findings, optic disc edema tends to be associated with diffuse, early fluorescein leakage whereas buried ONHD are characterized by late peripapillary staining, which could be either circumferential (80%) or nodular (20%) in appearance.[4] One disadvantage of fluorescein angiography, however, is that it is a relatively invasive procedure that poses some discomfort and potential risk to patients.

OPTIC NERVE HEAD DRUSEN: WHAT ADVANTAGES DOES OPTICAL COHERENCE TOMOGRAPHY OFFER?

Optical coherence tomography (OCT) is a noninvasive ocular imaging technique that can be used to quantify neuroaxonal integrity within the afferent visual pathway. As the "optical analog of ultrasound B-mode imaging" [5] OCT enables visualization and quantification of retinal nerve fiber layer (RNFL) and ganglion layer (GCL) structures. In a recent review, Rebolleda and colleagues [6] reported that OCT measured peripapillary RNFL and GCL values are reduced in ONHD eyes. As ONHD become more superficial, RNFL thickness tends to decrease. Moreover, there is an association between lower OCT-measured RNFL and GCL values, increased numbers of clinically visible ONHD, and worsening VF defects.[6] In eyes with buried ONHD, GCL measures are more likely to be abnormal than RNFL values. Thus, GCL analysis may be more useful for detecting early neuroaxonal damage in this context.[6] Lee and colleagues[7] used SD-OCT to identify features of ONHD that help differentiate these cases of from optic disc edema. They evaluated 45 patients with ONHD, 15 patients with optic disc edema, and 32 normal controls. Cases of ONHD revealed the drusen to be focal, hyper-reflective, subretinal masses with discrete margins.[7] The RNFL was deformed in cases of ONHD, demonstrating features of pseudo-edema and high reflectance.[7] The outer nuclear layer was shown to smoothly cover the drusen, which created a distinctive adjacent hypo-reflective, boot-shaped area.[7] These investigators also reported that in cases of ONHD, the RNFL thickness was thinner in the nasal area and thicker in the temporal areas than that in control eyes.[7] Moreover there was a negative correlation between the height of drusen and the RNFL thickness in the nasal region.[7] These investigators postulated that this finding may occur because sub-retinal drusen are usually located in the nasal area, and displace the RNFL into the superior, inferior, and temporal areas.[7] These displaced nerve fibers may, in turn alter the normal distribution of RNFL thickness patterns resulting in relatively thin nasal layers and correspondingly thick superior, inferior, and temporal layers.[7] They also hypothesized that the compressive effects of drusen might result in the atrophy of the nasal retinal nerve fibers, whereas increased thickness of other areas might result from the crowding effect caused by the reduced optic disc size they observed in ONHD eyes.[7]

Recently, Malmqvist and colleagues[8] performed a retrospective study involving 149 eyes of 84 ONHD patients (65% female; 76% bilateral ONHD cases) with the objective of comparing the peripapillary RNFL thickness and visual field defects with anatomic location of the drusen (superficial or buried). Visual field defects were seen in 81% of all eyes with a significant difference between superficial (88%) and buried (55%) ONHD cases ($p = 0.0004$). [8] In this study, OCT- measured RNFL thinning was more pronounced

in eyes with superficial ONHD compared with eyes with buried ONHD (p = 0.001).[8] Correlation analysis between mean peripapillary RNFL thinning and visual field defects showed worse visual field function was associated with decreased peripapillary RNFL thickness.[8] When the investigators stratified ONHD by anatomic location in the optic disc (superficial or buried), a significant correlation between RNFL loss and pattern mean deviation was only seen in the group of eyes with superficial drusen.[8] The investigators postulated that the difference in RNFL thinning between superficial and buried ONHD could be that "early" (buried) drusen do not affect the optic nerve head to the same degree as superficial drusen.[8] Specifically, they suggested that buried ONHD are less likely to be calcified, and by extension may be less damaging to optic nerve axons.[8] From their findings the authors recommended that future studies aimed at quantifying ONHD volume with measures of optic nerve function are needed.[8]

While SD-OCT has advanced our ability to detect ONHD, the disadvantage of this technology is that as depth increases, resolution decreases. This means that deeper ONHD are often poorly demarcated.[1] Recent advances including enhanced depth imaging (EDI-OCT) and swept source OCT (SS-OCT) have made it possible to quantify optic disc drusen dimensions and examine the integrity of neighboring structures in the retina and optic disc. These devices may therefore enhance our understanding of relationships between ONHD, RNFL and GCL loss, and visual field defects among ONHD patients. Specifically, EDI-OCT has made it possible to visualize structures 500–800µm deeper than with SD-OCT. Sato and colleagues [9] demonstrated that EDI-OCT is effective in detecting ONHD, obtaining images of the posterior limits of disc drusen, and measuring drusen area. In a prospective comparative cross-sectional study, Merchant and colleagues[10] noted that EDI-OCT was able to detect ONHD more frequently than B-scan ultrasonography. In this study superficial ONHD visible on the optic disc surface were identified by both EDI-OCT and B-scan ultrasonography.[10] However, in 25 eyes with *suspected* ONHD, EDI-OCT detected drusen in 17 eyes compared to B-scan which detected drusen in only 7 eyes.[10] In the study by Merchant and colleagues,[10] ONHD were evident either as signal-poor regions surrounded by short hyper-reflective bands, or as isolated hyper-reflective bands without a signal poor core. EDI-OCT also has the advantage of being able to assess the shape and structure of the drusen; and, has utility in establishing correlations between ONHD and RNFL.[1] EDI-OCT has shown a negative correlation between the diameter of disc drusen and the mean RNFL thickness in ONHD eyes.[1] A significant positive correlation has been shown between disc drusen diameter and the number of sectors of thinned RNFL. Moreover, increased presence of drusen within the optic canal has been associated with thinner RNFL values in ONHD eyes.[1] Finally, EDI-OCT might aid in the detection of early drusen formation, by showing the presence of deep hyper-reflective bands within the optic nerve head.[1]

Swept Source OCT uses a laser that sweeps across a range of wavelengths to produce an image with a scanning speed of 100,000 Hz at the 1µm wavelength region.[1] The SS-OCT light source has a center wavelength of 1,050 nm, yielding approximately 8µm axial resolution. This OCT technique has been shown to significantly improve visualization of the posterior ocular structures compared to conventional OCT techniques.[1] Similar to EDI-OCT, SS-OCT has the advantage of providing a complete cross-sectional area of the druse.[1] SS-OCT also allows evaluation of drusen-associated RNFL thinning.[1] In the aforementioned study by Sato and colleagues, [9] SS-OCT demonstrated ONHD to be visible as ovoid regions of low reflectivity with hyperreflective curvilinear borders.

DISTINGUISHING OPTIC NERVE HEAD DRUSEN FROM PAPILLEDEMA

The ability to differentiate papilledema from pseudopapilledema caused by ONHD can be challenging, particularly when the degree of optic disc edema is mild.[11] Kulkarni and colleagues [12] attempted to define OCT differences in cases of buried ONHD and mild papilledema, but reported no statistically significant differences between the groups. In this study, the ability of 5 clinicians to differentiate buried ONHD from mild papilledema using the OCT images alone was poor, as was the inter-reader agreement.[12] Unfortunately, as previously stated, the challenge to using conventional SD-OCT techniques to detect ONHD is that as depth increases, the resolution of the OCT images decreases, leading to poor demarcation of deeper drusen.[12] The posterior limits of drusen are also difficult to visualize due to the hyper-reflective anterior surface, which causes shadowing.[12] As an alternative Savini and colleagues[13] have proposed using the sub-retinal hyporeflective space, which is located between the retinal pigment epithelium and the choriocapillaris, to differentiate cases of papilledema from ONHD. The subretinal hyporeflective space thickness tends to be greater in eyes with optic disc edema compared to those with ONHD.[13]

In a previous elegant review, Kardon has highlighted the merits of OCT in the evaluation of patients with papilledema. [11] One OCT-based feature, which provides information about the direction of force vectors at the optic disc in papilledema, is the deformation of Bruch's membrane surrounding the neural canal. This deformation is due to a pressure differential between the retrobulbar optic nerve and vitreous cavity.[11] The angling of Bruch's membrane towards the vitreous, can help monitor the force differential over time as the intracranial pressure changes, and may also help to differentiate papilledema from pseudopapilledema.[11] EDI-OCT and SS-OCT could potentially provide even greater resolution of deeper structures, such as Bruch's membrane, even in the presence of optic disc edema.[11] Going forward, the next step is to map other OCT and fundus-based features in cases of papilledema to a continuous scale of disc volume.

This will further enhance the ability to differentiate papilledema from other forms of optic disc edema and pseudopapilledema. According to Kardon, [11] this approach will also allow features of digital fundus photographs (including obscuration of optic disc margins, discontinuity of optic disc vessels, and texture of the peripapillary RNFL) to be mapped to OCT disc volume. [11] In this manner, it may be possible to provide a continuous scale software measure of papilledema that can be derived and embedded in teleretinal imaging devices at the site of image capture for immediate diagnosis.[11]

CONCLUSIONS

As OCT technology continues to advance, there may be a means to quantify optic ONHD dimensions, and evaluate the integrity of functionally eloquent structures in the retina and optic nerve. If OCT can enhance our understanding regarding the relationships between optic disc drusen, RNFL loss, and visual field defects, this technology may facilitate longitudinal assessment, and enhance the care of ONHD patients.

CME ANSWERS

1. d
2. d
3. a

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OCT ANGIOGRAPHY

Guy V. Jirawuthiworavong, MD, MA

Southern California Permanente Medical Group
La Palma, CA

LEARNING OBJECTIVES

1. Describe the technique of Optical Coherence Tomography Angiography (OCTA) of the eye
2. Explain potential clinical ophthalmic and neuro-ophthalmic applications of OCTA
3. Describe the "pitfalls" of OCTA of the posterior segment of the eye

CME QUESTIONS

1. Which of the following areas of ocular vascular anatomy can be studied by OCTA?

    a. Superficial retinal vascular plexus
    b. Intermediate retinal vascular plexus
    c. Deep retinal vascular plexus
    d. Choriocapillaris
    e. All of the above.

2. Which of the following conditions have NOT been described using OCTA, in the current medical literature?

    a. Anterior ischemic optic neuropathy
    b. Leber hereditary optic neuropathy
    c. Dominant optic atrophy
    d. Primary open angle glaucoma
    e. Acute macular neuroretinopathy.

3. Current OCTA "pitfalls" include all of the following EXCEPT:

    a. Expensive technology
    b. Susceptible to projection/shadow artifact
    c. Affected by motion artifact
    d. Invasive procedure that requires fluorescein or ICG to be given intravenously
    e. Inability to visualize vascular leakage or dye staining of the retina/optic nerve.

KEYWORDS

1. Optical Coherence Tomography
2. Angiography
3. Retinal Vascular Plexus

INTRODUCTION

Optical coherence tomography angiography (OCTA) is a non-invasive approach to visualize ocular microcirculation of the capillary plexuses. OCTA is currently in its infancy and can potentially make a significant impact in ophthalmology and neuro-ophthalmology in the future, just as its predecessor, optical coherence tomography (OCT) has changed dramatically how we practice. The advent of OCTA would not have been possible without the advances in laser technology, algorithms for image acquisition, and software. OCTA provides magnification of the ocular posterior pole *en face* and in cross-section at the level of cellular structure of the retinal capillary beds and deep choroidal structures. OCTA can also be used to evaluate the optic nerve vasculature in healthy and diseased states such as glaucoma. The famed 20th century medical illustrator of human anatomy, Frank H. Netter, M.D., would have been delighted with the resolution of detail that OCTA provides. The complexity of the microcirculation can now be studied without invasive dye that is used in fluorescein angiography (FA) and indocyanine green angiography (ICG). With new technology comes its shortcomings. OCTA pitfalls can only be appreciated after becoming familiar with: 1) different instrumentation and algorithms, 2) the manual adjustments made during post-processing, and 3) the role of OCTA in multi-modal imaging in conjunction with other ancillary testing, i.e. perimetry and electrophysiology.

Optical coherence tomography (OCT) has revolutionized the diagnosis and management of patients in ophthalmology. Greater than 20,000 articles about OCT in humans have been be published in PubMed. Of these 20,000 or so articles, 15,000 are related to the eye and its ocular structures. An area of advancement in OCT that is rapidly gaining attention is the technique of OCT Angiography (OCTA). PubMed currently shows approximately 4,000 articles that are related to OCTA in human eyes, which accounts for one quarter of the human OCT literature.

Optical coherence tomography angiography is a technique that provides in depth selective visualization of the retina and choroidal vasculature. The technique of OCTA is based on OCT. OCT takes advantage of the property of light in which a light source is directed upon a tissue of interest, is scattered and reflected to a mirror and absorbed and converted as acquired data for analysis of structure of the tissue. The raw data acquired is then analyzed and processed into a three-dimensional display of the interested tissue. The use of longer wavelength lasers (infrared) as light sources has allowed deeper penetration

of tissue. OCTA uses OCT to measure the property of either the velocity of the red blood cells in a vessel as used in Doppler techniques or that of the shadowing or projection of the moving red blood cells, thus outlining as an aggregate, the blood vessels. In the projection technique, data from successive scans generate enough profiles to cast a projection that can then be analyzed as the outline of the vasculature. The projection technique has gained much popularity recently in the literature. Simply said, OCTA technology takes advantage of the shadowgraphic projection of the motion in the blood vessel by the variation in reflected OCT signal amplitude between consecutive cross-section scans.

Without the transition from time-domain OCT (TD-OCT) to spectral-domain OCT (SD-OCT) to swept-source OCT (SS-OCT), OCTA would not have been possible. Different protocols have been applied to SD-OCT to develop spectral-domain OCTA (SD-OCTA). Furthermore, the use of tuneable laser technology with high speed image acquisition, has enabled the development of swept-source OCTA (SS-OCTA) with the added advantage of visualization of the choroidal vasculature that was not fully appreciated before. Prior imaging of the choroid layers was limited due to: 1) blood flow artifact from the dense choriocapillaris, 2) near confluent cellular structures that are relatively deep to the light source and 3) interference fringe washout. SD-OCTA and enhanced depth imaging (EDI) played roles in the understanding of anatomy of the choroid and has laid the foundation for OCTA of the choriocapillaris, Sattler's layer and Haller's layer of the choroid.

Over the last 25 years scan resolution has improved dramatically from TD-OCT to SD-OCT to SS-OCT, and now OCTA. Advantages and disadvantages between SD-OCTA and SS-OCTA are currently being studied as well as the development of adaptive optics OCTA (AO-OCTA).

Current Image acquisition algorithms:

1. Doppler
2. Optical Microangiography (OMAG)
3. Use of the Amplitude of signal to visualize flow via a) speckle variance or b) amplitude decorrelation
4. Use of the Phase of the signal to compute flow signal, also termed as phase variance
5. Correlation mapping

An in-depth description of these algorithms is beyond the scope of this introduction of OCTA and currently, many of these algorithms are still being developed. The algorithms are very complex, to say the least, and various authors have compared and contrasted each algorithms' merits.

Each commercial instrument as well as academic prototypes have it's own proprietary post-processing image enhancement techniques that improves resolution. Averaging improves signal-to-noise ratio, resolution, and detail of the capillary plexuses. The split-spectrum method of data analysis has become popular in its application in the technique of split-spectrum amplitiude-decorrelation angiography, (SSADA). Split-spectrum technique processes the data by enhancing flow detection and rejects axial bulk noise due to motion. As compared to full spectrum amplitude method, split-spectrum technique improves the signal-to-noise ratio by a factor of two when the spectral splits are at least four-fold. As a result, high quality OCT angiograms are generated with SSADA. This is available in current commercial OCTA systems. OMAG also seems to produce equivalent high quality images as that of SSADA. With either protocols and techniques, normalization and thresholding of raw data are essential in the post-acquisition phase of image processing.

The acquired data is usually transformed to 3-D *en-face* as well as cross-sections of the interested levels of vasculature of the posterior pole. Each research lab and proprietary company have different methods for identifying the retinal layers to segment. Some systems' applications require manual adjustments for retinal segmentation. "Slab" sizes currently are arbitrary and not fixed among different OCTA machines. For example, superficial retinal arteries in OCTA, cause projection artifacts on the deeper layers of the retina in *en-face* OCT angiographs. With post-processing, these projection artifacts can be "filtered out" so that large caliber superficial retinal vessels will not be viewed on angiographs.

These protocols are unique to each lab and company. Published studies use combinations of automated software adjustment and manual manipulation that may not be similar. Standardization of pre- and post-processing protocols may be of benefit in the future.

Despite these challenges, the published literature has revealed new insight of the retinal capillary microcirculation. OCTA studies of retinal anatomy show three distinct retinal plexuses that were under appreciated in classic fluorescein angiography. These capillary plexuses are divided into the superficial, intermediate and deep capillary plexuses. They lie within the inner retina which has been delineated by some authors as the borders of the inner limiting membrane and the outer portion of the outer plexiform layer. Furthermore, the choroid can now be scanned as part of the entire retina as a complete volumetric slab. Via post-processing, layers of the choroid can be distinctly divided into the choriocapillaris, Sattler's layer and Haller's layer. The choroid can now be better analyzed by OCTA. Studies on the pathophysiology of the choroid circulation and its relation to retinal conditions have emerged.

Optical coherence tomography angiography is NON-INVASIVE. OCTA gathers information about capillary plexuses yet does not require an invasive dye such as in FA and ICG. Evaluation with OCTA has a role in assisting clinicians to better understand vascular pathophysiology of posterior pole ocular diseases. It must be emphasized though that OCTA is not to replace, in the author's opinion,

traditional FA and ICG but to complement these other modalities. Furthermore, it must be cautioned to not use OCTA outside of the context of structural OCT, clinical history, and microscopic (indirect, slit-lamp) evaluation of the patient. OCTA presently serves as an ancillary tool in its infancy. Much like OCT, its predecessor, only time will ensure OCTA's legacy in daily clinical practice.

A list of current clinical applications for OCTA is listed. This list (at the time of publication) is not to be comprehensive but exemplary of OCTA and its application in the fields of retina, glaucoma, neuro-ophthalmology, and uveitis. OCTA's utility in the anterior segment is another area of current advancement. A reference for OCTA of the anterior segment is provided in the bibliography.

Retina

1. Diabetes
    a. Identification of capillary drop out & macroaneurysms
    b. Use in combination with vascular flow indices of areas of non-perfusion
    c. Diabetic macular edema (DME) therapy
2. Macular degeneration
    a. Evaluation of choroidal neovascular membranes in wet macular degeneration
    b. Understanding choroidal vasculature in geographic atrophy and drusen in dry macular degeneration
    c. Response to anti-VEGF therapy in wet macular degeneration
3. Retinal artery and vein occlusion (CRAO, CRVO, BRAO, BRVO)
4. Macular telangiectasia
5. Sickle cell anemia
6. Central serous chorioretinopathy
7. High myopia

Glaucoma

1. Comparison to healthy and glaucoma suspects
2. Relation to glaucomatous visual field loss

Neuro-ophthalmology

1. Chiasmal compression
2. Anterior ischemic optic neuropathy
3. Leber hereditary optic neuropathy
4. Acute macular neuroretinopathy

Uveitis

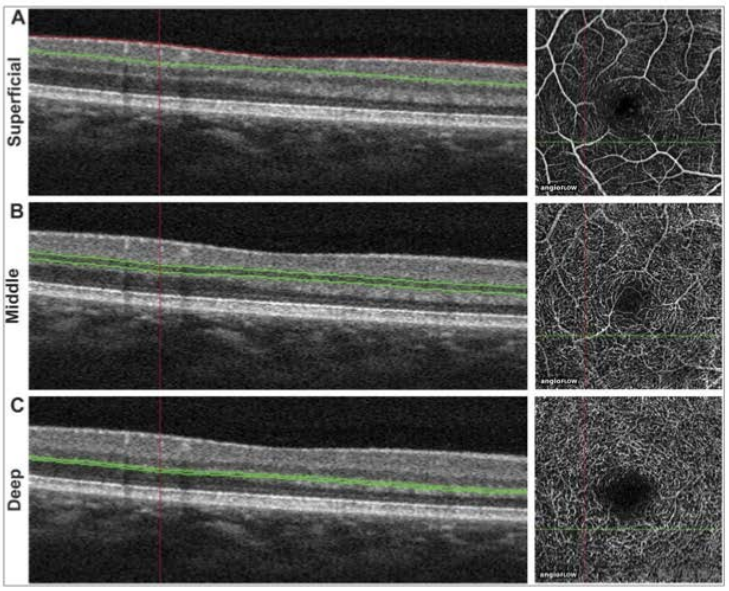
1. Acute macular neuroretinopathy
2. Toxoplasmosis chorioretinopathy
3. Birdshot chorioretinopathy

There are disadvantages to any new form of technology and there is no exception for OCTA. Here is a list of the pitfalls of OCTA.

Pitfalls of OCTA

1. Shadowgraphic projection artifact (fluctuating shadows casted by large inner retinal vessels that cause variation of the deeper layer signals)- requires post-processing
2. No dye leakage or staining of tissue
3. Post-processing (segmentation) and visualization tools are dissimilar across platforms
4. Expensive
5. Time consuming
6. Limited field of view but can be montaged
7. Susceptible to blink/motion artifact (similar to OCT) but can be adjusted pre- and post-image acquistion

Optical coherence technology angiography is constantly evolving. Recent advances and future directions for OCTA have included the incorporation of adaptive optics allowing for higher resolution and magnification in adaptive optics OCTA (AO-OCTA). Other advances include ultra-widefield OCTA, and the use of nano-sized particle contrast agents to label cells in OCTA. Much like SD-OCT has largely supplanted TD-OCT, it is the author's opinion that SD-OCT will be supplanted by SS-OCT and AO-OCT. OCTA will also benefit along the way of the evolution of OCT. Advancement in OCTA scanning, flow detection, segmentation, displaying and quantification of vascular microcirculation will add new insights into pathophysiology, diagnosis and treatment of neuro-ophthalmic and retinal disease. Technical artifacts from imaging will be identified so the trained clinician will interpret the OCTA appropriately in conjunction with other imaging modalities and ancillary testing. Regardless of the future changes in OCTA imaging, keeping a systematic approach in using OCTA will transform to better understanding of the retina and optic nerve in ways that are unfathomable with current FA and ICG techniques.



CHARACTERIZATION OF THE MIDDLE CAPILLARY PLEXUS USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN HEALTHY AND DIABETIC EYES

Park, Justin J.; Soetikno, Brian T.; Fawzi, Amani A.

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Fig. 1. Optical coherence tomography angiography segmentation used to visualize the 3 capillary plexuses in Method 3. A. The SCP boundaries encompass the nerve fiber layer, GCL, and IPL. The inner boundary was set at 3 μm beneath the internal limiting membrane, and the outer boundary was set at a 25 μm offset from the IPL. B. The MCP was captured with a 30-μm band to encompass the INL. The inner boundary was set at 0 μm beneath the IPL and the outer boundary was set at 30 μm below the IPL. C. The DCP was set using a 15-μm band set on the OPL. The inner boundary was set at 45 μm beneath the IPL and the outer boundary was set at 60 μm beneath the IPL.

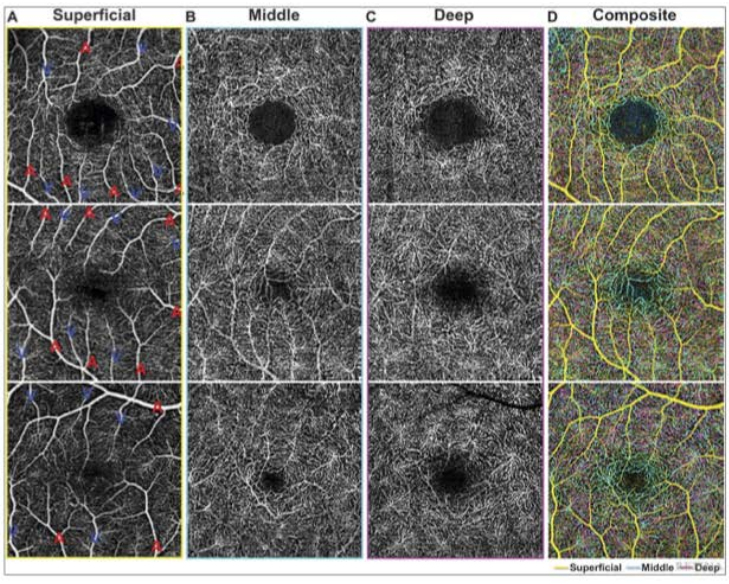

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Fig. 2. Optical coherence tomography angiography segmentation used to visualize the level of the three capillary plexuses. A–C. Demonstrate the three capillary plexuses of three different eyes from healthy control patients (each row). Arterioles and veins are labeled with a red A or blue V, respectively, in the SCP (column A). In the MCP (column B), the border of the FAZ is best observed as a well-demarcated and clearly circumscribed area, with a border that is composed of branches from both arterioles and venules in the MCP. This regular FAZ border is not observed in the DCP (column C). The composite image (column D) shows an overlay of all three capillary plexus layers, with the SCP in yellow, MCP in cyan, and DCP in magenta. In the composite image, there is significant overlap between the capillary networks, but a distinct area of cyan is observed in the FAZ region, whereas the magenta DCP does not approach the FAZ region to the same extent. Consequently, the FAZ is appreciably larger in the DCP compared with the MCP.

CME ANSWERS

1. e
2. c
3. d

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OPTICAL COHERENCE TOMOGRAPHY (OCT) AND MULTIPLE SCLEROSIS (MS)

Steven L. Galetta MD

NYU Langone Medical Center
NYU School of Medicine
New York, NY

LEARNING OBJECTIVES:

1. Discuss the utility of OCT in the differential diagnosis of optic neuritis
2. Discuss the time course of RNFL and Ganglion Cell layer loss after optic neuritis
3. Discuss the utility of OCT in the management of multiple sclerosis

CME QUESTIONS:

1. For every line of low contrast acuity loss, approximately how much RNFL is lost in microns?

   a. 5
   b. 10
   c. 15
   d. 20
   e. 25

2. After about of optic neuritis, the majority of the loss of the retinal ganglion cell layer occurs

   a. After 6 weeks of the onset of the visual loss
   b. After 3 months of the onset of the visual loss
   c. After 6 months of the onset of the visual loss
   d. After 1 year of the onset of the visual loss.
   e. Very quickly, within weeks of the visual loss

3. The loss of RNFL in patients that are labeled as having benign multiple sclerosis

   a. Is equal to controls
   b. Similar to those with a clinically isolated syndrome
   c. Similar to those with relapsing remitting multiple sclerosis
   d. Similar to those with secondary progressive multiple sclerosis

KEYWORDS

1. Optic Neuritis (ON)
2. MS-Associated Optic Neuritis (MSON)
3. Optical Coherence Tomography (OCT)
4. Retinal Nerve Fiber Layer (RNFL)
5. Total Macular Volume (TMV)
6. Ganglion Cell/Inner Plexiform Layer (GCL+IPL)
7. Microcystic Macular Edema (MMO)

BACKGROUND

The Optic Neuritis Treatment Trial (ONTT)[1-5] was a landmark study in the field of neuro-ophthalmology. This study provided a large-scale systematic view into the course and clinical characteristics of acute demyelinating optic neuritis (ON). ON may be the first clinical demyelinating event in up to 20% of patients with multiple sclerosis (MS)[6] and the overall cumulative probability of developing clinically-definite MS, defined as a second clinical event, was 50% by 15 years after the onset of acute ON.[7] Presence of magnetic resonance imaging (MRI)-detected brain lesions and oligoclonal bands[7, 8] were found to be associated with an increased risk of developing clinically definite MS (CDMS), defined by a second clinical demyelinating event. Patients with one or more MRI lesions at baseline had a 56% risk of CDMS at 10 years and a 72% risk at 15 years.[7,9] While visual recovery from ON as a first demyelinating event and in the setting of established MS is said to be good,[5,10] studies of vision in MS have shown that patients will have continued deficits that are not well captured by high-contrast visual acuity (VA) alone. Visual symptoms in MS may result from a variety of pathological processes, including inflammation, demyelination, and axonal degeneration in the afferent visual pathways.[11,12] Subclinical optic neuropathy and involvement of the optic chiasm or post-chiasmal regions of the visual pathway have been reported.[13-15]

Significant progress has been made in understanding the additional ways to assess qualitative and quantitative visual function in patients with MS. Tests of low-contrast vision, particularly low-contrast letter acuity (LCLA), have emerged as methods that demonstrate the greatest capacity to capture visual impairment in patients with MS.[16-19] Vision-

specific quality of life (QOL), measured by 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) and the 10-Item Neuro-Ophthalmic Supplement has been shown to be reduced among patients with worse visual function by low-contrast letter acuity and with structural changes of RNFL and GCL+IPL thinning by OCT.[20-22] These measurements from an ongoing collaborative study[23] of visual structure, function and QOL in MS are presented in Table 1.

OPTICAL COHERENCE TOMOGRAPHY (OCT) IN MS

Optical coherence tomography (OCT) is a non-invasive technique that is close to a tissue level *in vivo* optical biopsy of the retina. During the past decade, OCT has become increasingly recognized as a highly sensitive method for imaging the retina and optic disc. Imaging of the RNFL, both in the peripapillary region (pRNFL) and in the macula (mRNFL), represents a unique opportunity in the central nervous system to image axons without myelin sheaths (retinal ganglion cell axons are not myelinated until they traverse behind the lamina cribosa). Measures of ganglion cell layer/inner plexiform layer (GCL+IPL) thickness and total macular volume (TMV) also reflect neuronal loss in the anterior visual pathway.

OCT IN PATIENTS WITH MS AND ON

As OCT imaging has advanced to provide retinal detail that is nearly histologic in its level of detail, autopsy studies have likewise have shown that up to 94%–99% of MS patients have detectable optic nerve lesions.[24, 25] The earliest application of OCT technology to the study of ON in patients with MS was reported by Parisi et al. in 1999,[26] utilizing a first-generation OCT technology. In those patients with MS-associated ON (MSON), pRNFL thickness was reduced by an average of 46 % in eyes with an ON history, compared to disease-free control eyes. Even fellow eyes had RNFL thickness reductions of 28%. In 2005, Trip et al.[27] reported further findings using time-domain (TD-) OCT. This study revealed a 33% reduction in pRNFL thickness in eyes with a history of ON and incomplete recovery. Unaffected eyes in this study had a 27% reduction in pRNFL thickness compared to controls. Eyes with a history of ON had macular volume reductions of 11%. These first reports of OCT were thus able to show both axonal loss and retinal ganglion cell loss.

In 2010, Petzold et al.[28] performed a meta-analysis of available published reports on OCT in patients with MS and found pRNFL thinning by an average of 20.38 µm (95% CI 17.91–22.86, n=2063, p<0.0001) in MS eyes with a history of acute ON, and by an average of 7.08 µm (5.52–8.65, n=3154, p<0.0001) in MS eyes without an ON history compared to disease-free controls. Peripapillary RNFL thickness also was found to correlate with visual and neurological functioning.

In 2006, Costello et al.[29] reported that the majority of patients (approximately 75%) with acute ON, 94% of whom had a clinically isolated syndrome, will sustain 10–40 µm thinning of the pRNFL within a period of 3 to 6 months following the acute event. Importantly, pRNFL thinning to the level of 75-80 µm in that study was found to be a "threshold level" below which there were more severe decrements in visual function, as measured by automated perimetry mean deviation. To provide perspective on these measurements, normal pRNFL thickness by TD OCT is approximately 105 µm, with an estimated physiological loss due to aging of only about 0.017% per year from age 18 years onward (approximately 10–20 µm loss over 60 years).[30]

Pro et al.[31] demonstrated mild, relative thickening of the pRNFL in 8 patients with clinical retrobulbar optic neuritis (no visible optic disc swelling on ophthalmoscopy). Even though these OCT findings were subtle, and were within the range of the normal (100.7 µm in affected eye versus 92.9 µm in unaffected eye), the authors pointed out that these represented true change, as the unaffected eye remained stable over follow up. There was subsequent RNFL thinning in these affected eyes below the expected value for disease-free control eyes.[31] The RNFL thinning was seen as early as 2-4 months following the acute ON. OCT was thus able to identify very mild, and in some cases clinically undetectable, optic disc edema in eyes with acute ON. These findings represent one way in which OCT has helped to refine the clinical profile of acute ON and of visual pathway structure in MS even in the absence of ON.

OCT CHANGES IN THE SUBACUTE PHASE AND RECOVERY FROM ON

The time course of RNFL axonal loss following acute ON may be important for determining the "window of opportunity" for potential intervention with therapies that could protect and repair the nervous system. Reductions in pRNFL thickness in affected eyes, usually by 10–40 µm, are maximal after acute ON within 3–6 months. This pattern of rapid RNFL thinning suggests that significant axonal degeneration follows immediately after the primary demyelinating event.[29, 32] There is stabilization of RNFL thickness within 7–12 months from the beginning of the disease.[32] However, we now recognize that thinning of the GCL-IPL layer begins within weeks of the onset of acute ON and may precede the thinning of the RNFL narrowing the window of therapeutic window of neuro-repair.[93]

Henderson et al.[32] performed comprehensive qualitative and quantitative visual assessments in a study of 23 patients with acute clinically isolated unilateral ON. The mean time to 90% of maximum loss from baseline in pRNFL thickness for affected eyes was 2.38 months. Ninety-nine percent of the degree of pRNFL loss occurred by an average of 4.75 months. The time of first detectable pRNFL thinning compared to the baseline fellow eye value was 1.64 months (95% CI, 0.96–2.32; p<0.05). Eyes with poor recovery had a significantly greater decline of

RNFL from baseline to 3 months (p=0.002). Macular volumes also declined significantly at the time of last follow-up. We have now learned that GCL/IPL thinning occurs way before pRNFL thinning and in a matter of weeks after the onset of visual loss.

OCT IN MS SUBTYPES

Costello et al.[33] demonstrated that patterns of OCT RNFL thinning may be able to distinguish MS disease subtypes. For ON eyes among the different MS subtypes, differences among groups were noted in the overall and temporal RNFL regions. Patients with CIS had the highest overall RNFL thickness values (mean 87.8 µm), while patients with secondary progressive MS (SPMS) had the greatest degree of thinning compared to control reference values (mean RNFL thickness 70.8 µm). For MS non-ON eyes, RNFL thickness was reduced in patients with primary progressive MS (PPMS, average 94.3 µm p=0.04), relapsing remitting MS (RRMS, average 99.6 µm, p=0.02), and SPMS (average 84.7 µm, p<0.0001) relative to eyes of patients with CIS (average RNFL thickness 105.7 µm). RNFL thickness may thus represent an important structural marker of disease progression.

In a study by Pulicken et al.,[34] progressive MS patients showed more marked decreases in RNFL and macular volume than relapsing-remitting MS. However, even patients with "benign MS" may have pRNFL axonal loss that is as marked as that of typical RRMS and have reduced vision and QOL. While overall neurologic impairment may be mild in such cases, visual dysfunction may account for a substantial degree of disability in benign MS.[35]

RNFL THICKNESS IN ASYMPTOMATIC FELLOW EYES IN ON

Thinning of RNFL has been observed not only in the eyes with a history of ON, but also in the asymptomatic fellow eyes of MS patients, as well as in MS patients without a clinical history of ON. The average pRNFL thickness was found to be between 91.08 and 109.3 µm in the fellow eye in patients with MSON.[27, 31, 34, 36-48]

In MS patients with no history suggestive of ON, the average RNFL thickness was between 93.9 and 110.9 µm.[34, 48-51] These findings emphasize the common occurrence of subclinical anterior visual pathway axonal loss in patients with MS even in eyes without history of ON.

RNFL THINNING AND VISUAL LOSS

One of the most important findings that has resulted from the use of OCT MS studies is the association of RNFL thinning to visual loss, as measured by low-contrast letter acuity.[23] In 2006, Fisher et al.[39] conducted a cross-sectional study that compared RNFL thickness among MS eyes with a history of ON (MS ON eyes), MS eyes without a history of ON (MS non-ON eyes), and disease-free control eyes. These investigators found that RNFL thickness was reduced significantly among MS eyes as a group overall (92 µm) vs. controls (105 µm , p<0.001, generalized estimating equation models, accounting for age and within-patient, inter-eye correlations) and particularly reduced in MS ON eyes (85 mm, p<0.001). Furthermore, lower visual function scores were associated with reduced average overall RNFL thickness in MS eyes; for every 1-line decrease in low-contrast letter acuity or contrast sensitivity score, the mean RNFL thickness decreased by 4 µm. These findings supported the validity of low-contrast visual assessment and suggested a potential role for OCT in trials that may examine neuroprotective and other disease-modifying therapies. Several other investigations have demonstrated correlations between RNFL thinning and visual loss.[52-54] Costello et al.[55] found that RNFL thickness after an episode of isolated ON cannot be used to predict the risk of MS.

RELATION OF RNFL THICKNESS TO VISUAL EVOKED POTENTIAL (VEP) AND MRI FINDINGS

Several recent studies have highlighted the structure function-correlations provided by neuroimaging (MRI) and electrophysiological testing (visual evoked potentials).[56-59] In a retrospective study, visual evoked potential (VEP) latency was found to be sensitive for detecting demyelination,[60] while RNFL thickness reflects more structural aspects of optic nerve damage following acute ON. As might be expected, OCT RNFL thickness correlated well with VEP amplitude, but not with the latency.[42] In another study, retinal ganglion cell (RGC) axonal loss was associated with retinal dysfunction in eyes of MS patients without a history of ON and evidence of post-chiasmal involvement of the visual pathway.[61] In a study that compared 112 partners of patients with MS to a control group of 93 volunteers, abnormal VEP latency in 5 of the partners and one clinically definite case of MS was found. Studies of OCT among partners of people with MS may provide further context for this finding.[62]

In terms of brain MRI studies, RNFL thickness has been shown to reflect the volumes of brain white and gray matter as well as the normalized volumes of whole brain and white matter.[52,63] The correlations between RNFL thickness and MRI measurements of brain atrophy were more significant in the subset of patients with no clinical history of ON than in those who had an ON history in either eye. Studies also suggest that RNFL thickness measurements could be considered a marker for brain atrophy in MS.[39] The relation of RNFL thicknesses and brain parenchymal fraction (BPF), measured using high-resolution MRI was also recently shown to reflect the likely global nature of axonal and neuronal loss in MS.[48] A correlation between RNFL thickness, volume of T1 and T2 lesions, gray matter atrophy, MTR and diffusion tensor

imaging measures (DTI) measurements in MS patients with or without a history of ON was also reported.[38] These MRI parameters also correlated with low-contrast letter acuity measurements, consistent with prior studies suggesting that both posterior and anterior visual pathway disease contribute to visual function in MS.[64] Interestingly, in MS patients with optic radiation lesions, a correlation was found between the volume of the lesion and RNFL thickness ($p<0.001$).[65]

ROLE FOR OCT IN MONITORING MS THERAPY ADVERSE EVENTS AND EFFICACY

Fingolimod, an oral sphingosine-1-phosphate receptor modulator approved for treatment of MS, has been shown in clinical trials to cause macular edema in 0.3-1.2% of patients, with uveitis and other ocular pathology elevating risk.[66] Patients present with blurred vision, decreased visual acuity or eye pain. Macular edema resolves in most cases when fingolimod treatment is discontinued.[66,67] OCT studies of patients on fingolimod have shown elevations in macular volume consistent with diffuse macular edema; some of these patients were symptomatic, presenting with metamorphopsia and blurred vision.[68] Ophthalmologic evaluations, including OCT scans of the macula, are recommended before initiating treatment. Follow-up at 3-4-month intervals is also recommended.

Though not common, cases of retinopathy associated with interferon-beta 1a treatment in MS have been reported.[69-72] This retinopathy was characterized by clinical/OCT findings of retinal hemorrhages or cotton wool spots at the posterior fundus and improved with discontinuation of medication.

In a prospective study of 94 MS patients and 50 healthy subjects followed over 3 years, the authors evaluated whether treatment with interferon 1a, interferon 1b or glatiramer acetate was associated with reduced degrees of RNFL thinning. Progressive RNFL thinning was detected in both the treated and untreated groups, but untreated patients had lower mean RNFL thicknesses. Otherwise, no differences in the treatment groups were noted.[73]

Another study showed that the peripapillary RNFL, ganglion cell layer thicknesses, and macular volumes measured by OCT were all reduced among patients with or without disease modifying therapy when compared with controls. The abnormal findings were more prominent for MS eyes with an ON history.[74] Using various databases and registries, we hope to define meaningful OCT changes in order to help guide therapeutic decisions and to potentially develop criteria to diagnose an asymptomatic optic nerve lesion.

MICROCYSTIC INNER NUCLEAR LAYER ABNORMALITIES

Microcystic changes in the inner nuclear layer (MMO, microcystic macular oedema) are characterized by retinal microcysts in the inner nuclear layer and are easily identified perifoveally on macular spectral-domain OCT. These findings are typically not identifiable by direct ophthalmoscopy, and may be associated with reductions in VA. In many cases, a perifoveal hyporeflective crescent shape can be seen on confocal infrared laser fundus imaging directly correlating with the area of microcysts observed on OCT. It has been hypothesized that inner nuclear layer microcysts associated with various forms of optic neuropathy could be either a sign of inflammation,[75,76] autoantibodies against AQP4 and KIR4.1, microglial activation, blood–retina barrier breakdown or retrograde or anterograde trans-synaptic degeneration changes secondary to neurodegeneration.[77,78] Microcystic changes in the inner nuclear layers in eyes of patients with MS were first described by Gelfand et al.[75] These findings were seen in association with increased disease severity (4.7% of patients), with higher prevalence in patients with a history of ON.[75] Further evaluation of MMO found that patients with neuromyelitis optica (NMO), who are known to have a high incidence of ON, had a higher prevalence of MMO (20-26%).[79,80] Microcystic inner nuclear layer abnormalities are not specific to MS and ON and have been found associated with other optic neuropathies, including hereditary optic neuropathy.[81-91]

SEGMENTATION AND NEWER TRENDS

Segmentation of the macular retinal layers is now possible for use in the clinical and research setting. Thinning of the ganglion cell layer has been demonstrated to be greatest among patients with decrements in vision-specific QOL and among those with the highest degrees of visual loss.[92]

In a study by Gabilondo et al., retinal changes by OCT in ON were evaluated using the latest segmentation techniques. Changes in ganglion cell layer thickness within the first month were predictive of visual impairment by 6 months.[93] These studies, and others, have confirmed an important role for neuronal loss as measured by ganglion cell layer thickness in determining visual disability in MS. In the recent clinical trial of opicinimab in acute optic neuritis, most RGCL/ IPL thinning occurred before the first administration of the drug or within weeks of the onset of the visual loss.[95] The implications are that any therapeutic agent is likely going to need to be administered within two weeks and maybe sooner from the onset of the visual loss.

OCT angiography is a newer technique that demonstrates the optic nerve blood flow, which may be reflective of the metabolic demand. This is hypothesized to be a sensitive measure of axonal loss. Wang and colleagues showed that eyes of patients with MS and ON had lower flow indices as compared to controls and MS eyes without an

ON history. In addition, the flow index was abnormal in a greater proportion of eyes with a history of ON than was the peripapillary RNFL.[94] One caution in interpreting these findings might be the very high threshold (thickness below 5th percentile) for categorizing an RNFL thickness measurement as abnormal.

CONCLUSIONS

OCT has provided a basis for correlating structural aspects of anterior visual pathway axonal and neuronal loss with visual function in ON as well as in MS. It is now known that patients with MS have thinning of the retinal nerve fiber layer (RNFL, axons) and ganglion cell/inner plexiform layer (GCL+IPL, neurons) even in the absence of a history of acute ON. Such patients have clinically meaningful worsening of vision and quality of life (QOL). Furthermore, OCT is useful in patients with MS for distinguishing retinal disease from ON, and for monitoring patients for macular edema associated with use of fingolimod. OCT is a powerful tool that may be used to assess neuro-repair and neuroprotective mechanisms in both acute and chronic optic nerve injury. We are now on the verge of using OCT in MS to make therapeutic decisions as we better understand the values that translate into meaningful clinical change.

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From the Departments of Neurology (R.C.N., K.N, L.J.B., S.L.G.), Population Health (L.J.B.), Ophthalmology (L.J.B., S.L.G.), New York University School of Medicine, New York, NY, USA.

CME ANSWERS

1. A
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Table 1. Mean reference values from recent investigations of vision, QOL, and OCT in MS

	Disease-Free Controls	All MS	MS, No History of ON	MS, History of ON
High-contrast visual acuity (VA), ETDRS, number of letters correct	59 ± 6 (n=52 eyes)	53 ± 10 (n=559 eyes)	55 ± 7 (n=301 eyes)	52 ± 12 (n=252 eyes)
Binocular testing	62 ± 4 (n=26 pts)	58 ± 7 (n=273 pts)	59 ± 6 (n=147 pts)	57 ± 8 (n=123 pts)
Low-contrast letter acuity (2.5%), number of letters correct	35 ± 6 (n=52 eyes)	25 ± 12 (n=550 eyes)	27 ± 11 (n=296 eyes)	23 ± 13 (n=248 eyes)
Binocular testing	44 ± 4 (n=26 pts)	34 ± 11 (n=273 pts)	36 ± 9 (n=147 pts)	32 ± 112 (n=123 pts)
Low-contrast letter acuity (1.25%), number of letters correct	21 ± 9 (n=52 eyes)	13 ± 11 (n=550 eyes)	15 ± 11 (n=296 eyes)	11 ± 11 (n=248 eyes)
Binocular testing	32 ± 5 (n=26 pts)	23 ± 11 (n=271 pts)	25 ± 11 (n=146 pts)	21 ± 12 (n=122 pts)
NEI-VFQ-25 composite score, best score=100	98 ± 2 (n=27 pts)	85 ± 15 (n=264 pts)	88 ± 14 (n=142 pts)	82 ± 15 (n=119 pts)
10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25, best score=100	97 ± 5 (n=28 pts)	78 ± 18 (n=256 pts)	83 ± 16 (n=137 pts)	73 ± 18 (n=117 pts)
Time-domain (TD) OCT				
Peripapillary RNFL thickness, µm	104.5 ± 10.7 (n=219 eyes)	92.5 ± 16.7 (n=1,058 eyes)	95.6 ± 14.5 (n=730 eyes)	85.7 ± 19.0 (n=328 eyes)
Total macular volume, mm^3	6.84 ± 0.36 (n=219 eyes)	6.54 ± 0.51 (n=1,058 eyes)	6.63 ± 0.48 (n=730 eyes)	6.36 ± 0.53 (n=328 eyes)
Spectral-domain (SD) OCT				
Peripapillary RNFL thickness, µm	93.0 ± 9.0 (n=48 eyes)	83.1 ± 12.9 (n=529 eyes)	86.4 ± 10.9 (n=287 eyes)	79.1 ± 14.1 (n=236 eyes)
Ganglion cell + inner plexiform layer (GCL+IPL), µm	88.9 ± 6.9 (n=61 eyes)	84.1 ± 8.4 (n=239 eyes)	87.0 ± 6.6 (n=150 eyes)	79.7 ± 9.2 (n=87 eyes)
Macular Thickness, µm	10.1 ± 0.4 (n=50 eyes)	9.8 ± 0.6 (n=509 eyes)	9.9 ± 0.5 (n=282 eyes)	9.7 ± 0.6 (n=221 eyes)

Abbreviations: MS = multiple sclerosis; ETDRS = Early Treatment Diabetic Retinopathy Study; QOL = quality of life ; NEI-VFQ-25 = 25-Item National Eye Institute Visual Functioning Questionnaire; TD = time-domain (OCT-3 platform); SD = spectral-domain (Cirrus platform); OCT = optical coherence tomography; RNFL = retinal nerve fiber layer.

OPTICAL COHERENCE TOMOGRAPHY (OCT) AND NEURODEGENERATION OF ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

Victoria S. Pelak, MD

University of Colorado School of Medicine
Aurora, CO

LEARNING OBJECTIVES

1. Be able to place into context the current research findings and potential utility of OCT of the retina in Alzheimer's disease (AD) and Parkinson's disease (PD).
2. Apply the current understanding of disease pathology in Alzheimer's disease and Parkinson's disease to OCT retinal thickness measures.
3. Educate patients about the implications of OCT of the retina and neurodegeneration in Alzheimer's disease and Parkinson's disease.

CME QUESTIONS:

1. OCT of the RNFL and macula are biomarkers that reflect ocular pathology due to retinal neuritic plaques and neurofibrillary tangles and retinal alpha-synuclein aggregates in AD and PD, respectively.
   a. True
   b. False
2. OCT of the retina can be used to stage and monitor the neurodegenerative changes that occur with AD and PD.
   a. True
   b. False
3. Patients with visual symptoms related to AD or PD are more likely to have decreased retinal OCT measures.
   a. True
   b. False

KEYWORDS

1. Optical Coherence Tomography (OCT)
2. Alzheimer's disease
3. Parkinson's disease
4. Neurodegenerative disease
5. Retinal Nerve Fiber Layer

I. INTRODUCTION

Given that post-mortem human and animal histopathological studies reveal that degeneration of the inner retina occurs in Alzheimer's disease (AD) and Parkinson's disease (PD), optical coherence tomography (OCT) of the retina is being investigated as a potential biomarker for AD and PD. Dramatic changes in our understanding of AD and PD, the two most common and devastating neurodegenerative diseases of aging, have occurred in the last two decades. The major driver of recent advancements is the recognition of the impending health care crisis that will occur mid-century as the population continues to age and no disease-modifying treatments become available for AD and PD. Although symptomatic drug treatments and supportive care for both conditions, particularly for PD, provide significant improvements in quality of life, there are currently no treatments that alter the course of disease for either disorder. Biomarkers that allow for early diagnosis, staging, and assessment of therapeutic responses hold a key to the discovery of treatments that will alter the course of the disease. Other biomarkers that predict prognosis or the need for a specific treatment approach will also be valuable.

As our knowledge about AD and PD grows, it is necessary to place OCT measures of the retina into the broader context of disease and consider the long, progressive course of neurodegeneration that defines AD and PD, including the preclinical and clinical stages. For instance, biomarkers that provide evidence of neuronal loss, such as OCT of the retina, may signify disease that has progressed to the late *preclinical* stage and/or the early *clinical* phase. Early evidence suggests that this might be the case for OCT of the retina and AD, but it is not yet clear for PD. Results from retinal OCT studies in AD and PD populations over the past decade are reviewed for the reader. In order to provide the background necessary for interpretation of results, a brief review of the current framework being used to define the preclinical and clinical stages of AD and PD and the types and role of disease biomarkers for both conditions is provided.

II. ALZHEIMER'S DISEASE (AD)

A. AD: THE BURDEN OF DISEASE

Alzheimer's disease (AD) is a progressive, degenerative central nervous system disorder and is the most common cause of age-related dementia with selective loss of allocortical and neocortical neurons. Currently, AD dementia affects over 5.4 million people in the United States (US), including one in nine people over the age of 65 years.[1] The lack of disease modifying treatment has driven AD to become the 6th leading cause of death in the US.[1] The burden of managing the disease is evident in the *direct* health care dollars spent on caring for people with AD, which is approximately $236 billion in direct costs annually in the US.[1] As the populations in the US and worldwide continue to age, the prevalence of AD and dementia is expected to nearly double every 20 years, and consume nearly 25% of Medicare spending when baby boomers enter the eight and ninth decade of life in 2040.[1,2]

B. THE DIAGNOSIS OF AD DEMENTIA AND AD PRODOMAL PHASES: PRESYMPTOMATIC AD AND MILD COGNITIVE IMPAIRMENT DUE TO AD (MCI-AD)

Presentations of the disease are heterogenous, and cognitive decline appears in domains of memory, language, executive functions, as well as visuoperception, visuospatial, and visuomotion processing. Recently, Noh and colleagues reported anatomical subtypes based on cortical thickness that included bilateral medial temporal-dominant atrophy, biparietal dominant atrophy, and diffuse atrophy.[3] These subtypes appear to correlate with the dominant cognitive presentation, although specific clinicopathologic correlations have not been fully confirmed.[4] Interestingly, the parietal dominant subtype appears to progress more rapidly,[3,4] which is of particular importance to neuro-ophthalmology given that the most common manifestations of the biparietal subtype is presumptively visuospatial and visuomotion dysfunction.

A definitive diagnosis of Alzheimer's disease requires evidence of brain pathology by autopsy revealing intracellular neurofibrillary tangles containing tau protein and extracellular neuritic plaques containing beta-amyloid protein. However, a pre-mortem clinical diagnosis of probable AD is greater than 90% accurate if the 1984 National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical criteria are used,[5,6] Since 1984, it became evident that AD dementia is preceded by a long preclinical phase of up to 20 to 25 years whereby pathophysiological changes due to the disease occur before a person develops symptoms of cognitive impairment. Following the preclinical phase, early but mild memory and/or cognitive symptoms follow, and this is referred to a mild cognitive impairment due to AD or MCI-AD. See Figure 1. This understanding was fueled by major discoveries in the field of AD dementia that included the following: the discovery of deterministic genes that cause AD, the recognition of distinguishing features for other, non-AD dementias, the discovery of AD biomarkers, and the appreciation of the heterogeneous clinical spectrum of AD, including non-memory presentations such as visual-predominant forms. In 2011, the National Institutes of Aging and the Alzheimer's Association published three papers to update core clinical criteria for the diagnosis of AD dementia, to provide core clinical criteria for the diagnosis of *MCI-AD*, and to develop a research framework and research criteria for *presymptomatic AD*.[7-10] The updated diagnostic guidelines integrate core clinical criteria for AD and MCI-AD with biomarker evidence, but biomarker evidence is not necessary for the clinical diagnosis.[8,9]

C. OPTICAL COHERENCE TOMOGRAPHY (OCT) OF THE RETINA AND AD BIOMARKERS

OCT allows for non-invasive, cross-sectional, micrometer imaging of the retina. Circumpapillary (cp) retinal scans with automated segmentation of the retinal nerve fiber layer (RNFL) give reliable measures of the RNFL thickness surrounding the optic nerve head. OCT scans of the macula can provide retinal ganglion cell layer- inner plexiform layer (RGC-IPL) thickness measures using automated segmentation. Additionally, macular volume scanning protocols can be used with manual manipulation of predetermined inner or outer limits of the scan, in order to measure the RNFL, RNFL+GCL, retinal ganglion cell complex (RNFL, GCL, IPL), or outer retina layer thickness.[11] Each of these OCT approaches have been used to study retinal changes in AD.

Measures of inner retina thickness by OCT reflect loss of retinal ganglion cell bodies, RGC axons (i.e. RNFL), and synaptic density (i.e. IPL). When one considers the role that OCT of the retina might have as a biomarker for AD, it is important to consider the entire spectrum of Alzheimer's disease, which may span *over 40 years or more* from the early prodromal phase to the late clinical phase. Based on converging lines of evidence, amyloid accumulates early in the disease process followed by synaptic dysfunction, tau accumulation, brain atrophy, cognitive dysfunction, and finally the loss of functional capabilities. AD biomarkers can be categorized as reflecting one of the following pathophysiologic changes that occur during progression of disease: 1) amyloid and tau deposition in the central nervous system (CNS), 2) evidence of CNS neuronal injury or loss and/or CNS metabolic dysfunction, 3) CNS biochemical and/or inflammatory changes, and 4) primary CNS cognitive dysfunction. The specific types of biomarkers under consideration to aid in diagnosing and characterizing AD dementia and the prodromal phases of AD are noted in Table 1. Our current understanding of the clinical disease stage in association with known biomarkers for AD appear to follow a specific longitudinal pattern, as noted in Figure 1. For now, retinal OCT measures would be considered a potential marker of neuronal injury in AD, and findings from several studies over the past decade are reviewed below.

First, historical and recent evidence of pathological changes in the retina of patients with AD is reviewed in order to put into perspective the pathological changes retinal OCT might be measuring. For instance, do retinal thickness and volume measures reflect injury within the eye or further downstream within the thalamus and cerebral cortex where AD neuritic plaques and tangles are found? This is currently unknown, but historical pathological studies and more recent studies shed light on potential mechanisms to consider.

Table 1. Alzheimer's disease biomarker categories and measures modified from Albert and colleagues.[9]

Biomarkers of Amyloid Beta (Aβ) deposition

- Cerebral Spinal Fluid (CSF) $A\beta_{42}$
- PET amyloid imaging

Biomarkers of neuronal injury, metabolic dysfunction, or both

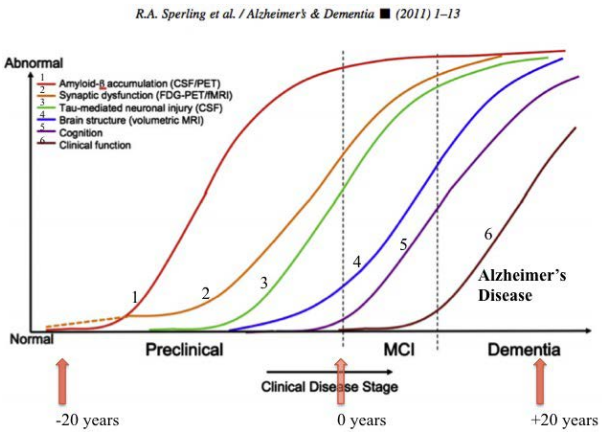
- CSF tau/phosphorylated-tau
- Hippocampal volume or medial temporal atrophy by MRI volumetric measures or visual rating
- Rate of brain atrophy
- FDG-PET imaging
- Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
- Unknown role: OCT of the Retina

Associated biochemical change

- Inflammatory biomarkers (cytokines)
- Oxidative stress (isoprostanes)
- Other markers of synaptic damage and neurodegeneration such as cell death

Abbreviations: Aβ, beta-amyloid protein; CSF, cerebrospinal fluid; PET, positron emission tomography; FDG, fluorodeoxyglucose; SPECT, single photon emission tomography; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; BOLD, blood oxygen level-dependent; MR, magnetic resonance.

Figure 1. Longitudinal biomarker and clinical changes in Alzheimer's disease. Adapted from Sperling et al. 2011.[10]

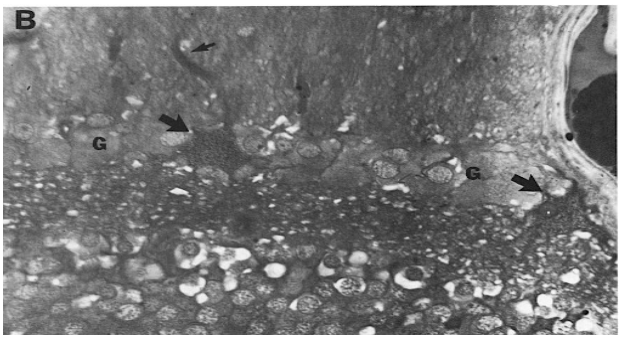


D. PATHOLOGICAL CHANGES IN THE RETINA GANGLION CELL (RGC), THE RETINAL NERVE FIBER LAYER (RNFL), AND THE OPTIC NERVE IN PATIENTS WITH AD

In the late 1980s and early 1990s, Sadun and colleagues reviewed pathological specimens of retinas from people with AD and compared results to age-matched controls and discovered that AD patients had evidence of retinal ganglion cell loss and degeneration, retinal ganglion cell axonal loss and degeneration, optic nerve axonal loss and degeneration, intracranial optic nerve angiopathy.[12-15] See Figure 2 for histopathology. The cause for this degeneration of the RGC, RNFL, and optic nerve remains unknown.

In one of the original retinal histopathological studies, no evidence of neuritic plaques, neurofibrillary tangles, and angiopathy were found in the retina of AD patients.[14] Intracranial optic nerve capillaries and small arterioles were noted to be abnormally thickened in AD patients, however. Evidence of vascular amyloid deposits could not be confirmed by Congo red staining (equivocal results) or Thioflavin S fluorescence (negative results), however.[14] Based on the pattern and distribution of retinal degeneration, Sadun and colleagues suggested that the primary site of injury may be intracranial and selectively affect the M-type of RGC, which projects to the magnocellular lateral geniculate nucleus.[14] Blanks and colleagues systematically counted retinal ganglion cells from post-mortem retina of 11 patients with definite AD and 11 age-matched controls and found greater RGC loss in AD of approximately 26% within a 1.0 mm radius of the foveola and an approximately 47% from a radius of 1 to 1.5 mm of the foveola.[15] The distribution of RGC diameter was not different in AD versus controls.

Figure 2. Retina paraphenylene-diamine (PPD) stain in AD patient from Sadun et al. 1990.[14] Degenerating retinal ganglion cell bodies (large arrows) and degenerating retinal ganglion cell axon entering the nerve fiber layer (small arrow) are seen to stain darkly by PPD and are amongst healthy ganglion cell bodies (G) in the post-mortem retina of a patient with AD.



More recent studies using immunohistochemical techniques have failed to identify retinal deposits of beta-amyloid,[16-17] fibrillary tau,[16] or phosphorylated-tau,[16] in post-mortem human AD retinas. The one exception comes from a study by Koronyo-Hamaoui and colleagues, who used human post-mortem retinal whole mounts and immunohistochemistry, thioflavin-S, and curcumin staining and found evidence for beta-amyloid in the retina of eight definite AD and six possible AD patients and no evidence for such in control retinas.[18] One explanation for the disparate results is the use of retinal whole mounts by Koronyo-Hamaoui and colleagues, which might have increased the sensitivity for beta-amyloid detection. In AD transgenic mice models with amyloid precursor protein mutations, beta-amyloid retinal deposits have been detected by several groups[18-20] and these studies provided the impetus for successful in vivo imaging of retinal beta-amyloid using intravenous curcumin and non-invasive, endoscopic fundus spectral imaging in transgenic mice models.[18,21] In summary, histopathological evidence revealing loss and degeneration of the inner retina exists in post-mortem human AD retinas, but it is not clear whether that injury reflects brain pathology, retinal pathology, or both.

E OPTICAL COHERENCE TOMOGRAPHY (OCT) OF THE RNF AND RGC LAYERS IN AD

Retinal Nerve Fiber Layer (RNFL): Using OCT, cpRNFL scans and macular scans measuring RNFL have revealed reduced RNFL thickness in patients with AD dementia compared to age-matched controls in several studies using time domain and spectral domain OCT imaging.[11,22-33] See Table 2 for a summary of past studies. In August 2015, PLoS ONE published a meta-analysis of RNFL OCT in AD by Coppola and colleagues[34] that included studies published between 2001 and 2014. Although important issues exist with the analysis (for instance, inclusion of total macular thickness in analysis of RNFL differences), the results revealed that RNFL thickness measures are lower in AD subjects compared to normal controls for the total average and for all quadrants or sectors. All but two studies, Chi 2010 and Moschos 2012, listed in Table 2 were included in the meta-analysis. Results from Chi 2010[28] (n=29) were not consistent with the meta-analysis, but results from Moschos 2012 (n=60) were consistent.[26] Most studies included the criteria used for exclusions that could affect retinal OCT measures such as glaucoma, diabetes, optic disc disease, macular degeneration and others. Several important issues should be considered, however, when interpreting the results of these preliminary studies of AD and normal controls. *First*, characterization of the populations was incomplete for both the AD and normal controls (NC) in most studies. The NC populations did not have any cognitive testing or had only mini-mental state examination testing. Typically 1984 or DSM IV criteria were used for AD diagnosis and no amyloid imaging or CSF biomarkers were noted. Furthermore, the control for age differences varied, and when age and gender were reported, some changes to significance were found.[23] *Second*, the total decrease in RNFL thickness for AD compared to NC, as a percent of total thickness, is minimal for the latest studies. Reports range from 59% in the earliest study in 2001 (where the age of NC is not given) [33] to 96% in the latest study with the largest number of subjects using spectral domain techniques.[22,33] Furthermore, in this latest study by Larrosa 2014, the OCT machine played a role in whether results were significant.[22] For example, using Cirrus there were no differences between AD and NC for total average and nasal thickness measures, but use of Spectralis revealed statistically significant lower total thickness for AD versus NC. Surprisingly, *AD subjects had statistically greater thickness than NC* for superior, temporal superior, and nasal sectors using Spectralis. See Table 2 for specific details. These details are extremely important when using biomarkers at the individual patient level. Thus sensitivity becomes and issue. Given the number of exclusions necessary in this population (glaucoma, macular degeneration, diabetes, etc…) it is difficult to understand what the specificity be were retinal OCT be applied to a general aging population.

Retinal Ganglion Cell Layer (RGCL): No study noted in Table 2 obtained measurements of RGCL thickness alone. Marziani and colleagues combined macula RNFL + GCL and differences between AD and NC were significant.[11]

Table 2. Published optical coherence tomography studies examining circumpapillary (unless where noted) RNFL thickness in Alzheimer's Disease (AD). Statistical significance is indicated by bold and * ($p < 0.05$) and non-significance is noted by Not Sig for AD versus normal controls (NC). In column 1, studies included in a published 2015 meta-analysis are marked by #.

Author Year	**Subjects (AD/NC) Age**	**Total Average RNFL AD v. NC (% of NC)**	**Superior RNFL AD v. NC (% of NC)**	**Inferior RNFL AD v. NC (% of NC)**	**Nasal RNFL AD v. NC (% of NC)**	**Temporal RNFL AD v. NC (% of NC)**	**OCT Technique**
Larrosa 2014#	151/61 75y AD 75y NC	Cir: Not Sig **Sp: (96%)***	**Cir: (96%)*** Sp: NS Not Sig **Sp: TS (114%)***	**Cir: (95%)*** **Sp: NI (96%)*** **Sp: TI (85%)***	Cir: Not Sig **Sp: (115%)***	**Cir: (95%)*** Sp: NS Not Sig	SD
Ascaso 2014#	18/14 NA AD 73y NC	**RE: (63%)*** **LE: (63%)***	**RE: (58%)*** **LE: (62%)***	**RE: (64%)*** **LE: (64%)***	**RE: (56%)*** **LE: (61%)***	**RE: (75%)*** **LE: (75%)***	TD
Kirbas 2013#	40/40 69y AD 69y NC	**(86%)***	**(72%)***	Not Sig	Not Sig	Not Sig	SD
Moreno-Ramos 2013#	10/10 73y AD 70y NC	**(88%)***	NA	NA	NA	NA	SD
Marziani 2013#	21/21 79y AD 77y NC	Macular RNFL sector ranges **Sp: RNFL* (80-89%)** **R: RNFL+GCL* (87-92%)**	NA	NA	NA	NA	SD
Moschos 2012	30/30 72y AD NA NC	NA	**RE: (85%)*** **LE: (95%)***	**RE: (84%)*** **LE: (86%)***	RE: Not Sig **LE: (82%)**	**RE: (94%)*** **LE: (82%)***	TD
Kesler 2011#	30/24 74y AD 71y NC	**(90%)***	**(90%)***	**(86%)***	Not Sig	Not Sig	TD
Chi 2010	12/17 NA	Not Sig	NA	NA	NA	NA	NA
Lu 2010#	22/22 73y AD 68y NC	***only graph shown**	***only graph shown**	***only graph shown**	Not Sig	Not Sig	TD
Berisha 2007#	9/8 74y AD 74y NC	NA	**(81%)***	Not Sig	Not Sig	Not Sig	TD

Table 2 continued. Published optical coherence tomography studies examining circumpapillary (unless where noted) RNFL thickness in Alzheimer's Disease (AD). Statistical significance is indicated by bold and * ($p < 0.05$) and non-significance is noted by Not Sig for AD versus normal controls (NC). In column 1, studies included in a published 2015 meta-analysis are marked by #.

Author Year	**Subjects (AD/NC) Age**	**Total Average RNFL AD v. NC (% of NC)**	**Superior RNFL AD v. NC (% of NC)**	**Inferior RNFL AD v. NC (% of NC)**	**Nasal RNFL AD v. NC (% of NC)**	**Temporal RNFL AD v. NC (% of NC)**	**OCT Technique**
Paquet 2007#	26/15 78y AD 76y NC	Mild AD/NC **(87%)*** Severe AD/NC **(75%)***	NA	NA	NA	NA	TD
Iseri 2006#	14/15 70y AD 65y NC	**(77%)***	**(82%)***	**(72%)***	**(66%)***	Not Sig	TD
Parisi 2001#	17/14 70y AD NA NC	**(59%)***	**(68%)***	**(67%)***	**(53%)***	**(44%)***	TD

Abbreviations: Not Sig, Not statistically significant; AD, Alzheimer's disease; NC, normal control; Cir, Cirrus; Sp, Spectralis; NS, nasal superior; TS, temporal superior; NI, nasal inferior; TI, temporal inferior; N, nasal; T, temporal; R, RTVue-100; SD, Spectral domain; TD Time domain; NA, not available or unknown; RE, Right eye; LE, left eye

F. OCT OF THE RNFL AND MILD COGNITIVE IMPAIRMENT (MCI)

Very few studies have assessed RNFL in MCI.[23,27,31] Ascaso and colleagues noted reduced circumpapillary RNFL thickness (total and quadrant) for subjects with amnestic MCI (N=21) compared to normal controls (N=41) and greater RNFL loss of AD (N=18) than for amnestic MCI (aMCI) for measures of total average and for all quadrants.[23] Total average circumpapillary RNFL thickness was also decreased in MCI (N=40 eyes) compared to NC (N=38 eyes) in a study by Kesler and colleagues, but there was no difference between MCI and AD (N=52 eyes).[27] Similarly, the earliest study in 2007 revealed decreased RNFL total average thickness in amnestic MCI (N=22) versus NC (N=15) and mild or severe AD (N=26) versus NC, but there were no differences between aMCI versus mild AD (N=14) or severe AD (N=12) were found.[31] Thus, in terms of "staging" the degree of functional impairment, the role of retinal OCT awaits further study with larger cohorts.

G. OCT OF OTHER MACULA PARAMETERS AND AD

Studies of OCT measures of macula thickness and macula volume have revealed varied results, with some showing decreased thickness in AD versus NC,[11,22] while others showed no difference when controlling for age and sex.[23] Central sectors (fovea) thickness measures have not shown significant differences between AD and NC in several studies.[11,22,23] Of note, however, amnestic MCI subjects in one study had *increased* macular volume and thickness, including the foveal region, versus AD and NC.[23] The significance of these findings are unknown. If the result is repeatable, consideration for increased synaptic density at the time of very early RGC loss could be one possibility that would be easy to assess.

H. OCT AND COGNITIVE MEASURES IN AD/MCI

Some of the studies reviewed above assessed the relationship of RNFL to mini-mental state examination (MMSE) scores and found negative correlations,[11,25] while others found no associations.[27,31-33] In one additional study, RNFL inferior quadrant thickness was inversely correlated to episodic memory tests in NC (N=52), indicating worse performance with thicker RNFL; with the MCI (N=23) subjects, it was the opposite: the thinner the RNFL, the worse the MCI subjects performed on episodic memory tests. Overall, there was no difference in RNFL and macular volume or thickness in MCI versus NC.[35] This latter study highlights the need for greater characterization of the NC population given the very long prodromal phase of AD.

I. CONCLUSIONS OCT AND AD

There have been several studies that confirm that loss of RNFL in AD can be measured by retinal OCT within the circumpapillary and macular regions. This reduction in RNFL is also measurable in amnestic MCI in most cases, indicating that loss of RNFL may occur early in the clinical phase of AD before dementia develops. These findings indicate that we have a means to detect the histopathological changes,

noted by Sadun and colleagues in the 1980s and 1990s, revealing loss of retinal nerve fiber layer axons, loss of retinal ganglion cells, and changes of the optic nerve axons in eyes of AD patients. Whether AD pathology within the eye or brain is responsible is unknown, and the one study that demonstrated definitive deposits beta-amyloid awaits confirmatory evidence from other groups. Neuritic plaques and neurofibrillary tangles have never been detected in the eyes of patients with AD. In the context of our current understanding of AD biomarkers, it remains unclear whether retinal OCT will be able to function as a biomarker of AD. It will be necessary to conduct longitudinal studies with larger cohorts of better-characterized AD, MCI, and normal controls using formal neuropsychological assessments and markers of amyloid (CSF and/or PET), and atrophy (MRI), before the role of OCT retinal imaging can be determined. Finally, just as with other measures of pathological changes in AD, it will be important to investigate the longitudinal profile of retinal OCT measures in well-characterized, large cohorts to understand associations of retinal OCT measures to cognitive profiles, which is currently not known.

II. IDIOPATHIC PARKINSON'S DISEASE (PD)

A. PD: THE BURDEN OF DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder with motor and non-motor manifestations, and approximately one million people in the US have PD with the incidence expected to double in the next two decades as the population ages.[36] It is the most common neurodegenerative disorder after Alzheimer's disease. The combined direct and indirect costs are estimated to be 25 billion dollars per year.[36] Similar to Alzheimer's disease, the lack of treatments that alter the course of disease has made PD more deadly as the population ages and is currently the 14th leading cause of death in the US.[37]

Abbreviations: REM, rapid eye movement; CSF, cerebrospinal fluid; PARK2, RBR E3 ubiquitin protein ligase gene; GBA, glucocerebrosidase beta gene; PINK1, PTEN- induced kinase 1 gene; SNCA, synuclein alpha gene; LRRK2, leucine-rich repeat kinase gene; PARK7 gene, Parkinsonism associated deglycase; SPECT, Single photon emission tomography; PET, Positron Emission Tomography.

Table 3. Potential biomarkers for Parkinson's disease.

Clinical: Non-Motor Signs and Symptoms

- Gastrointestinal
- REM sleep behaviour disorder
- Anosmia
- Depression

Biochemical

- CSF, blood, or saliva assessment for alpha-synuclein
- Gastic alpha-synuclein deposits
- CSF DJ-1 protein
- Plasma Apo A1 (a component of high density lipoprotein)

Gene mutations

- PARK2, GBA, PINK1, SNCA, LRKK2, PARK7

Imaging

- SPECT or PET with radiotracers: 6-[18F] fluorodopa, or [11C]dihydrotetrabenazine (DTBZ), or 2-beta-[11C] carbomethoxy-3-beta-4-fluorophenyltropane (CFT) reflecting membranous dopamine transporter (DAT) Transcranial sonography
- Structural MRI

B. THE DIAGNOSIS OF PD

The common motor symptoms, that have long-been recognized since the description by James Parkinson in 1817, include slowing of movements and gait (i.e. bradykinesia), tremor predominantly at rest, postural instability, and rigidity. However, recognition of non-motor symptoms has altered the diagnosis, approach to treatment, and understanding of the pathophysiology in the past decade with recognition that non-motor symptoms such as hyposmia, autonomic dysfunction, sleep dysfunction and psychiatric dysfunction often precede motor symptoms. These symptoms stem for involvement of central and peripheral neurons that are considered "non-dopaminergic".[38]

The diagnosis of PD depends upon post-mortem examination with evidence of dopaminergic neuronal loss in the substantia nigra and α-synuclein-containing neuronal inclusions termed Lewy bodies and Lewy neuritis. Alpha-synuclein aggregates also drive disease pathogenesis beyond Lewy body pathology. Although clinical diagnosis can be straightforward, several other disorders are very difficult to distinguish from Idiopathic Parkinson's Disease (IPD) by clinical evaluation alone. Indeed, many clinical features overlap to such an extent that the non-specific term "parkinsonism" is used for non-IPD disorders that cannot be more specifically categorized.

Many of the same reasons that led to updates in AD diagnostic criteria, generated the impetus for updates to the diagnostic criteria for PD and research criteria for pre-clinical PD. In 2015, two publications by the International Parkinson and Movement Disorder Society (MDS) task force[39,40] proposed three stages for early PD: 1) preclinical PD with presence of neurodegeneration but no clinical symptoms or signs, 2) prodromal PD with symptoms, signs, or both but below a threshold to meet diagnostic criteria for clinical PD, and 3) clinical PD that meets specific diagnostic criteria. There has been a change in how dementia is considered in the diagnosis, which is of importance to the neuro-ophthalmology community since patients with dementia with Lewy bodies have prominent visual and visuospatial dysfunction. The MDS criteria do not consider dementia that begins early, or prior to significant parkinsonism, as an exclusion to the diagnosis of PD, and patients with dementia with Lewy Bodies can qualify as "PD-dementia with Lewy bodies" subtype if criteria for PD is met.[40]

C. BIOMARKERS AND PD

Compared to Alzheimer's disease, biomarker research for PD is in earlier stages of development and understanding. The Parkinson Progression Marker Initiative is an international, multi-center study sponsored by the Michael J. Fox Foundation to discover and develop biomarkers of disease and progression for PD-modifying clinical trials. Table 3 outlines some of the current lines of investigation for PD biomarkers.[41] The new criteria for the diagnosis of PD and preclinical or prodromal PD do not incorporate biomarkers for clinical or research purposes, unlike the new criteria for AD as noted above. See Sharma et al. for an extensive review of biomarkers in PD.[42]

D. RETINAL PATHOLOGY IN PD

Dopamine is an important neurotransmitter in the retina, and dopamine *receptors* have been found in association with outer and inner layer cells including bipolar axons in the inner plexiform layer, amacrine cells, retinal ganglion cell bodies, horizontal cells in the outer plexiform layer, and photoreceptors. Dopaminergic amacrine cells types have been previously characterized.[43] Post-mortem retinas from PD patients without prior exposure to levodopa have been shown to have lower concentrations of dopamine compared to controls and dopamine naïve PD patients.[44] Additionally, there is evidence that dopaminergic cells in the retina participate in modulation of functions related to color vision and spatial contrast sensitivity, which are functions that have been shown to be reduced in patients with PD.[45] Recent investigations regarding the histopathological changes within the retina indicate that alph-synuclein may be distributed differently in aging versus PD and may aggregate in the inner retina.[46] For these reasons, there has been growing interest in measuring retinal thickness in PD, particularly the inner layers of the retina, over the past decade.

E. OCT OF THE RNF AND RGC LAYERS IN PD

Using OCT, cpRNFL scans and macular scans have revealed reduced RNFL thickness in patients with PD compared to age-matched controls in several studies using time domain and spectral domain OCT imaging.[24,45-59] See Table 4 for a summary of past studies, which indicate that mixed results exist for associations between PD and total average and quadrant RNFL thickness. However, a recently published meta-analysis60 did show that average total RNFL and superior, inferior, nasal and temporal quadrants are reduced in PD versus NC. Important considerations include the disease duration included in the studies, which mostly involved subjects with PD duration of 3 years or more years.

F. OCT OF OTHER MACULA PARAMETERS AND PD

Since cellular dysfunction due to dopamine deficiency may affect the retina as a whole and particularly the inner nuclear layer, the outer plexiform layer, and the inner plexiform layers, many studies noted in Table 4 included macular volume and macular thickness OCT scans,[45,49,55,56,58,61,62] and some studies showed significant differences in total macular volume, specific sectors, or both, [45, 49, 58] while others showed no significant differences in total macular volume for PD versus NC.[55,56]

Table 4. Published optical coherence tomography studies examining circumpapillary (cp) RNFL thickness (unless otherwise noted) and macular findings Parkinson's Disease. Statistically significance indicated by bold and * ($p < 0.05$) for PD versus normal controls. Non-significance is noted by Not Sig. In column 1, studies included in a published 2014 meta-analysis[60] is indicated by ^.

Author Year	**Subjects (PD/NC) Age**	**Total Average RNFL PD v. NC (% of NC)**	**Superior RNFL PD v. NC (% of NC)**	**Inferior RNFL PD v. NC (% of NC)**	**Nasal RNFL PD v. NC (% of NC)**	**Temporal RNFL PD v. NC (% of NC)**	**OCT Technique**
Chorostecki 2015	101/46 66y PD 60y NC	Not Sig	NA	NA	NA	NA	SD
Bittersohl 2015	108/165 64y PD 57y NC	Not Sig	NS: Not Sig TS: Not Sig	NI: Not Sig TI: Not Sig	Not Sig	Not Sig	SD
Bayhan 2014	20/30 66y PD 64y NC	NA	IL: Not Sig CL: Not Sig	IL: Not Sig CL: Not Sig	IL: **(90%)*** CL: **(89%)***	IL: Not Sig CL: NS Not Sig	SD
Satue^ 2013	100/100 64y PD 64y NC	Cir: Not Sig Sp: Not Sig	Cir: Not Sig Sp: Not Sig	**Cir: (94%)*** **Sp: (94%)***	Cir: Not Sig Sp: Not Sig	Cir: Not Sig Sp: Not Sig	SD
Kirbas^ 2013	42/40 59y PD 57y NC	**(92%)***	Not Sig	Not Sig	Not Sig	**(88%)***	SD
2013 La Morgia^	43/86 66y PD 66y NC	Not Sig	Not Sig	Not Sig	Not Sig	**(90%)***	TD
Sen^ 2014	33/11 64y PD 61y NC	**(92%)***	**(97%)***	**(89%)***	SN: Not Sig IN: Not Sig	ST: Not Sig IT: **(78%)***	SD
Garcia-Martin^ 2012	75/75 64y PD 64y NC	Cir: **(93%)*** Sp: **(96%)***	Cir: Not Sig Sp: Not Sig	Cir: **(93%)*** Sp: Not Sig	Cir: Not Sig Sp: Not Sig	Cir: Not Sig Sp: Not Sig	SD
Rohani^ 2013	27/25 55y PD 55y NC	**(89%)***	**(89%)***	**(87%)***	**(92%)***	**(91%)***	SD
Tsironi^ 2012	34/24 67y PD 64y NC	Not Sig	Not Sig	Not Sig	Not Sig	Not Sig	TD
Albrecht^ 2012	40/35 61 PD NA NC	Not Sig	Not Sig	Not Sig	Not Sig	Not Sig	SD
Archibald^ 2011	51/25 72y PD 71y NC	RE: **(107%)*** LE: Not Sig	Not Sig	Not Sig	Not Sig	Not Sig	TD

Table 4 continued. Published optical coherence tomography studies examining circumpapillary (cp) RNFL thickness (unless otherwise noted) and macular findings Parkinson's Disease. Statistically significance indicated by bold and * (p <0.05) for PD versus normal controls. Non-significance is noted by Not Sig. In column 1, studies included in a published 2014 meta-analysis[60] is indicated by ^.

Author Year	Subjects (PD/NC) Age	Total Average RNFL PD v. NC (% of NC)	Superior RNFL PD v. NC (% of NC)	Inferior RNFL PD v. NC (% of NC)	Nasal RNFL PD v. NC (% of NC)	Temporal RNFL PD v. NC (% of NC)	OCT Technique
Moschos^ 2011	16/20 57y PD 52y NC	Not Sig	Not Sig	**(90%)***	Not Sig	**(88%)***	TD
Aaker^ 2010	9/16 64y PD 67y NC	Not Sig	ST: Not Sig SN: Not Sig	IT: Not Sig IN: Not Sig	Not Sig	Not Sig	SD
Altintas^ 2008	17/11 59y PD 58y NC	**(86%)***	**(90%)***	Not Sig	**(76%)***	Not Sig	TD
Inzelberg^ 2004	10/10 57y PD 52y NC	NA	Not Sig	**(96%)***	Not Sig	**(80%)***	NA

Abbreviations: Not Sig, not statistically significant; NC, normal control; PD, Parkinson's disease; SD, Spectral domain; TD Time domain; NA, not available or unknown; IL, ipsilateral eye to PD predominant side; LC, contralateral eye to PD predominant side; Cir, Cirrus; Sp, Spectralis; NS, nasal superior; TS, temporal superior; NI, nasal inferior; TI, temporal inferior; N, nasal; T, temporal;

Due to improved capabilities for segmentation of the retina by OCT, Chorostecki and colleagues suggest study of the retina in PD must take into consideration the possibility for increase in thickness for some layers due to potential for alpha-synuclein deposits, while reduction in thickness may occur in other layers with cell death or synaptic changes.[46] This same group studied retinal OCT with more specific segmentation and found reduced GCL, inner plexiform layer (IPL), inner nuclear layer, and outer nuclear volumes as well as increased outer plexiform layer volumes for PD versus NC.[46] Other studies also have also shown decreased GCL-IPL,[63] outer nuclear,[64] and photoreceptor thinning in PD.[64]

G. OCT RETINA, FUNCTION, PD DISEASE STAGE OR DURATION

Fewer studies have assessed retinal OCT measures with measures of function, in terms of visual function or disease-related stage and duration. Studies that have done so are reviewed below. Mixed results likely reflect the small subject number and different approaches, but there is a potential that structural changes in the retina, as measured by OCT, are not responsible for the variety of functional changes that occur in PD. Instead, changes in metabolism and physiology may occur prior to significant visual functional changes.

Visual Evoked Potential (VEP), Multifocal ERG (mfERG), Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn-Yahr (H-Y) Stage, PD Duration. Altintas and colleagues studied correlations between OCT retinal measures and visual evoked potentials (VEP), UPDRS scores, and duration of PD in 17 patients diagnosed with PD using UK Brain Bank criteria, and data for normal controls were not reported.[58] The study found *no correlation* between VEP P100 and disease duration with RNFL average, foveal thickness, or total macular volume. The only significant finding was a negative correlation between UPDRS score to foveal thickness (r=-0.660, P.0004), but the authors also reported no statistically significant difference in foveal thickness between PD and normal controls. In a study by Kaur and colleagues with 20 PD subjects, pattern VEP latency correlated with RNFL but not GCL-Inner Plexiform Layer (GCL-IPL) thickness, while both RNFL and GCL-IPL did correlate to changes on mfERG.[65] In the same study, RNFL inversely correlated to UPDRS subscale, but interestingly, neither RNFL or GCL-IPL correlated to disease duration. In a different study of 20 patients diagnosed with PD by UK Brain Bank criteria, the ganglion cell complex (RNFL, GCL, and IPL) parameters for each eye were assessed for correlations to UPDRS total, UPDRS motor, and H-Y stage.[48] Negative correlations were found between GCC average and

inferior sectors for the ipsilateral eye (i.e. same side of the predominant PD disease) and UPDRS (total and motor) scores as well as negative correlations for GCC inferior sector for the ipsilateral eye and H-Y stage. The rest of the 25 correlations were not statistically significant. Satue and colleagues found the H-Y stages for subjects correlated to inner and outer sectors on macular OCT thickness measures (except outer superior sector) using Spectralis, but not Cirrus, and H-Y stages also correlated with nasal RNFL but only with Cirrus and not Spectralis.[66] Fovea thickness showed no correlation to H-Y stage for either machine.

Contrast Sensitivity, Visual Field. In a small study of PD (N=14), Adam and colleagues found no correlation between contrast sensitivity and inner retinal layer (RNFL, GCL, IPL) thickness.[67] Similarly, despite diminished contrast sensitivity in PD subjects, no differences in RNFL or macular volume or thickness measures were found between PD (N=51) and NC (N=25).[56] Tsironi et al. found depressed visual field perimetry in a small group of PD patients (N=24) compared to NC (N=24), but no differences in RNFL.[54]

Visual hallucinations. Very few studies have assessed visual symptoms and retinal OCT in neurodegeneration. Two studies evaluated OCT of the RNFL and visual hallucinations (VH) in populations of PD and NC; one found an association to RNFL thinning,[61] and while another found no association with RNFL.[68] Neither study found an association between macular thickness and macular volume and VH.

H. CONCLUSIONS OCT AND PD

Patients with Parkinson's disease show evidence for structural loss of inner and, in some cases outer, retinal thickness as measured by OCT, which has been confirmed by a meta-analysis despite variable results over many studies. Some investigators have suggested that structural changes in the retina of PD patients vary between layers due to alpha-synuclein aggregation versus neuronal loss, which might increase thickness in some regions and decrease thickness in other regions. Further understanding of these potential changes (thinning versus "thickening") awaits studies that make use of improved segmentation techniques with advance OCT imaging technology that continues to improve signal to noise. Structural-functional relationships, using retinal OCT and various physiologic measures of vision, as well as PD-specific functional measures, are complex and will become more evident with larger cohorts of well-characterized patients. Longitudinal studies of changes in retinal OCT measures and functional measures will allow us to understand how these measures change over time and relate to disease stage, duration, and progression. Thus, the role of retinal OCT as a biomarker in PD is yet to be determined.

III. CONCLUSIONS

Alzheimer's disease and Parkinson's diseases both have prolonged preclinical phases with loss of neuronal populations before symptomatic, clinical manifestations occur. It is unknown whether OCT of the retina will be a useful biomarker for AD or PD, but evidence reveals that significant thinning of the inner retina can be detected compared to controls in some populations of patients with AD and PD. Longitudinal studies with well-characterized patient populations will be critical to obtain a better understanding of the role that retinal OCT might play as a biomarker in the assessment of Alzheimer's disease and Parkinson's disease.

CME ANSWERS

1. False: The cause for the changes in OCT measures of the retina is not yet fully understood. One group has recently found beta-amyloid deposits within the human retina, but neuritic plaques and neurofibrillary tangles have not been found within the human retina of people with AD. Furthermore, it is possible that some of the changes in retinal OCT measures in AD reflect changes beyond the eye and within the optic nerve beyond the globe and/or the visual pathways beyond the optic nerve. In PD, retinal OCT changes may be directly related to loss of dopamine-producing retinal cells (i.e. amacrine cells) and/or due to alpha-synuclein aggregates within the retina, but our current understanding OCT retinal measures is limited to cross-sectional studies of living patients and the origin of the changes in OCT measures is unknown.

2. False: Nearly all of our understanding of OCT retinal changes come from cross-sectional studies with limited studies related to structure-function relationships or staging. In fact, some studies show no correlation to disease duration or stage in both AD and PD. Better characterization of populations, larger cohorts, and longitudinal studies are necessary before OCT retinal measures can be considered for use to stage or monitor neurodegenerative disease associated with AD and PD.

3. False: In patients with AD, visual functional-structural relationships using retinal OCT have not been investigated. With PD, there have been limited studies correlating measures of visual function and symptoms to OCT retinal measures, and studies thus far show mixed results. For visual symptomatology alone, no studies have investigated the relationship between visual symptoms and OCT measures in AD and PD.

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THE FUTURE OF OPTICAL COHERENCE TOMOGRAPHY: MERGING STRUCTURE AND FUNCTION

Robert C. Sergott, MD

Wills Eye Hospital Neuro-Ophthalmology Service, Thomas Jefferson University
Philadelphia, PA

LEARNING OBJECTIVES

1. Review the technical and clinical backgrounds surrounding optical coherence tomography [OCT] and neuro-ophthalmology.
2. Describe the newer developments with widefield OCT scanning.
3. Explain how in the future structural changes with OCT will be integrated with functional markers using fluorescent lifetime ophthalmoscopy and two photon microscopy.

CME QUESTIONS

1. Why would structural endpoints in clinical trials be preferable to visual acuity and visual field testing?
2. Define fluorophore and fluorescence lifetime.
3. What "tissue environmental" factors influence the fluorescence lifetime of a chemical compound with fluorescent properties?

KEYWORDS

1. Optical coherence tomography including widefield imaging
2. Flourescent lifetime ophthalmoscopy [FLIO]
3. Two-photon microscopy
4. Reactive oxygen species
5. Stargardt Disease

INTRODUCTION

Optical coherence tomography [OCT] has established itself as a pivotal imaging procedure for both clinical neuro-ophthalmology as well as clinical research and clinical trials. While the current spectral domain technology provides well-defined and reproducible structural metrics, the future will bring not only improved visualization of the histology of the optic nerve and retina including widefield imaging of the retinal periphery but also will integrate metabolic, physiological assays.

The technologies of the future will ingeniously harness the natural fluorescent properties of compounds and molecules occurring in healthy and diseased tissue. These in vivo contrast agents or flourophores re-emits light after being excited by light of specific wavelengths. Each compound has its unique flourscent signature enabling its detection and quantification in both cross-sectional and longitudinal studies. While still in the developmental stage, recent peer-reviewed studies have used fluorescent lifetime ophthalmoscopy with two-photon microscopy in Stargardt Disease, retinal artery occlusions and Alzheimer Disease.

Although initially developed for glaucoma and retinal diseases such as age-related macular degeneration and diabetic retinopathy, OCT has now permeated neuro-ophthalmology for: [1] enhancing diagnostic accuracy; [2] monitoring disease subclinical disease progression; and [3] providing objective data for regulatory clinical trials.

OCT technology has visualized and quantified retinal and optic nerve changes where we never believed they existed, especially in neuro-degenerative diseases, such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, fronto-temporal dementia, and traumatic brain injury.

While many challenged the relevance of OCT for neuro-ophthalmology, a Google search for "OCT Neuro-Ophthalmology", December 1, 2016, yielded 176,000 results in 0.97 seconds. Skepticism about new technologies is quite common, and justifiable, until the metrics are validated against standard imaging modalities, correlated with histopathological findings, and ultimately add value to patient care. Computerized tomography [CT] and magnetic resonance imaging [MRI] shared similar critiques early in their developmental cycle.

We have decisively entered the spectral domain OCT era [SD-OCT] era discarding the highly pixelated images and poor tissue differentiation of time domain OCT [TD-OCT] as a historical footnote. As the scanning speeds [number of A-scans per second], laser strengths, and image stabilization have improved, OCTs have reached 6 micron resolution. These technical achievements have enhanced the test/retest variability of serial measurements into the 3.5 – 4.5% range; whereas with TD-OCT the variability often exceeded 50%.

The original OCT technology commercially available in 2002 was time-domain OCT. It used an infrared light source with a wavelength of approximately 840 nm. Using an infrared

light source of 840 nm, TD-OCT depended upon the motion of a mirror to adjust the reference beam. SD-OCT employs Fourier domain technology that replaces the mobile mirror with a series of sensors that enables speeds of up to 200 times faster than TD-OCT.

Predicting the path forward for OCT and neuro-ophthalmology is the challenge for this manuscript. While OCT is the most recognizable "brand name" in ophthalmic imaging, similar to MRI scanning, we are seeing transformations of traditional OCT scanning of the retinal nerve fiber layer and macula into "non-traditional" OCT scanning with diverse imaging modalities that include fundus auto-flourescence [FAF], multicolor OCT [MC-OCT], optical coherence tomography angiography [OCT-A] and two-photon microscopy (TPM) and fluorescence lifetime imaging ophthalmoscopy (FLIO).

PRE-REQUISITES FOR CLINICAL SIGNIFICANCE AND VALIDATION

Clinical neuro-ophthalmology, in my opinion, should take its lead from the United States Food and Drug Administration [FDA] paralleling their guidelines for endorsing new traditional and non-traditional OCT ophthalmic imaging modalities.

The insights provided by Wiley Chambers, MD, Deputy Director Division of Transplant and Ophthalmology Products, Center for Drug Evaluation and Research, FDA, Silver Spring, Md, are very instructive in establishing the benchmarks required for regulatory and clinical acceptance of new technologies. Dr. Chambers' remarks focus primarily on glaucoma but they are easily transferred to neuro-ophthalmology:

> "To be approved for treatment of glaucoma, the expectation is that a drug would demonstrate the ability to alter the disease or the expected outcome of the disease, meaning that it improves the optic neuropathy or visual function. Structural endpoints showing an effect on the optic neuropathy would be preferred but unfortunately, for now, efficacy measures are limited to tests of visual function.
>
> Structural methods would be better because they're likely to be more consistent than visual function tests and they're not expected to have a learning curve."[1]

Dr. Chambers indicated that the structural analyses must pass the "so what" test which means that they must have "clinical utility". The anticipation is that loss or alteration of retinal and optic nerve structure will become structural endpoints for regulatory approval after correlation and validation with specific, reproducible, and sensitive clinical findings.

The FDA has moved to acceptance of structural markers in phase 2 and 3 clinical trials when the natural history of the disease is well-defined and masked, prospective placebo-controlled clinical trials are employed such as the approval of ocriplasmin [Jetrea] for vitreo-macular traction and macular holes.[2]

FASTER AND WIDER OCT

Accelerating advances in the identification of genetic mutations in retinal degenerative diseases coupled with the ability to transfer genetic material to target cells has created the need and demand for imaging the peripheral retina, the site of many initial pathological changes.

The current OCT devices were designed to image the macula with 6-9 mm B-scan length. The OCT technicians may have patients move their eyes to obtain images outside the usual areas but the resolution of the images often suffers.

Using higher acquisition speeds, progress has been made with imaging the peripheral retina. The other promising approach has been the use of special widefield lenses. Excellent images are now available with a 55 degree view of the fundus.

The wide-field imaging will allow better definition of the extent of a disease process within the retina and also will be especially valuable to practitioners without training and expertise in indirect ophthalmoscopy.

FLOURESCENCE: THE IN VIVO CONTRAST AGENT

The history of progress in medicine correlates with an almost perfect linear relationship with advances in medical imaging dating back to Madame Curie and the first "X-rays" and continuing through CT, MRI, and OCT. Flourescent imaging appears to be the next frontier of medical imaging physics that will impact clinical care. This technology will enable a form of "metabolic OCT" to track molecular locations and movement over time within the retina.

First, basic terminology must be defined. A **fluorophore** is a fluorescent chemical compound that re-emits light after it has been excited by light of specific wavelengths. The **fluorescence lifetime [FLT]** is the time that the fluorophore remains in the excited state before reverting to the baseline state. Every fluorophore has a specific FLT dependent upon its environment such as pH, temperature, polarity and ion concentration.

Autoflourescence has evolved into a standard retinal imaging technology, depending upon the fluorescence of lipofuscin. Autoflourescence is often distinctive for specific tissues.

For fluorescence lifetime imaging, photons have to be attributed to different pixels by correlating the arrival time of the photon to the arrival time of the laser pulse. The scanner of the confocal microscope records signals to classify the timeline of photons into different pixels.

Autoflourescence of dense tissues is measured by two-photon microscopy [TPM]. The autoflourescence is obtained only from the focused plane therefore the cellular autoflourescence may be obtained from different retinal cells including the retinal pigment epithelium [RPE], photoreceptor ellipsoid and myoid zones as well as the endothelial cells of the retinal blood vessels.

Fluorescence lifetime imaging microscopy (FLIM) is the technique that maps the spatial and temporal distribution of fluorescence lifetimes in microscopic images. Fluorescence lifetime is a fluorophore-intrinsic property. This technique avoids the use of injectable dyes. The other main advantages of FLIM include reduced photo-toxicity and better penetration depth, required for in vivo measurements especially in tissue samples.

RECENT INVESTIGATIONS USING FLIO

Reactive oxygen species [ROS], intrinsic free radicals, are produced by normal cellular metabolism. Increases in ROS concentrations leads to oxidative stress which harms various physiological processes including DNA damage, lipid peroxidation, and protein alterations. This process has been postulated to play a role in many diseases, including neuro-degenerative conditions. Therefore, methods to detect ROS may be a critical biomarker to diagnose early disease activity and to track the effect of various treatment paradigms.[3-5]

Miura and his colleague found that FLIM can detect retinal oxidative stress in tissue culture systems. They reported a dramatic alteration of fluorescence lifetime of the RPE and outer retina under oxidative stress conditions [slides]. With this technology lipid droplets display a granular appearance.

These excellent work on tissue specimens has been followed by equally elegant work in patients with Stargardt Disease. FLIO measurements detected a wide-range of fluorescence lifetimes within Stargardt lesions. FLIO demonstrated a heterogeneity of FLIO signals with lesions demonstrating identical autoflourescence patterns. Some of the lesions were found to have shorter flourescent lifetimes than the surrounding retina. These shorter lifetime lesions then transitioned into lesions with longer lifetimes. These objective measurements may be able to detect pathological changes that occur extremely early in Stargardt Disease; thus, making it possible to design and monitor potential therapeutic strategies.

Dysli, Wolf and Zingernagel have studied 24 patients with central or branch retinal artery occlusions with FLIO using the contralateral healthy eyes as controls.[6] Mean retinal fluorescence lifetimes were extended by 50% in the short spectral channel and 20% in the long spectral channel for 3 days after the onset of the occlusion. After the first 3 days, no differences were found. These findings may lead to a biomarker to identify and potentially modify in acute ischemic damage to the retina.

In a study of 16 Alzheimer's patients, FLIO retinal parameters of the second [long] fluorescent component correlated with the patient's cognitive status as well as p-tau181 protein concentration in the cerebrospinal fluid. There was no correlation with retinal nerve fiber layer thickness, optic disc excavation, and macular thickness to the Alzheimer's disease status or cerebrospinal fluid analyses.

CONCLUSIONS

SD-OCT scanning of the retina and optic nerve is analogous to the MRI scanning of the brain and spinal cord. Higher and higher resolution images will be obtained with SD-OCT extending to the peripheral retina which will provide a complete dataset of the entire retina for neuro-ophthalmic clinical evaluation and research.

And, just as MRI laid the foundation for positron emission scanning [PET] scanning to investigate the metabolic activity of the central nervous system, OCT has created the framework for fluorescence imaging of the retina which will yield new information about the metabolism of the retina in healthy eyes and eyes affected directly by vision threatening diseases as well as eyes affected by neuro-degenerative diseases.

CME ANSWERS

1. Less variability, more consistent results and no learning curve effect as can be present with visual field testing
2. A fluorophore is a fluorescent chemical compound that re-emits light after it has been excited by light of specific wavelengths. The fluorescence lifetime [FLT] is the time that the fluorophore remains in the excited state before reverting to the baseline state.
3. Temperature, pH, polarity and concentration

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PLATFORM SESSION I

Monday, April 3, 2017 • 5:00 pm - 7:00 pm

Moderators: Matthew J. Thurtell, MBBS, FRACP & Michael S. Vaphiades, DO

**Please note that all abstracts are published as submitted.*

Monday, April 3rd from 5:00pm-5:15pm
Tocilizumab in Patients With Giant Cell Arteritis: Results From a Phase 3 Randomized Controlled Trial

Susan Mollan[1], Katie Tuckwell[2], Sophie Dimonaco[2], Micki Klearman[3], Neil Collinson[2], John Stone[4]

[1]University Hospitals Birmingham NHS Trust, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham B15 2GW, United Kingdom, [2]Roche Products Ltd., Welwyn Garden City, United Kingdom, [3]Genentech, South San Francisco, California, USA, [4]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, Massachusetts, USA

Introduction:
The efficacy and safety of tocilizumab (TCZ), an IL-6 receptor-alpha inhibitor, was evaluated in patients with giant cell arteritis (GCA) in GiACTA, a randomized, double-blind, placebo-controlled trial.1 Data for week 52 outcome measures are presented.

Methods:
Patients with confirmed active GCA were included. Patients were randomly assigned 1:1:2:1 to 4 groups: short-course prednisone (PBO+26) or long-course prednisone (PBO+52) (26-week or 52-week prednisone taper + weekly subcutaneous [SC] placebo, respectively) or weekly (TCZ-QW) or every-other-week (TCZ-Q2W) SC TCZ 162 mg + 26-week prednisone taper. Randomization was stratified by baseline prednisone dose (≤30 or >30 mg/day) as selected by the investigator (20-60 mg/day). Prednisone doses <20 mg/day were blinded. Sustained remission was defined as absence of flare, normalization of C-reactive protein, and adherence to the protocol-defined prednisone taper from week 12 to week 52. The primary and key secondary end points were the proportions of patients in sustained remission, comparing TCZ groups with the PBO+26 and PBO+52 groups, respectively (significance level, 0.005). Prednisone exposure was a secondary end point.

Results:
Among 251 patients randomly assigned (mean±SD age, 69±8.2 years), 56.0% and 53.1% in the TCZ-QW and TCZ-Q2W groups, respectively, achieved sustained remission compared with 14.0% in the PBO+26 group ($p<0.0001$) and 17.6% in the PBO+52 group ($p\leq0.0002$). Median cumulative steroid exposure was 1862.0 mg in both TCZ groups versus 3296.0 mg for PBO+26 and 3817.5 mg for PBO+52 ($p<0.001$). Adverse events (AEs) were similar among the 4 treatment groups. Serious AEs were reported in 15.0%, 14.3%, 22.0%, and 25.5% of TCZ-QW, TCZ-Q2W, PBO+26, and PBO+52 patients, respectively. No deaths or new visual loss occurred.

Conclusions:
TCZ plus 26-week prednisone taper was superior to PBO+26 and PBO+52 tapers in achieving sustained remission at 52 weeks. TCZ plus prednisone led to significant reductions in the cumulative prednisone doses required to control GCA.

References: 1. Unizony SH, Dasgupta B, Fisheleva E, et al. Design of the tocilizumab in giant cell arteritis trial. Int J Rheumatol. 2013;2013:912562.

Keywords: Vascular disorders, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy

Financial Disclosures: Received financial support from Roche, the parent company of Genentech during the conduct of the study.

Grant Support: None.

Monday, April 3rd from 5:15pm-5:30pm
Headache Outcomes in the Idiopathic Intracranial Hypertension Treatment Trial

Deborah Friedman[1], Peter Quiros[2], Prem Subramanian[3], Luis Mejico[4], Michael McDermott[5]

[1]University of Texas Southwestern Medical Center, Dallas, Texas, USA, [2]Jules Stein Eye Institute, UCLA, Pasadena, California, USA, [3]University of Colorado School of Medicine, Denver, Colorado, USA, [4]SUNY Upstate Medical University, Syracuse, New York, USA, [5]University of Rochester Medical Center, Rochester, New York, USA

Introduction:
Headache is the most common symptom of IIH. The IIHTT prospectively enrolled 165 participants with mild visual field loss to assess whether acetazolamide (ACZ) plus dietary management was superior to placebo (PBO) tablets plus dietary management in improving visual function [1]. We report the headache outcomes of participants in the IIHTT.

Methods:
Participants completed the Headache Impact Test -6 (HIT) and headache symptom questionnaires at each study visit. The Short Form-36 (SF-36) and National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and neuro-ophthalmic supplement (NOS) assessed quality of life at baseline and at 6 months [2]. Group comparisons pertaining to HIT-6 total score were performed using two-sample t-tests. Group comparisons of proportions were performed using chi-square tests. Bivariate associations between variables were assessed using Spearman rank correlation coefficients. Logistic regression analyses determined the associations between baseline variables and the development of headache after baseline.

Results:
139 (84%) enrollees had headaches at baseline and another 21 (13%) reported headaches in follow-up. 69% in the ACZ group and 68% in the PBO group had persistent headaches at 6 months. There was no statistically significant difference in HIT-6 scores between treatment groups at 6 months. Development of headache after enrollment was not associated CSF opening pressure (OP) at baseline (OR 0.997, 95% CI 0.991-1.003, p=0.32), baseline papilledema grade (OR 1.88, 95% CI 0.74-4.81, p=0.19), or baseline BMI (OR 1.02, 95% CI 0.97-1.08, p=0.39). HIT-6 score at 6 months was not significantly correlated with CSF OP at 6 months (r=0.12, p=0.29) or the maximum dose of study drug taken (r=-0.09, p=0.48) or weight lost (r=0.02, p=0.80). THE NEI-VFQ-25 total score and NOS, the SF-36 physical and mental component summaries and SF-36 subscale scores were significantly correlated with the number of headache days at 6 months.

Conclusions:
CSF pressure and headache are independent features of IIH.

References: 1. Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Scron EB, Kupersmith MJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss. JAMA Neurol 13(16):1641-51, 2014.
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Keywords: High intracranial pressure/headache, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: National Eye Institute (1U10EY017281-01A1, 1U10EY017387-01A1, 3U10EY017281-01A1S1, 1U10EY017387-01A1S1, 3U10EY017281-01A1S2)

Monday, April 3rd from 5:30pm-5:45pm

Determining the Optimal Angle of Two-Dimensional Optical Coherence Tomography Scans to Detect Abnormal Intracranial Pressure

Kiran Malhotra[1], Megh Patel[2], Zainab Shirazi[1], Heather Moss[3]

[1]University of Illinois at Chicago College of Medicine, Orland Park, Illinois, USA, [2]University of Illinois at Chicago Department of Engineering, Chicago, Illinois, USA, [3]Stanford University, Department of Ophthalmology and Visual Sciences, Palo Alto, California, USA

Introduction:
Peripapillary Bruch's Membrane(pBM) shape has been shown to correlate with chronic intracranial pressure(ICP) magnitude on horizontal optical coherence tomography(OCT) B-scans of the optic nerve head(ONH). The objective of this project was to compare OCT B-scans taken at different angles through the ONH with regards to discriminating elevated from normal ICP based on measures of pBM shape.

Methods:
Six OCT B-scans of the ONH(0o=horizontal,30o,60o,90o=vertical,120o,150o,radial scan pattern,Spectralis,Heidelberg Engineering) were obtained in 21 adults(age 23-86) prior to lumbar puncture. ICP was measured as opening pressure. pBM shape on each image was defined by 16 equidistant points extracted from the pBM contour as independently segmented by two raters. Geometric morphometric analysis identified principal components(PC) of pBM shape for all images and within each scan angle. Repeated measures(rm) ANOVA tested for shape difference between scan angles and eyes. Generalized estimating equation(GEE) models, accounting for within-subject correlations, tested for associations between PC magnitude and ICP at each scan angle. Receiver operating curve(ROC) analyses determined ability of PC magnitudes at each scan angle to discriminate elevated(≥25cm H2O) from normal(<20cm H2O) ICP and to confirm normal ICP.

Results:
PC(all images) magnitudes were similar between left and right eyes, but differed across scan angles($p<0.005$, rmANOVA). ICP was associated with PC1 magnitude at each scan angle($p<0.005$ for all,GEE). PC1 magnitude of scans taken at 90o and 120o showed the best ability to differentiate elevated from normal ICP(AUC=0.984,CI[0.936,1.000]). PC1 magnitude of scans taken at 60o showed the best ability to confirm normal ICP(AUC=0.913,CI[0.792,1.000]).

Conclusions:
pBM shape, as defined using ONH OCT B-scans, differ by scan angle. Vertical(90o) and superonasal-inferotemporal(120o) scans are best for differentiating elevated from normal ICP, while superotemporal-inferonasal(60o) scans are best for confirming normal ICP. Further study is needed to validate PC magnitudes as derived from pBM shape analysis of ONH OCT B-scans as a diagnostic test for ICP.

References: 1. Gampa A, Vangipuram G, Shirazi Z, Moss HE. Change in Peripapillary Bruch's Membrane Shape Can Be Detected 1 Hour After Lowering of Intracranial Pressure by Lumbar Puncture. Poster presented at: The North American Neuro-Ophthalmology Society Annual Meeting; March 2016; Tucson, AZ.
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Keywords: High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

Grant Support: NIH K23-EY024345, Research to Prevent Blindness Unrestricted Grant to the UIC Department of Ophthalmology, Research to Prevent Blindness Special Scholar Award, Illinois Society for the Prevention of Blindness

Monday, April 3rd from 5:45pm-6:00pm
Oscillopsia and Reading Abnormalities in Patients with Down-Beating Nystagmus

Carmel Mercado[1], M. Ali Shariati[2], Jeehey Christine Song[2], Y. Joyce Liao[2]

[1]Department of Ophthalmology, Byers Eye Institute at Stanford, Palo Alto, California, USA, [2]Byers Eye Institute at Stanford, Palo Alto, California, USA

Introduction:
Reading difficulties can be due to poor vision, abnormal eye movements, higher order cognitive issues, or combinations of the above. In this study, we examined the impact of down-beating nystagmus (DBN) (1-5) on reading.

Methods:
We conducted a case-control study on 23 DBN patients and 24 age-matched controls. We measured reading speed using the King-Devick test and performed more detailed gaze analyses using 500-Hz infrared oculography (RED500, SMI). We compared these findings with LogMAR visual acuity, vision disability with the National Eye Institute Visual Functioning Questionnaire (VFQ-25) and 10-Item Neuro-Ophthalmic Supplement (NO-10).

Results:
DBN patients (mean age 61y, range 24-87y, male 39%, female 61%) self-reported oscillopsia (83%), diplopia (65%), balance issues (61%), dizziness (44%), and significantly greater vision disability on questionnaires (VFQ-25: P=0.0006; NO-10: P=0.003). DBN was associated with significantly slower reading on the King-Devick book test (P=0.004). Despite good acuity (mean LogMAR visual acuity 0.18 ± 0.05 or 20/30), on infrared oculography, DBN patients exhibited 10 times greater extraneous eye movements during fixation on a small circle (DBN: 55.4 ± 18.1, control: 5.5 ± 1.3, P=0.008) and greater gaze dispersion (P=0.005). During single-digit number reading on a desktop computer monitor, DBN patients read slower (P=0.004), which was related to significantly greater number of saccades (DBN: 75.7 ± 10.5, control: 48.4 ± 2.5, P=0.006), smaller amplitudes (P=0.001) but not slower velocities (P=0.105). DBN patients tried gabapentin (70%), 4-aminopyridine (39%), and 30% deferred, with 33% patients improved on 4-aminopyridine and 19% improved on gabapentin.

Conclusions:
Relatively isolated eye movement abnormality such as DBN can significantly impact reading despite good visual acuity, leading to significantly slower reading. Impaired gaze holding and abnormal saccades are important contributing factors. Although therapeutic options are limited, a trial of 4-aminopyridine or gabapentin should be considered.

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Keywords: Nystagmus, Ocular Motility, Ocular manifestations of vestibular disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: NANOS Pilot Grant

Monday, April 3rd from 6:00pm-6:15pm
Role of SIRT1 Activity and pAKT Signaling in ST266-Mediated RGC Neuroprotection

Kenneth Shindler[1], Reas Khan[1], Kimberly Dine[1], Larry Brown[2]

[1]University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]Noveome Biotherapeutics, Inc., Pittsburgh, Pennsylvania, USA

Introduction:
Optic neuritis occurs during multiple sclerosis (MS) and induces retinal ganglion cell (RGC) loss. Thus, neuroprotective therapies are needed. We previously showed that intranasally delivered ST266, the biological secretome of Amnion-derived Multipotent Progenitor cells, attenuated loss of vision and RGCs in experimental optic neuritis, but mechanisms of its actions are not known. Potential mechanisms were examined in the experimental autoimmune encephalomyelitis (EAE) model of MS.

Methods:
C57/BL6 EAE mice, induced by immunization with myelin oligodendroglial glycoprotein peptide, were treated daily with 6uL intranasal phosphate buffered saline (PBS) or ST266 beginning day 15 through sacrifice (d22, d30 or d42). Optic nerves were stained with superoxide indicator MitoSOX red. Western blots were performed on retinal and optic nerve proteins. ST266-mediated RGC neuroprotection was further examined in retinal cell cultures exposed to staurosporine±ST266 and challenged with inhibitors of SIRT1 and pAKT.

Results:
MitoSOX red staining showed that ST266 treatment lead to a reduction ($p<0.01$) in reactive oxygen species in EAE optic nerves on d22 and d42. Western blots showed ST266-treated EAE mice had increased expression of SIRT1 deacetylase (d22, $p<0.05$) and mitochondrial coenzyme PGC1α (d22 and d30, $p<0.05$) in the retina, as compared to PBS-treated EAE mice. Retinal and optic nerve levels of mitochondrial enzyme SDHβ increased by d30 ($p<0.05$). pAKT levels were also higher ($p<0.05$) in retinas of ST266-treated EAE mice on d30; however, PDK1 phosphorylation was not increased. In retinal cultures, ST266 treatment (diluted 1:20) attenuated RGC loss, and co-administration of either SIRT1 inhibitor EX527 or pAKT inhibitor X blocked protective effects of ST266.

Conclusions:
Increased SIRT1 expression and mitochondrial enzymes in ST266-treated EAE mice suggest ST266 stimulation of SIRT1 deacetylase activity promotes RGC survival through increased mitochondrial biogenesis and reduced oxidative stress. In vitro studies using specific inhibitors confirm that ST266-stimulated SIRT1 and pAKT signaling mediate RGC survival. Results demonstrate two mechanisms involved in ST266-mediated neuroprotection.

References: None.

Keywords: Optic neuropathy, Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The therapy tested in this study was provided to the Shindler Laboratory at no cost by Noveome Biotherapeutics, Inc. Kenneth Shindler has received honoraria and consulting fees from Noveome. for discussions sharing general expertise in optic neuritis. No speaker fees have been received for this presentation, nor for the studies described in this presentation. Larry Brown is a full time employee of Noveome and contributed knowledge about the composition of the ST266 therapy and i's effects in other disease models, but he played no role in the design, conduct, or analysis of the studies described in this presentation.

Grant Support: NIH Grant EY019014; Research to Prevent Blindness; and the F. M. Kirby Foundation

Monday, April 3rd from 6:15pm-6:30pm
Effect of Combined Systemic Erythropoietin and Steroid, on Non-Arteritic Anterior Ischemic Optic Neuropathy

Mohammad Pakravan[1], Hamed Esfandiari[1], Kiana Hassanpour[1], Sarvnaz Razavi[1], Parastou Pakravan[2]

[1]Ophthalmic Epidemiology Research Center, Shahid Beheshti Uni of Medical Sciences, Tehran, Iran, [2]Orange Coast College, Irvine, California, USA

Introduction:
To investigate the effect of combined intravenous erythropoietin and corticosteroid as well as systemic steroid alone for the treatment of non-arteritic anterior ischemic optic neuropathy (NAION).

Methods:
In this prospective interventional comparative case series, 113 consecutive patients diagnosed with recent onset (less than 14 days) NAION were included. Patients were categorized into 3 groups. Forty patients received systemic corticosteroid combined with recombinant human erythropoietin (rhEPO) (group 1), 43 patients received systemic corticosteroid alone (group 2), and 30 Patients were enrolled as control group (group 3). Functional and structural outcomes were analyzed at 3 and 6 months after treatment. Best corrected visual acuity (BCVA) was the main outcome, and mean deviation (MD) and peripaillary retinal nerve fiber layer thickness (PRNFLT) were secondary outcomes measures.

Results:
The mean BCVA (± SD) at the time of presentation was 0.98 (± 0.65), 0.96 (± 0.67), and 1.02 (± 0.63) log MAR in group 1, 2, and 3, respectively (P=0.95). At month 3, the corresponding values were 0.73 (± 0.45), 0.76 (± 0.49), 0.8 (± 0.45) logMAR (P=0.80), and at 6 months follow up, were 0.76 (± 0.45), 0.71 (± 0.4), 0.71 (± 0.46) log MAR, respectively (P=0.87). There was no statistically significance difference in BCVA between month 3 and 6, which implies stabilization of visual acuity by month 3. Considering visual field, within 6 months follow up after disease onset; MD index improved in all groups with no statistically significant differences between them (P=0.82).

Conclusions:
we found no beneficial effect of either systemic steroid alone or combined with erythropoietin in visual outcome of NAION patients.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Monday, April 3rd from 6:30pm-6:45pm
Saccade Sequences and Rapid Number Naming in Chronic Concussion

Weiwei Dai[1], Doria Gold[1], John Ross Rizzo[1], Todd Hudson[1], Ivan Selesnick[1], Lisena Hasanaj[1], Laura Balcer[1], Steven Galetta[1], Janet Rucker[1]

[1]New York University, New York, New York, USA

Introduction:
The King-Devick (K-D) test is sensitive for concussion detection on athletic sidelines, with longer test times in concussion largely due to inter-saccadic interval (ISI) prolongation. The ISI is a measure of time between saccades that represents a combination of fixation duration and saccade latency. K-D saccade latency cannot be directly measured, as numbers are simultaneously displayed. We assessed saccade latency in classic saccade sequences independent of K-D test.

Methods:
Twenty-seven chronically concussed participants (mean age 32+/-13 years, range 17-61) and 19 healthy controls (mean age 29+/-8 years, range 19-48) performed K-D and saccade sequences: reflexive, gap, overlap, and antisaccades. Eye movements were recorded with video-oculography (EyeLink 1000+).

Results:
K-D test times were longer in concussion (54.6s vs 41.5s, p=0.001), as were ISIs (301.9ms vs 241.4ms, p=0.01). Longer reflexive and overlap latencies (reflexive: 198.1ms vs 176.7ms, p=0.04; overlap: 222.3ms vs 182.8ms, p=0.003) and worse accuracy were seen in concussion. Gap latencies showed no difference (160.6ms vs 148.8ms, p=0.13). Antisaccade latencies were longer in concussion (204.9ms vs 182.3ms, p=0.04) for saccades initially made in the incorrect direction, though there was no difference in error rates. Peak velocity and duration versus amplitude relationships showed no differences between groups.

Conclusions:
ISI prolongation during K-D performance could be due to increased saccade latencies and/or attention and cognitive impairment. In this study, saccade latency prolongation is seen in several saccade types in concussion, suggesting that it may, indeed, contribute to K-D ISI prolongation in concussion. Further, overlap saccade latency prolongation suggests that pre-saccade visual fixation disengagement is altered in concussion. These results suggest that saccade motor planning is impaired in concussion, possibly from damage to frontal lobe saccade control centers prone to traumatic injury.

References: None.

Keywords: Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Monday, April 3rd from 6:45pm-7:00pm
Visual Structure and Function in Contact Sport Athletes

Danielle Leong[1], Christina Morettin[1], Leonard Messner[1], Robert Steinmetz[1], Yi Pang[1], Laura Balcer[2], Steven Galetta[3]

[1]Illinois Eye Institute, Illinois College of Optometry, Chicago, Illinois, USA, [2]New York University, Departments of Neurology, Ophthalmology, Population Health, New York, New York, USA, [3]New York University, Departments of Neurology, Ophthalmology, New York, New York, USA

Introduction:
To investigate retinal structure and visual function in contact sport athletes compared to age-matched controls.

Methods:
In this cross-sectional study, athletes(n=46) with history of professional,contact sport exposure (Boxing,n=14;Football,n=29;Hockey,n=3) and non-contact sport athletes or non-athlete controls(n=104) underwent measures of peripapillary retinal nerve fiber layer(RNFL) and macular ganglion cell complex(GCC) using spectral-domain optical coherence tomography(OCT). High-contrast visual acuity(HCLA;100%), low-contrast letter acuity(LCLA;1.25%,2.5%), and vision-specific quality of life(QOL) using the 25-Item National Eye Institute Visual Functioning Questionnaire(NEI-VFQ-25) and 10-Item Neuro-Ophthalmic Supplement(NOS) were also assessed.

Results:
Average peripapillary RNFL thickness was a significant predictor of athlete vs. control status, accounting for age ($p=0.01$,GEE models accounting for within-subject,inter-eye correlations). Specifically, athletes had a 4.8-micron average thinning compared to controls. Boxing athletes had thinner average RNFL($p<0.001$) with a 10.8-micron average thinning compared to controls. Average GCC thickness was similarly reduced in boxers (76.7±2.1µm) vs. controls(81.6±0.5µm,$p=0.02$,GEE models accounting for within-subject,inter-eye correlations) with a 5.0-micron average thinning. Football athletes were not significantly different from controls in both measures. LCLA(2.5%) was a significant predictor of control vs. athlete status($p<0.01$,GEE models accounting for age and within-subject inter-eye correlations). Boxers demonstrated reduced acuity compared to controls (binocular HCLA,$p<0.01$;binocular LCLA(2.5%),$p<0.01$;monocular HCLA,$p<0.01$;linear regression accounting for age). NEI-VFQ-25+NOS was a significant predictor of control vs. athlete status($p<0.01$,linear regression accounting for age). Football athletes scored lower than controls($p<0.05$,GEE models accounting for age).

Conclusions:
Visual structure and function deficits are evident in contact sport athletes and may serve as important biomarkers of sport-related TBI exposure. Visual dysfunction and structural changes associated with TBI that can be detected in vivo represent a unique opportunity to further study related mechanisms of neurodegeneration and aid development of future potential therapies targeted at neuroprotection and repair.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility, Higher visual functions, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: None.

Grant Support: Study supported by the Illinois Society for the Prevention of Blindness Research Grant.

North American Neuro-Ophthalmology Society

43rd Annual Meeting

April 1 – April 6, 2017
Washington Marriott Wardman Park • Washington, DC

Program Schedule

TUESDAY, APRIL 4

6:00 am - 6:45 am	**Yoga Class**	**Washington Room 1**
6:30 am - 12:30 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
6:30 am - 7:30 am	**Breakfast**	**Exhibit Hall C**
6:30 am - 10:30 am	**Exhibits**	**Exhibit Hall C**
6:30 am - 7:30 am	**JNO Editorial Board Meeting**	**Hoover**
7:30 am - 12:00 pm	**Scientific Platform Presentations: Session II [3.75 CME]** *Moderators: Y. Joyce Liao, MD, PhD & Steven A. Newman, MD*	**Thurgood Marshall Ballroom**
9:15 am - 9:30 am	**Update: The Journal of Neuro-Ophthalmology** *Lanning Kline, MD, Editor-in-Chief*	**Thurgood Marshall Ballroom**
9:30 am - 10:00 am	**Coffee Break**	**Exhibit Hall C**
12:00 pm - 6:00 pm	**Free Afternoon**	
12:30 pm - 4:30 pm	**Optional Excursions: Capitol Tour, Segway Tour & Mount Vernon**	
6:00 pm - 9:30 pm	**Poster Session II: Scientific Advancements in Neuro-Ophthalmology**	**Exhibit Hall C**

Dinner buffet is included. Guests are welcome. Event is complimentary for attendees but guests must purchase tickets. Tickets are available for $50 per person.

9:00 pm - 10:00 pm	**Abstract Committee Meeting**	**Hoover**

PLATFORM SESSION II

Tuesday, April 4, 2017 • 7:30 am - 12:00 pm

Moderators (before the break): Y. Joyce Liao, MD, PhD & Steven A. Newman, MD

Moderators (after the break): Laura Balcer, MD, MSCE & Ruth Huna-Baron, MD

**Please note that all abstracts are published as submitted.*

Tuesday, April 4th from 7:30am- 7:45am
Retinal Vascular Complications in Obstructive Sleep Apnea

Clare Fraser[1], Jessica Tong[1], Irene Yue[1], Stuart Graham[1], Claude Farah[2]

[1]Department of Clinical Medicine, Faculty of Medicine and Health Sciences, Macquarie University, Australia, [2]Macquarie Respiratory and Sleep, Macquarie University, Australia

Introduction:
Obstructive sleep apnea (OSA) is an independent risk factor for cardiovascular mortality; however the link with cerebral small-vessel disease remains to be elucidated. The retina offers an in-vivo assessment of microvascular end-organ damage to the cerebral circulation in OSA. Our study examined the relationship between OSA severity and retinal vascular caliber.

Methods:
A prospective cross-sectional study was performed to recruit adult participants undergoing diagnostic polysomnography studies. OSA severity was defined by the apnea-hypopnea index (AHI): severe >30, moderate >15-30, mild 5-15, and controls <5. Of 118 participants recruited, there were 41 severe, 35 moderate, 27 mild OSA participants and 15 controls. Static retinal vascular caliber was measured as the average diameter of retinal arterioles (CRAE) and venules (CRVE), and summarized as the arteriovenous ratio (AVR) (Vesselmap3, Jena/Germany). Dynamic retinal vascular caliber was evaluated as the average pulsation amplitude of retinal arterioles (SRAP) and venules (SRVP) (Dynamic Vessel Analyzer, Imedos, Jena/Germany). Comparisons across groups were performed using multivariate linear regression and binomial logistic regression analyses. A p-value<0.05 was considered significant.

Results:
Of 118 participants (73 males), the mean age was 57.8 ± 12.7 years. Increasing AHI was significantly associated with decreasing AVR (p=0.005) and CRAE (p=0.01). A significant trend was demonstrated between increasing AHI and attenuated retinal vascular pulsation amplitude (arterioles p=0.001; venules p=0.003). Compared with controls, severe OSA predicted significantly increased odds of reduced retinal venous pulsatility (OR: 31.7, p=0.02). All results were adjusted for age, body mass index and mean arterial pressure.

Conclusions:
Severe OSA is independently associated with retinal arteriolar narrowing and attenuated vascular pulsation amplitude. These findings demonstrate that the retinal vascular diameter and pulsatility are altered in OSA, and may provide a quantitative measure of systemic vascular dysfunction. Future longitudinal studies may establish a role for retinal imaging as a means of stratifying cerebral small-vessel disease risk in OSA.

References: None.

Keywords: Vascular disorders, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 7:45am- 8:00am

Optical Coherence Tomography Angiography in Patients with Migraine with Aura Demonstrates Deceased Macular Vessel Density

Melinda Chang[1], Nopasak Phasukkijwatana[2], Stacy Pineles[2], Mansour Rahimi[2], David Sarraf[2], Mollie Johnston[3], Andrew Charles[3], Anthony Arnold[2]

[1]Stein Eye Institute, UCLA; Doheny Eye Institute, UCLA, Los Angeles, California, USA, [2]Stein Eye Institute, UCLA, Los Angeles, California, USA, [3]Department of Neurology, UCLA, Los Angeles, California, USA

Introduction:

Patients with migraine with aura have an increased risk of cerebral and retinal vascular ischemic complications. We studied the retinal capillary vasculature in patients with a history of migraine using optical coherence tomography angiography (OCTA).

Methods:

Adults with migraines with aura (MA) or without aura (MO), as well as controls without migraines based on ICHD3 criteria were recruited from ophthalmology and neurology clinics. Subjects with retinal or optic nerve pathology or known microvascular disease were excluded. All subjects underwent 3.0x3.0mm macular angiography scans using the RTVue XR 100 Avanti OCTA device (Optovue, Fremont, CA). Macular vessel density (MVD) in the superficial (SCP) and deep retinal capillary plexus (DCP) and foveal avascular zone (FAZ) area were measured. Foveal thickness was also measured. Statistical analysis was performed with the Mann-Whitney test. P-values less than 0.05 were considered significant.

Results:

We recruited eight MA subjects, six MO, and 19 age-matched controls. The mean age was 44±11 years and did not differ among groups (p=0.55). The MVD of the SCP in the MA group was significantly lower than controls (30.6±2.6% vs. 32.7±3.3%, p=0.01) and the superficial FAZ was significantly larger in MA subjects compared to controls (0.28±0.07mm2 vs. 0.23±0.07mm2, p=0.03). The deep MVD and FAZ did not differ between MA subjects and controls (p>0.22). There were no differences between the MO group and controls in superficial or deep MVD or FAZ (p>0.21). There was no difference in foveal thickness between controls and either migraine group (p>0.51).

Conclusions:

Migraine with aura, but not without aura, is associated with an enlarged FAZ and decreased MVD at the SCP level. Further studies are necessary to determine if retinal vascular abnormalities correlate with cerebrovascular changes and risk of ischemic complications in migraineurs. OCTA may potentially be useful as a biomarker in patients with migraine with aura.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 8:00am- 8:15am
Reduction of the Photopic Negative Response in Optic Neuropathy: Assessment Using a New Handheld Device

Shira Simon[1], Cole Starkey[2], Michael Wall[3], Matthew Thurtell[3], Randy Kardon[1]

[1]University of Iowa Department of Ophthalmology, Iowa City, Iowa, USA, [2]University of Iowa, Iowa City, Iowa, USA, [3]University of Iowa Department of Ophthalmology, Department of Neurology, Iowa City, Iowa, USA

Introduction:
Our purpose was to evaluate the utility of a new handheld portable device to quickly ascertain the extent of optic nerve dysfunction by measuring light-evoked retinal ganglion cell function proximal to the site of optic nerve damage. Understanding the function of the retinal ganglion cells and metabolic coupling to blood flow may provide important prognostic information for recovery of vision. A portable device circumvents conventional requirements of foveal fixation, image clarity, an ERG laboratory, trained technician, and corneal electrodes.

Methods:
A portable handheld ERG unit (RETeval/LKC) was used to record non-mydriatic photopic negative responses (PNR) from surface eyelid electrodes. A miniature Ganzfeld stimulus provided 58 Td-sec red flashes, at 3.4 Hz, on a 380 Td blue background over 60 seconds under photopic conditions. 17 eyes with optic neuropathy due to ischemia, optic neuritis, or compression were compared to 31 normal eyes. The PNR was assessed using four parameters (microvolts at 72 microseconds, P ratio, W ratio, and most negative amplitude). Retinal blood flow was assessed in each eye using laser speckle flowgraphy (Softcare Inc, Japan).

Results:
There was a statistically significant decrease in the photopic negative response across all four parameters in eyes affected by optic neuropathy compared to normal control eyes, using unpaired non-parametric statistics (Mann-Whitney Rank Sum Test; p=0.002 for microvolts at 72 microseconds, p=0.001 for P ratio, p=0.014 for W ratio, and p=0.002 for most negative amplitude). Retinal blood flow was also significantly reduced in the eyes with optic neuropathy (p=0.001).

Conclusions:
The PNR measured with a portable, easy-to-use handheld instrument in a clinic exam room is a fast and effective way to assess retinal ganglion cell function proximal to the site of optic nerve injury. The PNR and retinal blood flow may provide unique prognostic tools in the future to assess potential for visual recovery.

References: Mortlock, et al. “Inter-subject, inter-ocular and inter-session repeatability of the photopic negative response of the electroretinogram recorded using DTL and skin electrodes.” Doc Ophthalmol, 121, 123-134 (2010). Moss et al. “The Photopic Negative Response in Idiopathic Intracranial Hypertension.” IOVS, 56, Invest 3709-3714 (2015). Nakamura et al. “Focal macular photopic negative response in patients with optic neuritis.” Eye (Lond), 25, 358-364 (2011). Preiser, et al. “Photopic Negative Responses versus Pattern Electroretinogram in Early Glaucoma.” IOVS, 54, 1181-1191 (2013). Viswanathan et al. “The photopic negative response of the flash electroretinogram in primary open angle glaucoma.” IOVS, 42, 514-522 (2001).

Keywords: Optic neuropathy, Optic nerve trauma and treatment

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 8:15am- 8:30am
The Useful Dynamic Ranges for Visual Field Progression with Stimulus Sizes III and V.

Michael Wall[1], K. Zamba[2], Paul Artes[3]

[1]University of Iowa, Department of Neurology, Iowa City, Iowa, USA, [2]University of Iowa, School of Public Health, Iowa City, Iowa, USA, [3]School of Health Professions, Peninsula Allied Health Centre Plymouth University, Plymouth, United Kingdom

Introduction:
It has been shown that due to variability, the effective or useful dynamic range for standard automated perimetry (SAP) with Goldmann size III stimuli is about half as large as previously thought1. Size V testing has a substantially larger useful dynamic range with lower variability and is therefore an excellent candidate for detecting visual field change. "Censoring" or not using size III threshold estimates < 20 dB has little effect on the ability to detect glaucomatous progression.2 The effect of stimulus size on the ability to detect visual field progression is unknown. Our goal is to compare the effect of censoring on visual field progression glaucoma with these two stimulus sizes.

Methods:
Pointwise Linear Regression was performed on 120 glaucoma subjects and 60 normals tested every six months for 4 years with SAP with stimulus sizes III and V. Data was censored at each dB level, and hit rates for progression were derived for a series of slope and p-value criteria for: 1) all progressing test locations, 2) 3 or more progressing locations, and 3) 4 or more contiguous progressing locations.

Results:
The results show that size V stimuli performed at least as well or slightly better than size III stimuli at measuring change over time (progression). Omitting threshold estimates below 20 to 25 dB had little effect on the progression rates in glaucoma patients.

Conclusions:
There is no clinically meaningful loss of sensitivity to show visual field progression when threshold estimates < 20 dB are removed for both stimulus sizes. Size V performed at least as well or better than size III and with its substantially larger useful dynamic range and lower retest variability is an excellent candidate when testing for visual field change.

References: Wall, M, Woodward, KR, Doyle, CK, et al. The effective dynamic ranges of standard automated perimetry sizes III and V and motion and matrix perimetry. Arch Ophthalmol. 2010; 128:570-576. Gardiner, SK, Swanson, WH, and Demirel, S. The Effect of Limiting the Range of Perimetric Sensitivities on Pointwise Assessment of Visual Field Progression in Glaucoma. Invest Ophthalmol Vis Sci. 2016; 57:288-294. O'Leary, N, Chauhan, BC, and Artes, PH. Visual field progression in glaucoma: estimating the overall significance of deterioration with permutation analyses of pointwise linear regression (PoPLR). Invest Ophthalmol Vis Sci. 2012; 53:6776-6784.

Keywords: Visual fields, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: Veterans Administration Merit Review

Tuesday, April 4th from 8:30am- 8:45am
Seasonal Variation In Non-visual, Light-dependent Responses Mediated By Melanopsin

Myriam Ladaique[1], Mirjam Münch[2], Ségolène Roemer[1], Kattayoon Hashemi[1], Aki Kawasaki[1]

[1]Hôpital Ophtalmique Jules Gonin, Lausanne, Switzerland, [2]Charité University Medicine, Institute of Physiology, Berlin, Germany

Introduction:
This study aimed to examine the influence of the seasonal change in daylight on non-visual functions mediated by melanopsin in healthy adult subjects. We assessed for differences between subjects without and with cataracts (attenuated blue light transmission).

Methods:
Fifty-two healthy adults aged 47 to 78 years (30 with cataracts and 22 age-matched pseudophakic subjects) were tested twice, around the winter and summer solstices. After a screening ophthalmic examination (including perimetry, OCT, ERG), pupil responses to a 1s light stimulus with pre-selected wavelengths and intensities under dark and light adapted conditions were recorded during daytime. During 5 hours before habitual bedtime, salivary melatonin was collected hourly under dim light conditions, before and after a 30-minute bright light exposure, and subjective sleepiness was assessed by questionnaires.

Results:
There were no significant ocular differences, including visual acuity (mean=1.0 in both groups), between the two groups except for mild cataracts (LOCS III; range=2-4). Compared to pseudophakic subjects, those with cataracts had lower sleep quality and tendency to reduced pupil contraction to dark-adapted dim blue light stimuli. For seasonal differences, all subjects were less sleepy in the evening during the winter testing compared to summer testing ($p=0.0001$). In pseudophakic subjects but not in subjects with cataracts, the melanopsin-mediated pupil response was significantly larger in winter than in summer. Salivary melatonin concentrations were lower in winter than summer for both groups ($p<0.0001$). The degree of nocturnal melatonin suppression by light was slightly greater for pseudophakic subjects ($p=0.6$, ns); there was no significant seasonal variation for either group.

Conclusions:
In assessing melanopsin functions, the pupil but not the hormonal marker demonstrated seasonal variation in pseudophakic healthy adults. A greater melanopsin-mediated pupil response in winter suggests central adaptation to the decreased daylight levels over a long period of time. Mild cataracts appear to dampen this variation.

References: None.

Keywords: Pupils Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: Open Eyes Foundation

Tuesday, April 4th from 8:45am- 9:00am
The Study of Posterior Cortical Atrophy Using Online Surveys and Social Media

William Hills[1], Jennifer Olds[2], Victoria Palek[3]

[1]Casey Eye Institute/Oregon Health & Science University, Portland, Oregon, USA, [2]Naval Medical Center San Diego, San Diego, California, USA, [3]University of Colorado Denver School of Medicine, Aurora, Colorado, USA

Introduction:
Posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome with prominent cortical visual dysfunction that is most commonly associated with Alzheimer's disease (AD) pathology.(1) Greater insights into PCA have the potential to inform our understanding of AD, but the rarity of the disorder creates significant barriers to further study. The use of social media to investigate this rare disorder has never been attempted, but could be a viable option to as demonstrated by other studies.(2)

Methods:
After IRB approval, three surveys were launched with two targeted to patients and caregivers on a PCA patient Facebook site and another sent to NANOSnet physician members. Surveys were designed to characterize PCA clinical history, past medical and family history, caregiver burden, and examination findings. RedCap was used for secure online data collection.

Results:
A total of 65 surveys were completed by patients (28) and physicians (37), which represents the largest case series on PCA to date. Patients reported difficulty reading (94%) and driving (96%) as the most common and bothersome symptoms, with decreased color vision (77%) and hemianopic visual field defects (73%) reported as the most common finding on examination by physicians. Caregiver responses are pending.

Conclusions:
For patients with normal ophthalmic examination and complaints of visual difficulty when reading and/or driving, PCA should be considered in the differential diagnosis. Social media holds promise for study of rare disorders such as PCA. Although there are inherent validity issues, insights gained can promote awareness and provide new directions for investigators.

References: 1. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol. 2012 Feb;11(2):170-8. doi: 10.1016/S1474-4422(11)70289-7.
2. Davies W. Insights into rare diseases from social media surveys. Orphanet J Rare Dis. 2016 Nov 9;11(1):151.

Keywords: Higher Visual Cortical functions, Miscellaneous, Visual fields, Neuroimaging, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 9:00am- 9:15am
The Effect of Amblyopia on the Developmental Calibration of Sound Localization

Agnes Wong[1], Michael Richards[2], Herbert Goltz[3]

[1]Department of Ophthalmology & Vision Sciences, The Hospital for Sick Children, Toronto, Canada, [2]Institute of Medical Science, University of Toronto, Toronto, Canada, [3]Program in Neuroscience & Mental Health, The Hospital for Sick Children, Toronto, Canada

Introduction:
Amblyopia is a visual disorder caused by anomalous visual experience during a critical period in early childhood. While its impact on acuity is typically limited to the amblyopic eye, more complex sensory abnormalities have been shown to affect the fellow eye and even the integration of multisensory signals (e.g., diminished sensitivity to the McGurk effect). Interestingly, other forms of early vision loss have been shown to diminish sound localization ability and to alter the representation of auditory space in the superior colliculus, an early locus of audiovisual spatial co-localization. Hypothesizing that amblyopia may have similar impact, we investigate the effect of amblyopia on auditory spatial resolution.

Methods:
In Experiment 1, amblyopic (n = 14) and visually normal (n = 16) participants judged whether the second click of a pair was located to the left or right of the first. Clicks were presented in darkness at 11 virtual target positions within the central 30 degrees. One click of each pair was always presented centrally. Click position was controlled by volume difference between stereo speakers. Experiment 2 involved 10 amblyopic (5 new) and 12 normal (8 new) participants, and replicated Experiment 1 using an 11-speaker array. All participants passed an audiometer-based hearing screen. Just noticeable differences (JND) for spatial resolution were derived from individual psychometric functions, and group differences were assessed using the Mann-Whitney U test.

Results:
In experiment 1, the median JND for the normal group was 3.2 degrees, compared to 4.0 degrees in the amblyopia group ($p = 0.028$). In experiment 2, the same pattern was found (2.1 degrees vs. 3.7 degrees, $p = 0.035$).

Conclusions:
Auditory spatial resolution is diminished in amblyopia. The spatial uncertainty of amblyopic vision may interfere with developmental calibration of the auditory spatial map guided by the retinotopic map in the superior colliculus.

References: None.

Keywords: Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by grant MOP 106663 from the Canadian Institutes of Health Research (CIHR), Leaders Opportunity Fund from the Canada Foundation for Innovation (CFI), the John and Melinda Thompson Endowment Fund in Vision Neurosciences, the Department of Ophthalmology

Tuesday, April 4th from 10:00am- 10:15am
Phase I/IIa Visual Acuity Outcomes 1.5-Years Post-Treatment with rAAV2/2-ND4, Investigational Gene Therapy for ND4 LHON

Catherine Vignal[1], Scott Uretsky[2], Nitza Thomasson[2], Céline Bouquet[2], Anne Galy[2], Jean Philippe Combal[2], Serge Fitoussi[2], Jose Aalin Sahel[3]

[1]Foundation Rothschild, Paris, France, [2]Gensight Biologics, Paris, France, [3]Centre Hospitalier National des Quinze Vingts, Paris, France

Introduction:
rAAV2/2-ND4 is an experimental gene therapy enabling allotopic transgene expression. We report visual acuity (VA) outcomes 1.5-years post-treatment in a Phase I/IIa (NCT02064569) open-label, dose-escalation safety study.

Methods:
LHON patients with G11778A-ND4 mutation with stable vision loss received a single intravitreal injection of rAAV2/2-ND4 in their worst-seeing eye. Three patients were included in each dose-escalation cohort (9x109, 3x1010, 9x1010, 1.8x1011 vg/eye) and the extension cohort (9x1010 vg/eye) for a total of 15 patients. Post-hoc analysis of patient groups with ≤2-years vs. >2-years of vision loss at treatment and excluding the worst baseline VA (LogMAR>2.79) was performed.

Results:
At baseline (N=15) mean/median (range) LogMAR in treated-worst and untreated-best eyes was 2.29/2.79 (1.10-3.01) and 2.03/2.01 (1.00-3.18) respectively; the difference between means is 0.265 (p=0.0342). Mean (range) vision loss duration was 72.3 months (8-271; median 22). All patients completed 48-week follow-up; one patient withdrew consent and 14 patients have completed 1.5-year follow-up. Mean LogMAR changes from baseline to 1.5-years post-treatment are as follows: For all patients (N=14): treated-worst eyes -0.612 vs. untreated-best eyes -0.308; mean difference -0.304. Excluding patients with baseline LogMAR>2.79: group with ≤2-years vision loss (N=5) treated-worst eyes -0.632 vs. untreated-best eyes -0.234; mean difference -0.398. In comparison, for this group, mean differences at weeks 24, 36 and 48 were: +0.136, -0.218, -0.338. In the >2-year vision loss group (N=6) treated-worst eyes -0.451 vs. untreated-best eyes +0.071; mean difference -0.523 with VA of 3/6 patients driving results.

Conclusions:
Mean LogMAR change at 1.5-years improved in treated-worst and untreated-best eyes; there is a sustainable, clinically relevant, greater improvement of ≥0.3LogMAR in treated-worst versus untreated-best eyes. For patients with ≤2-years vision loss, mean differences favoring treated-worst eyes are noted at 36-weeks and increase in magnitude at subsequent follow-up. Those affected >2-years show a clinically relevant (≥0.3LogMAR) mean difference for the first time at 1.5-years post-treatment.

References: None.

Keywords: Genetic Disease, Optic neuropathy

Financial Disclosures: Consultant for Gensight Biologics; provides scientific advice related to Leber Hereditary Optic Neuropathy and LHON disease management. Content in abstract is independent of the consultant role.

Grant Support: None.

Tuesday, April 4th from 10:15am- 10:30am
Metabolomic and Biomarker Profiling in Mitochondrial Optic Neuropathies

Patrick Yu-Wai-Man[1]

[1]Newcastle Wellcome Trust Centre for Mitochondrial Research; Moorfields Eye Hospital., Newcastle upon Tyne, United Kingdom

Introduction:
Mitochondrial optic neuropathies constitute an important cause of registrable blindness in both the paediatric and adult population. The two classical paradigms are Leber hereditary optic neuropathy (LHON), which is a primary mitochondrial DNA (mtDNA) disorder, and autosomal dominant optic atrophy (DOA) secondary to pathogenic mutations within the nuclear gene OPA1 (3q28-q29) that encodes for a mitochondrial inner membrane protein [1]. Recessive and dominant WFS1 mutations have also emerged as an important cause of both isolated and syndromic optic atrophy [2]. WFS1 (4p16.1) encodes for the transmembrane endoplasmic reticulum (ER) protein Wolframin that plays a critical role in calcium homeostasis and interorganellar cross-talk at areas of ER-mitochondria contacts [3]. The defining neuropathological feature of all these mitochondrial optic neuropathies is the preferential loss of retinal ganglion cells (RGCs), but the marked phenotypic variability observed in this patient group and the disease mechanisms that ultimately contribute to RGC loss still need to be clarified further [1].

Methods:
Serum samples were collected from: (i) 103 LHON carriers, (ii) 110 OPA1 mutation carriers, (iii) 8 WFS1 mutation carriers, (iv) 56 age-matched healthy controls, and (v) 41 patients with Parkinson disease as a neurodegenerative control group. Non-targeted high-resolution metabolomic profiling was performed on serum samples with the DiscoveryHD4 mass spectrometry platform (Metabolon, Cambridge, UK).

Results:
Our data indicates oxidative stress, impaired phospholipid metabolism and dysregulated steroidogenesis as important metabolomic signatures in patients with mitochondrial optic neuropathies. The analysis of prospectively collected longitudinal serum samples has also identified candidate biomarkers of disease progression and severity. Furthermore, the specific pathological pathways implicated are consistent with our in vitro and in silico experimental models.

Conclusions:
Metabolomic profiling is a powerful tool for dissecting the complex pathophysiology of mitochondrial optic neuropathies and the new insights gained will hopefully help guide candidate drug screening and early phase clinical trials.

References: 1. Yu Wai Man P, Votruba M, Burté F, La Morgia C, Barboni P, Carelli V. A neurodegenerative perspective on mitochondrial optic neuropathies. Acta Neuropathologica. 2016;132(6):789-806.
2. Majander A, Bitner-Glindzicz M, Chan CM, Duncan HJ, Chinnery PF, Subash M, Keane PA, Webster AR, Moore AT, Michaelides M, Yu Wai Man P. Lamination of the outer plexiform layer in optic atrophy caused by dominant WFS1 mutations. Ophthalmology. 2016;123(7):1624-6.
3. Burté F, Carelli V, Chinnery PF, Yu Wai Man P. Disturbed mitochondrial dynamics and neurodegenerative disorders. Nature Reviews Neurology. 2015;11(1):11-24.

Keywords: Genetic Disease, Optic neuropathy

Financial Disclosures: Consultant - GenSight Biologics

Grant Support: Medical Research Council (UK) Wellcome Trust (UK) National Institute for Health Research (UK) Fight for Sight (UK)

Tuesday, April 4th from 10:30am- 10:45am
Strabismus Measurements with Novel Video Goggles

Konrad Weber[1], Daniel Rappoport[2], Muriel Dysli[1], Tanja Schmückle Meier[2], Christopher Bockisch[3], Klara Landau[2], Hamish MacDougall[4]

[1]Departments of Ophthalmology and Neurology University Hospital Zurich, Zurich, Switzerland, [2]Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland, [3]Depts of Ophthalmology, Neurology, Otorhinolaryngology, University Hospital Zurich, Zurich, Switzerland, [4]School of Psychology, University of Sydney, Sydney, Australia

Introduction:
Measurement of ocular motility and alignment is essential for the diagnosis of strabismus, preparation for strabismus surgery, and post-surgical follow-up. The traditional Hess screen test is time-proven for documenting squint angles at different gaze directions, but the test is subjective and requires good patient cooperation.

Methods:
We designed novel strabismus video goggles with built-in laser target projection and LCD shutters for automated alternate occlusion of the eyes. We measured 41 adults and children ≥6 years with congenital or acquired paralytic or comitant strabismus and 17 healthy controls, and compared the results to the Hess screen test.

Results:
Measurements with strabismus video goggles and Hess screen test were closely comparable across patients and healthy controls, reproducing the individual strabismus patterns. Unlike with Hess screen testing, measurements with the strabismus video goggles were even possible in patients with comitant strabismus and visual suppression.

Conclusions:
The novel strabismus video goggles are simple, fast and accurate in measuring ocular deviations and the results are closely comparable to the conventional Hess screen test. The device can be used in patients with visual suppression, who are not suitable for the Hess screen test, as well as children as young as 6 years of age.

References: Hess WR. Eine neue Untersuchungsmethode bei Doppelbildern. Arch Augenhk. 1909;62:233-238. Lancaster WB. Detecting, measuring, plotting and interpreting ocular deviations. Archives of Ophthalmology. 1939;22(5):867-880.

Keywords: Ocular Motility, Adult strabismus with a focus on diplopia, Pediatric neuro-ophthalmology

Financial Disclosures: The author acts as an unpaid consultant and has received funding for travel from GN Otometrics. The study was conducted with a custom-built, non-commercial strabismus video goggles prototype.

Grant Support: The study was supported by the Albert Bruppacher Foundation for Eye Research, University Hospital Zurich, Switzerland; the OPOS Foundation, St. Gallen, Switzerland; the Dr. Dabbous Foundation, University of Zurich, Switzerland; and the Betty and David Koe

Tuesday, April 4th from 10:45am- 11:00am
The Effect of Retinal Deformations on Visual Dysfunction in Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

Mark Kupersmith[1], Patrick Sibony[2]

[1]New York Eye and Ear Infirmary and Icahn School of Medicine at Mount Sinai, New York, New York, USA, [2]Department of Ophthalmology, State University of New York at Stony Brook, Stony Brook, New York, USA

Introduction:
Optic nerve head (ONH) swelling due to NAION spreads edema into the retina that can extend to the macula. Vision loss is permanent but spontaneous improvement in visual acuity occurs, possible due to resolution of the retinal distortion. We hypothesized that eyes with spectral domain (SD) OCT-demonstrated retinal structural changes would have dissimilar vision at presentation and outcome than eyes without them.

Methods:
We prospectively studied eyes with NAION, within 2 weeks of vision loss and at 1-2 months, with SDOCT images of the optic disc and macula. Study eyes were evaluated for deformations including vitreous traction, peripapillary fluid (PPF), retinal folds (RF), choroidal folds (CF), and whether the macula was affected using transaxial and en face views. Deformations were evaluated in relation to the retinal nerve fiber layer (RNFL) thickness, LogMAR visual acuity (VA) and mean deviation (MD).

Results:
At presentation, 50 eyes had mean VA=0.65 ± 0.82, mean MD=-15.73 ± 9.75 dBs, mean RNFL= 224 ±75 µm, and no vitreous traction. VA and MD were similar in eyes with (76%) and without (24%) PPF, with (42%) and without RF (58%), and with (18%) and without (82%) macula edema/deformations. At 1-2 months, 39 eyes had mean RNFL=112 ± 40 µm, p =0.001 and unchanged mean VA=0.60 ± 0.91 and mean MD= -15.46 ± 10.33 dBs. Fewer eyes had PPF (p=0.001), RF (p=0.008) and none had macula deformations (p=0.008). VA and MD were similar for eyes with (18%) and without (82%) PPF, and with (13%) and without (87%) RF.

Conclusions:
Retinal deformations in NAION reflect dynamic stresses and strains due to local tissue changes and extracellular fluid. These deformations and their resolution are not correlated with vision loss or recovery, probably since most vision loss is due to optic nerve injury.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 11:00am- 11:15am
A Novel Mechanism for the Central Nervous System Transit of Aquaporin-4 Autoantibody in Neuromyelitis Optica

Jeffrey Bennett[1], Fumitaka Shimizu[2], Kristin Schaller[1], Gregory Owens[1], Anne Cotleur[2], Debra Kellner[2], Yukio Takeshita[3], Birgit Obermeier[2], Thomas Kryzer[4], Yasuteru Sano[3], Takashi Kanda[3], Vanda Lennon[4], Richard Ransohoff[2]

[1]University of Colorado Denver, Denver, Colorado, USA, [2]Neuro/Immuno Discovery Biology, Biogen, Cambridge, Massachusetts, USA, [3]Dept of Neurology and Clinical Neuroscience, Yamaguchi U Graduate School of Medicine, Yamaguchi, Japan, [4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

Introduction:
Neuromyelitis optica (NMO) is an autoimmune astrocytopathy caused by antibodies to the astrocyte water channel aquaporin 4 (AQP4). Cerebrospinal fluid (CSF) anti-AQP4 antibodies (AQP4-IgG) in NMO patients are the product of both passive diffusion and local autoantibody production. How AQP4-IgG and antibody producing cells (APCs) gain access to the CNS in NMO remain unclear.

Methods:
To identify serum antibodies that may facilitate AQP4-IgG blood-brain barrier transit, we applied either affinity-purified IgG or recombinant CSF antibodies (rAbs) from NMO patients to human brain microvascular endothelial cells (BMECs) and evaluated the effects on ICAM-1 expression and nuclear translocation of NF-kB p65 by OPERETTA High-Content Imaging. Affinity-purified IgG from systemic lupus erythematous and healthy patients were used as controls. Anti-BMEC rAbs were used to identify a target antigen by immunoprecipitation and mass spectroscopy.

Results:
Anti-BMEC autoantibodies were identified in pooled NMO-IgG, 3/4 individual NMO and 3/4 individual SLE samples, but not in control IgG samples. Anti-BMEC autoantibodies in NMO-IgG bound live BMECs and induced ICAM-1 expression and NF-kB p65 nuclear translocation. Anti-BMEC CSF rAbs were isolated from AQP4-IgG seropositive and seronegative patients and caused nuclear translocation of NF-kB p65, increased BMEC permeability, and facilitated BMEC transit of macromolecules and IgG. Immunoprecipitation and mass spectroscopy identified a molecular chaperone (MC) protein expressed in the cytoplasm and on the plasma membrane of BMECs. NMO-IgG immuno-adsorbed against purified MC protein displayed marked reduction in the activation of BMEC cultures as monitored by nuclear p65 translocation.

Conclusions:
NMO patient serum contains autoantibodies against a molecular chaperone expressed on the plasma membrane of BMECs. Anti-BMEC autoantibodies may open the blood-brain barrier for diffusion of AQP-4 IgG and aide in the CNS migration of APCs and inflammatory cells. Anti-BMEC autoantibodies could be involved in blood-brain barrier compromise in autoimmune diseases and provide a novel therapeutic target for prevention of disease activity.

References: None.

Keywords: Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy

Financial Disclosures: Research support from Guthy-Jackson Foundation, National Institutes of Health (EY022936, UM1AI110498) and the National Multiple Sclerosis Society

Grant Support: Guthy-Jackson Foundation (JLB; RMR); National Institutes of Health EY022936 (JLB), NS072141 (GPO), K2471540 (RMR) and UM1AI110498 (JLB, GPO) and the National Multiple Sclerosis Society (JLB, GPO)

Tuesday, April 4th from 11:15am- 11:30am
Effect of contrast sensitivity on pseudoisochromatic plate color vision tests

Anvesh Annadanam[1], Jiawei Zhao[1], Jiangxia Wang[1], Allen Eghrari[1]

[1]Johns Hopkins University, Baltimore, Maryland, USA

Introduction:
Color vision (CV) testing is often used to assess severity of CV loss from acquired or genetic diseases or drug toxicities. The impact of contrast sensitivity (CS) loss on the results of CV tests has not been extensively investigated. In this study, we used a model for CS loss to determine effect on scores of Ishihara and Hardy-Rand-Rittler (HRR) pseodoisochromatic plates, two commonly used CV tests.

Methods:
Eleven subjects with no significant ocular history were recruited to first undergo normal function assessment with a visual acuity chart, Pelli-Robson (PR) CS chart and Farnsworth D-15 (gold-standard CV test). Participants were then scored on their responses while cycling through randomly arranged pictures of PR, Ishihara, HRR, and D-15 tests with varying levels of contrast changes (high, medium, and low) applied to each one, to simulate CS loss in patients. Ishihara and HRR scores were compared to D-15 as well as their respective baselines.

Results:
At baseline, participants' mean (±SD) scores were 99.2% (±1.4), 97.8% (±2.6), and 100% (±0) for Ishihara, HRR, and D-15, respectively. PR scores for baseline, high, medium, and low contrast were 1.95, 1.82, 1.49, and 1.04, respectively ($p = 0.004$ for all). HRR scores at both the medium and low contrast settings were significantly lower than baseline ($p = 0.0033$). Ishihara scores were lower than baseline ($p = 0.0075$) at the low contrast setting only. HRR scores were significantly lower than D-15 scores at both medium and low contrast settings ($p = 0.009$). Ishihara scores were statistically equivalent to D-15 at all settings.

Conclusions:
Modeled CS loss had the most significant impact on HRR scores, corroborating previous research that showed a positive correlation between HRR and PR contrast sensitivity scores in optic neuropathy patients. HRR scores may not be an accurate reflection of CV in patients with CS loss.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 11:30am- 11:45am
Obligate Impairment of Vertical Vestibulo-ocular Reflexes in Internuclear Ophthalmolplegia

Gabor Halmagyi[1], Luke Chen[2], Michael Barnett[1], Michael Todd[3], Swee Aw[3]

[1]Royal Prince Alfred Hospital and the University of Sydney, Sydney, Australia, [2]St George Hospital, Sydney, Australia, [3]Royal Prince Alfred Hospital, Sydney, Australia

Introduction:
Internuclear opthalmoplegia (INO) is due to a medial longitudinal fasciculus (MLF) lesion causing adduction paresis of ipsilesional eye with abduction nystagmus of contralesional eye. The MLF is the final common pathway not only for all adducting eye movements, except convergence, but also for the vertical-torsional vestibulo-ocular reflex (VOR).

Methods:
We investigated the VOR in 27 MS patients 19 bilateral, 8 unilateral INO. Using binocular 3‐dimensional scleral search‐coils we measured VOR and catch-up saccades to high-acceleration passive stimulation of individual semicircular canals with the head impulse test (HIT).

Results:
Normal HIT VOR gains are ~0.95 from horizontal and ~0.8 from vertical canals. In bilateral INO, there were VOR gain deficits from all 6 canals: horizontal canal adducting eye 0.45, abducting eye 0.66; anterior canal 0.48; posterior canal 0.20. In unilateral INO, VOR gain from ipsilesional horizontal canal was: adducting eye 0.53, abducting eye 0.84 and contralesional anterior canal 0.62, posterior canal 0.29. Horizontal eye movement conjugacy (adducting eye velocity/abducting eye velocity; normal >0.80) for VOR was 0.67 but only 0.42 for catch‐up saccades. This unexpected partial preservation of horizontal canal VOR, with greater catch-up saccade than VOR impairment of the adducting eye suggests that the ascending tract of Deiters, an extra-MLF pathway from vestibular to oculomotor nuclei, also mediates the horizontal canal VOR in humans.

Conclusions:
Our conclusion is that INO patients have severe, obligate deficits of the vertical VOR, especially from the contralateral posterior canal (mediated solely via MLF), accounting for the vertical oscillopsia they experience during passive vertical head movement. During active horizontal head movements characteristic VOR deficits with impairment of horizontal catch-up saccade conjugacy cause horizontal gaze instability. Furthermore we suggest that a normal vertical VOR in a patient with adduction paresis excludes the diagnosis of MLF lesion and suggests an alternative diagnosis, e.g. the pseudo-INO of myasthenia.

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Keywords: Ocular Motility, Ocular manifestations of vestibular disorders, Demeylinating disease, Vestibular, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Tuesday, April 4th from 11:45am- 12:00pm
Visual Disability and Reading Difficulties in Patients with Parkinson's Disease

Yaping Liao[1], Caroline Yu[1], Mohammed Shariati[1], Veronica Santini[1], Kathleen Poston[1]

[1]Stanford University, Stanford, California, USA

Introduction:
Parkinson's Disease (PD) is the second most common neurodegenerative disease globally. While the majority of PD patients report difficulties with vision (1-3), few studies have examined reading in PD (4-5). The goal of this study is to better assess vision disability and reading difficulties in patients with PD.

Methods:
We recruited 112 subjects (59 PD, 53 age-matched controls) per approved protocol at a single academic institution. All subjects were assessed using National Eye Institute;s Visual Function Questionnaire (VFQ-25), 10-Item Neuro-Ophthalmic (NO-10) Supplement, and King-Devick test to assess reading speed. We performed 500-Hz infrared oculography (RED500, SMI) on some subjects (21 PD and 14 controls) during reading.

Results:
Per vision disability questionnaires, PD patients experienced greater visual dysfunction, with a significantly lower scores compared with that of controls (VFQ-25 $P<0.00001$; NO-10: $P=0.00002$; Mann-Whitney U test for all statistical analyses). Notably, the largest differences were observed in the near activities and mental health subscores ($P<0.0001$). On the King-Devick test, PD patients read significantly slower by 24% ($P=0.00002$), which correlated with VFQ-25 scores ($P=0.0009$) but not with Unified Parkinson's Disease Rating Scale scores ($P= 0.14$). Infrared oculography revealed that PD patients exhibited significantly slower number ($P=0.001$) and word reading ($P=0.024$) and made a greater number of saccades ($P=0.08$) and fixations per line ($P=0.025$). They also made smaller saccades ($P=0.035$), longer fixations, and more errors (regressive saccades).

Conclusions:
Our study is the largest so far to systematically assess vision disability and reading, which are significantly worse in PD, can occur early, is not necessarily correlated with Unified Parkinson's Disease Rating Scale, and likely directly impact quality of life and psychological health. Infrared oculography reveals that both fixation and saccade measurements are significantly affected during reading, and some PD patients also exhibited poor ocular motor planning and made more mistakes, likely related to issues impacting higher order processes.

References: 1. Hunt LA, Sadun AA, Bassi CJ. Review of the visual system in Parkinson's disease. Optometry and vision science : official publication of the American Academy of Optometry 72(2): 92-99.
2. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. Neurology 62(2): 177-180.
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5. Yu CY, Shariati MA, Liao YJ. Abnormal eye movement behavior during reading in Parkinson's disease. Parkinsonism and Related Disorders. 2016;32:130–132.

Keywords: Higher visual functions, Ocular Motility, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster Session II: Scientific Advancements in Neuro-Ophthalmology

Tuesday, April 4, 2017 • 6:00 pm - 9:30 pm

Authors will be standing by their posters during the following hours:
Odd-Numbered Posters: 6:45 pm - 7:30 pm
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**Please note that all abstracts are published as submitted.*

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149	Evaluating the Role of Electroretinography in Patients with Optic Neuritis.	Colin Bacorn
150	The Role of Neutrophil-to-Lymphocyte Ratio in Optic Neuritis and Multiple Sclerosis	Anne Katrine Bisgaard
151	MRI of the optic nerves and chiasm in patients with Leber hereditary optic neuropathy	Christelle Blanc
152	Evaluation of Optic Disc Vascularization in Patients with NAION using Optical Coherence Tomography Angiography (OCTA)	Alaa S. Bou Ghannam
153	Forme Fruste Central Retinal Vein Occlusion	Marc A. Bouffard
154	Negative ERG in Hereditary Optic Neuropathies	Gabriella Cammarata
155	Long-term structural changes of the anterior visual pathway after pituitary tumor resection	Fiona Costello
156	Very Poor Visual Acuity in Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)	Michael Dattilo
157	Prediction of intracranial hemorrhagic events based on retinal microvascular abnormalities: a meta-analysis	Oana M. Dumitrascu
158	Decellularization of Porcine and Primate Optic Nerve Lamina	Lilangi S. Ediriwickrema
159	Multifocal visual evoked potentials in optic neuritis and multiple sclerosis: A review	Mathias S. Falck Schmidt
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162	Assessing the Vitreopapillary Interface in Acute Nonarteritic Anterior Ischemic Optic Neuropathy	Sidney M. Gospe, III
163	Papilledema from Compression of Intracranial Venous Sinuses by Dural Meningiomas	Alexander Hartmann
164	Visual Outcome of Systemic Corticosteroids Treatment in Non-Arteritic Anterior Ischemic Optic Neuropathy	Ruth Huna-Baron
165	Dynamic contour tonometry to measure ocular pulse amplitude in patients with suspected giant cell arteritis	Edsel B. Ing
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167	Utility of Spectral Domain OCT (SD-OCT) to distinguish between Papilledema and Pseudopapilledema	Imran Jivraj
168	Brightness comparison testing quantification and relation with afferent pupillary defects	Emely Z. Karam
169	Transcorneal Electrical Stimulation in Optic Neuropathies	Umur A. Kayabasi
170	Long-term Change of Retinal Nerve Fiber Layer and Ganglion Cell Layer in Traumatic Optic Neuropathy	Dae Hyun Kim
171	Value of electrophysiology tests in the traumatic optic neuropathy	Kun Hae Kim
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173	Anatomical Correlates of Visual Field Defects in Patients with Optic Disc Drusen using EDI-OCT	Lasse Malmqvist
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175	Multifocal Visual Evoked Potential in Temporal Hemianopia from Pituitary Tumors. Correlation with Perimetry and OCT	Mario Luiz R. Monteiro
176	Dalfampridine in Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	Mark L. Moster
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179	Methanol Toxicity, Bangladesh Perspective	Sarwat Rahman
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183	Overdiagnosis of optic neuritis.	Leanne D. Stunkel
184	Vaccines and Optic Neuritis: a systematic review	Jette Lautrup Frederiksen
185	Optic Neuritis Associated with Anti-Myelin-Oligodendrocyte Glycoprotein Antibodies: a Case Series	Emilie E. Tournaire-Marques
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187	Characteristics And Visual Outcome Of Neuromyelitis Optica Spectrum Disorder-Related Optic Neuritis:Comparison Between Thais And Americans	Kavin Vanikieti
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203	"Idiopathic Intracranial Hypertension at a Public Ophthalmologic Hospital; Our casuistry and comparison with the IIHTT"	Mariana de Virgiliis
204	Lumbar Puncture in Idiopathic Intracranial Hypertension (IIH) Diagnosis: Frequencies of Altered Diagnoses in Typical Patients	Adam DeBusk
205	The Risk of Idiopathic Intracranial Hypertension and Papilledema among Patients Taking Cycline Antibiotics	Luai T. Eldweik
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208	Differential diagnosis of papilledema vs. pseudopapilledema using customized optical coherence tomography parameters	Laura P. Pardon
209	The Relationship Between Optic Nerve Head Volume, Intracranial Pressure and Macular Ganglion Cell Complex Volume	Megh D. Patel
210	Change in body mass index over time in non-overweight/obese children with Idiopathic Intracranial Hypertension (IIH)	Claire A. Sheldon
211	Bruch's Membrane Opening in Papilledema and Pseudopapilledema	Atalie C. Thompson
212	The Relationship between Central Corneal Thickness (CCT) and Papilledema from Idiopathic Intracranial Hypertension (IIH).	Caroline Vasseneix
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214	Utilizing the Visual System as a Proxy for Brain Function	Khizer R. Khaderi
215	Virtual Reality and Visual Ergonomics	Khizer R. Khaderi
216	What Do We Want? Results of the YONO 2016 Survey	Kevin E. Lai

217	Alterations in photic drive responses and pupillographic responses in epilepsy patients	Christian J. Lueck
218	LHON Genealogy Project – Identifying, Informing and Educating Maternal Relatives	Lissa Poincenot
219	Papilledema: Not A Good Surrogate For Elevated Intracranial Pressure In Cerebrospinal Fluid Shunt Diversion Failure	Alexander D. Port
220	Performance of a Portable Eye Tracker to Assess Eye Movements During the King-Devick Test	Jenelle Raynowska
221	Correlating Blindness with Patient Reported Outcomes, Demographics, and Performance in NMO	Meagan Seay
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228	Optical Coherence Tomography Segmentation Analysis in Relapsing Remitting versus Progressive Multiple Sclerosis	Raed Behbehani
229	Optic neuritis in patients with anti-MOG spectrum disorder: MRI and clinical features.	Damien Biotti
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231	Ganglion Cell Layer in Optic Neuritis and Multiple Sclerosis - A Systematic Review and Meta-analysis	Josefine Britze
232	Ganglion Cell Atrophy and Optic Nerve Cupping in Patients with Postgeniculate Homonymous Visual Field Loss	Rebecca Chen
233	Abnormalities of retinal vasculature in neurofibromatosis type I : Expansion of the ophthalmologic clinical spectrum	Bo Young Chun
234	OCT in Clinical Practice: An International Survey from a Consortium of MS Providers	Julie DeBacker
235	A Treatment Algorithm for Susac Syndrome	Robert A. Egan
236	Retinal Arterial Collaterals in Susac Syndrome	Robert A. Egan
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238	Reassessment Of Whether Herpes Zoster is Associated With Giant Cell Arteritis.	Charles Grose

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243	Characterization of Serological Markers (ESR, CRP, Platelets) of Healed/Healing Arterial Injury and Biopsy Positive GCA	Vinay Kansal
244	Analysis of Standard Visual Function Measures Among Children with Cortical Visual Impairment	Richard H. Legge
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252	Retinal Nerve Fiber Layer may be Better Preserved in MOG versus AQP4-Positive Optic Neuritis	Hadas Stiebel-Kalish
253	Pathologic markers for determining prognosis in patients with Giant Cell Arteritis	Harris C. Sultan
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268	Chronic Optic Neuropathies Demonstrate Decreased Peripapillary Capillary Density on OCT Angiography	John J. Chen
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Poster 147
Clinical Profile Of Pediatric Opticneuritis and Visual Outcomes in Indian Population

selvakumar AMBIKA[1], padma lakshmi[2], veena noronha[2], deepak arjundas[3]

[1]SANKARA NETHRALAYA a unit of Medical research foundation, CHENNAI ,TAMIL NADU, India, [2]SANKARA NETHRALAYA, CHENNAI, India, [3]vijaya hospitals, chennai, India

Introduction:
Optic neuritis in children is not an uncommon disorder following viral illness or vaccination.A limited literature is available on the clinical characteristics, treatment outcomes of pediatric optic neuritis in Indian children Hence we evaluated the clinical characteristics and visual outcome of pediatric optic neuritis patients who presented to a Neuro ophthalmology department of a tertiary eye care Institution in India

Methods:
Retrospective observational case series We reviewed the Medical case records of all optic neuritis patients who were less than 18 years of age . All these patients were evaluated and treated in our Neuro Ophthalmology services and a referral Neurology center during 1999-2016

Results:
117 eyes of 78 children with mean age of 11.84±4.58 years were identified . 42 (53.8%) were females and 36 (46.2%) were males.39 patients(50%) had bilateral involvement and 39 patients(50%) had unilateral involvement. 72 eyes(54.1%) had disc edema ,21 eyes (15.8%) had disc pallor , 38 eyes (28.6 %) had normal disc . 63 patients had undergone neuroimaging , Magnetic Resonance Imaging (36 patients) and Computerized Tomography (27 patients) . 12 patients had normal appearing MRI and 24 had abnormal MRI findings 59 patients had received intravenous methylprednisolone followed by oral steroids taper. 60 eyes (71.4 %) recovered visual acuity better than 20/40. There was a significant difference between initial visual acuity (logMAR) and final visual acuity (logMAR) in our patients which was statistically significant (P ≤0.001).

Conclusions:
Indian pediatric population had good visual recovery following optic neuritis treatment . Profound loss of visual acuity on presentation and bilateral involvement were significantly associated with poor visual outcome .

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Keywords: Optic neuropathy, Pediatric neuro-ophthalmology, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Demeylinating disease, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 148
Blood levels of mitochondrial micronutrients in parvocellular optic neuropathy

Carl Arndt[1], Frederique Arndt[1]

[1]Reims University Hospital, 51092 Reims, France

Introduction:
Features of parvocellular optic neuropathy associate visual acuity loss, acquired dyschromatopsy, central scotoma and retinal ganglion cell loss in the papillo-macular bundle. This group of diseases is believed to be linked to mitochondrial dysfunction. The purpose of the present study was to evaluate the prevalence of micronutritional deficiencies which could impact mitochondrial function in patients with paravocellular optic neuropathy of different causes.

Methods:
Patients with a typical parvocellular optic neuropathy were retrospectively included between January 1st 2014 and June 30th 2016. The blood levels of the following nutrients were evaluated routinely: vitamin B1, B3, B6, carnitine, coenzym Q10.

Results:
In the predefined time frame, 26 patients had a complete blood test. Vitamin B1 was found to be low in 6 cases, Vitamin B3 in 6 cases, Vitamin B6 in 4 cases, Carnitine in 14 cases and Coenzym Q10 in 2 cases. 20 of 26 patients presented with a deficiency for at least one mitochondrial micronutrient. 8 patients had Leber's Optic Neuropathy, 7 patients had dominant hereditary optic neuropathy, in the other cases no cause could be established.

Conclusions:
In the majority of the patients with parvocellular optic neuropathies, the blood status demonstrated a deficiency of micronutrients involved in mitochondrial function. These dificiencies could intervene in the development of parvocellular axonal loss particularily sensitive to mitochondrial dysfunction.

References: None.

Keywords: Optic neuropathy, Genetic Disease

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Grant Support: None.

Poster 149
Evaluating the Role of Electroretinography in Patients with Optic Neuritis.

Colin Bacorn[1], Courtney Dula[1], Samantha Lancia[1], Gregory Van Stavern[1], Robert Naismith[1]

[1]*Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA*

Introduction:
Electroretinography (ERG) has potential as a quantitative and objective measure of retinal and optic nerve function for patients with optic neuritis (ON). Multi-focal (mf) ERG response represents cone and bipolar cell activity, whereas the photopic negative response (PhNR) is more specific to ganglion cell activity. This study will investigate the clinical utility of ERG in prognostication of visual outcomes. ERG might be utilized to assess early response to neuroprotective agents following ON onset, when structural methods such as optical coherence tomography (OCT) are confounded by edema.

Methods:
Twelve previously healthy patients presenting within 30 days of developing ON will undergo ERG, OCT, VEP and Humphrey visual field testing at presentation and at three and six months following presentation. An additional 40 patients with a history of an episode of ON greater than one year prior to study inclusion will undergo the same evaluation.

Results:
Seven acute ON eyes were included in this preliminary analysis. Baseline averaged mfERG response density correlated with Pelli-Robinson contrast sensitivity at baseline (R2 = 0.4) and baseline Humphrey mean deviation (R2 = 0.37). Analysis of PhNR magnitude among three affected eyes revealed a significant decrease at baseline compared to unaffected eyes (19.5 ± 17.1μV vs 49.4 ± 5.1μV [p = 0.023]).

Conclusions:
These preliminary results demonstrate that the mfERG response has associations with other tests of visual function commonly used in the acute phase of ON. ERG responses could indicate primary macular and retinal dysfunction in optic neuritis. Assessments at later time points may determine whether mfERG and PhNR have prognostic significance.

References: Hood, Assessing retinal function with the multifocal technique. Prog Retin Eye Res, 19(5), 607-46, 2000 Wang, Cheng, Hu, Tang, Frishman, The photopic negative response of the flash electroretinogram in multiple sclerosis. Invest Ophthalmol Vis Sci, 53(3), 1315-23, 2012

Keywords: Optic neuropathy, Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Grant Support: None.

Poster 150

THE ROLE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS

Anne Katrine Bisgaard[1], Gorm Pihl-Jensen[1], Jette Lautrup Frederiksen[1]

[1]*Department of Neurology, Rigshospitalet Glostrup, University of Copenhagen, 2600 Glostrup, Denmark*

Introduction:
The blood neutrophil-to-lymphocyte ratio (NLR) has recently been identified as a potential predictor of systemic inflammation in several diseases. In optic neuritis (ON) and multiple sclerosis (MS) the NLR has been found significantly higher than in healthy controls (HC). Also, the NLR is found to be higher in relapses over remitting phases and in recurrent ON. This study evaluates the significance of NLR in ON and MS patients. The NLR is also measured in relation to relapse and remission. Monosymptomatic ON may be considered as a model of a first attack of MS.

Methods:
A total of 382 patients suffering from ON (n=140), RRMS (n=138), SPMS (n=30), PPMS (n=55), CIS (n=19) and 813 HC were included. Complete blood count, demographic, and clinical data from ON and MS patients were evaluated retrospectively. The NLRs were calculated and compared for all participants by Student's t-test.

Results:
The NLR is significant higher ($p<0.001$) in ON and MS patients compared to HC. Patients in relapse had a significant higher NLR ($p<0.005$) than patients in remission, but no significant difference in the CRP, ESR, ERYDRW and EDSS.

Conclusions:
ON and MS patients have a significantly higher NLR than HC, indicating the occurrence of chronic inflammation compared to HC. NLR may be measured as a marker of disease activity, because of the significantly higher NLR in patients with relapse compared to patients in remission.

References: None.

Keywords: Demeylinating disease

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Poster 151

MRI of the optic nerves and chiasm in patients with Leber hereditary optic neuropathy

Christelle BLANC[1], Françoise Héran[2], Christophe HABAS[3], Yannick Béjot[4], José Sahel[5], Catherine Vignal-Clermont[6]

[1]Neurology department CHU de DIJON, 21000 Dijon, France, [2]Department of Neuro-radiology, Foundation Adolphe de Rothschild, 25 rue Manin, 75019 Paris, France, [3]Department of Radiology, Centre hospitalier national des Quinze-Vingts, 75 571 Paris Cedex 12, France, [4]Department of Neurology, CHU de Dijon, 14 rue Paul Gaffarel 21000 Dijon, France, [5]Clinical Center of Investigations , Centre hospitalier national des Quinze-Vingts, 75 571 Paris Cedex 12, France, [6]Department of Neuro-Ophtalmology, Foundation Adolphe de Rothschild, 25 rue Manin 75019 Paris, France

Introduction:
Leber hereditary optic neuropathy (LHON) is a rare cause of optic neuropathy with a maternal mitochondrial transmission. This disease affects more frequently young men and leads to a severe bilateral and painless visual loss. The aim was to define cerebral and orbital magnetic resonance imaging (MRI) of patients with LHON to find some typical features in the aspect of optic nerve and chiasm.

Methods:
Our study included patients suffering from genetic confirmed LHON, followed in two French ophthalmologic hospitals between 2013 and 2015. A cerebral and orbital high resolution MRI was performed for each patient between three and twelve months after the onset of visual loss. We analysed each orbital MRI and classified the T2 high signals depending on their location.

Results:
We included 20 men and 8 women with a mean age of 38.3 years at the diagnosis. A 11778 mutation was found in 75% of cases. 19 patients (67.9%) had an hyperintense T2 lesion in the posterior part of both optic nerves and in the optic chiasm, and an enlargement of the chiasm was found in 16 patients (59.3%). No enhancement of optic nerve or chiasm has been found. There is no difference in the aspect of the hyperintense T2 lesion depending on the delay of the MRI performing, mutation type or sex type. Non-specific T2 white matter cerebral lesions were found in the MRI of 6 patients.

Conclusions:
The posterior involvement of optic nerves and chiasm was described previously in case reports of patients with LHON. We described here the most important cohort of LHON patients with a particular orbital MRI presentation within a year after the onset of the disease. The enlargement of the chiasm seems also to be in favour of the diagnosis. The use of specific slices and planes is primordial to find these particular MRI patterns.

References: None.

Keywords: Genetic Disease, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 152

Evaluation of Optic Disc Vascularization in Patients with NAION using Optical Coherence Tomography Angiography (OCTA)

Alaa Bou Ghannam[1], Prem Subramanian[1], Jeffrey Bennett[1], Victoria Pelak[1], Gabriel Lazcano Gomez[2]

[1]University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, [2]University of Colorado Anschutz Medical Center, Aurora, Colorado, USA

Introduction:

Non-Arteritic Ischemic Optic Neuropathy (NAION) is an ischemic disease caused by compromised perfusion of the optic nerve; OCTA of the optic nerve may assist in- identifying vascular defects associated with the condition

Methods:

OCTA of patients diagnosed with unilateral NAION at tertiary medical center will be obtained with measurement of total optic nerve head vessel density as well as superior and inferior disc vessel density. Clinical data, eye exams, visual field (VF) parameters, and spectral-domain OCT evaluation will be also evaluated. Comparison between normal eyes and eyes with NAION will be done

Results:

3 patients have been recruited so far, one of the patients had chronic NAION (150 days) and two had acute (5 and 10 days). All patients had vision acuity better than 20/40 with APD, mild decrease in color vision, and altitudinal visual field defect in the affected eye. The patient with chronic NAION had thinner RNFL with OCTA of the affected eye showing 18% drop of the vessel density on the optic nerve compared to the healthy nerve. There was also 50% difference in vessel density between superior and inferior part of the diseased nerve. Patients with acute NAION had 23% increase in the vessel density of the affected nerve compared to the normal nerve. No differential altitudinal difference in vessel densities was noted.

Conclusions:

This is a small sample of a study that will include more patients, but so far we can conclude that OCTA can show increase vessel density of the optic nerve in the setting of acute NAION. Chronically, vessel density will decrease below the normal levels, specifically along the area that was affected by ischemia.

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Keywords: Optic neuropathy, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 153
Forme Fruste Central Retinal Vein Occlusion

Marc Bouffard[1], Joseph Rizzo[1]

[1]*Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA*

Introduction:
Central retinal vein occlusion (CRVO) commonly presents with tortuous retinal veins, extensive retinal hemorrhage, and edema of the macula and optic nerve head. Identification of forme fruste CRVO, in which the above features are variably present or disproportionate to one another, remains equally important but may be more challenging. We present a series of 13 patients with atypical findings of CRVO, ranging from a normal optic nerve head with minimal venous dilation and retinal hemorrhage to disproportionate optic nerve head edema with respect to the degree of retinal hemorrhage. These patients often present with atypical complaints which are important to associate with forme fruste CRVO.

Methods:
We reviewed 13 cases of patients with variant CRVO who were seen at our institution between 2009 and 2016. Where physical examination was insufficient to make the diagnosis of CRVO, fluorescein angiography was performed.

Results:
Six patients reported transient monocular vision loss, 3 reported blurred vision, 2 reported vision loss, 2 reported photopsias, and 1 reported “kaleidoscopic” vision. Of the 6 patients who reported transient monocular vision loss, 5 had normal discs with mild venous congestion and mild retinal hemorrhage. In the 6th patient, whose examination demonstrated only mild venous engorgement, the diagnosis was confirmed with fluorescein angiography. The remaining 7 patients demonstrated disc edema markedly out of proportion to retinal findings.

Conclusions:
Forme fruste CRVO may present with optic nerve head edema which is out of proportion to retinal pathology or, if the presenting complaint is transient monocular vision loss, a normal optic nerve with mild venous tortuosity and minimal hemorrhage. Failure to appreciate the sometimes subtle features of a CRVO, or the confounding features of an ischemic ocular syndrome, may lead to an unnecessary diagnostic evaluation.

References: None.

Keywords: Vascular disorders

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Grant Support: None.

Poster 154
NEGATIVE ERG IN HEREDITARY OPTIC NEUROPATHIES

Gabriella Cammarata[1], Paola Ciasca[1], Lisa Melzi[1], Chiara Manclossi[1], Laura Cossa[1], Eleonora Lamantea[2], Davide Soranna[3], Antonella Zambon[3], Costanza Lamperti[4], Stefania Bianchi Marzoli[1]

[1]Neuro-Ophthalmology Service, Istituto Auxologico Italiano, Milan, Italy, [2]Unit of Molecular Neurogenetics, Neurological Institute C. Besta, Milan, Italy, [3]Istituto Auxologico Italiano, Milan, Italy, [4]Unit of Molecular Neurogenetics, Neurological Institute C. Besta, Milan, Italy

Introduction:
Negative ERG is a pattern of the full field electroretinogram (ffERG) characterized by a selective reduction of the b wave according to an inner retina dysfunction; it has been anecdotally reported in autosomal dominant optic neuropathy (ADOA) but not in Leber's hereditary optic neuropathy (LHON). Purpose: to investigate the presence of negative ERG in ADOA and LHON.

Methods:
Cross-sectional study involving 51 consecutive patients, 27 with ADOA (mean ±SD: 37±16, M:F= 14:12), 24 with LHON (mean age ± SD: 39±15 , M:F= 19:5) and 56 controls (mean age ±SD: 34±13; M:F=15:41). All patients underwent neuro-ophthalmologic evaluation including Humphrey perimetry, and ffERG according to ISCEV. Negative ERG was defined as a b:a wave ratio ≤1 in the DA 3.0 response at least in one eye.

Results:
The proportion of a negative ERG was 57% in patients vs 1% in controls (p-value <0.001), 93% in ADOA vs 17% in LHON (p-value <0.001) . No correlations were found with age, gender, BCVA, MD, and time to clinical onset

Conclusions:
ffERG data show evidence of inner retinal dysfunction in hereditary optic neuropathies. The absence of correlation with time to clinical onset suggests that these finding may not be related to retrograde retinal degeneration. A possible mutation/polymorphism in another gene working synergistically with the primary mutation might be considered.

References: Nakamura M, Miyake Y. Optic atrophy and negative electroretinogram in a patient associated with a novel OPA1 mutation. Graefe's Arch Clin Exp Ophthalmol 2006; 244:274-275 Weleber RG, MiyaKe Y. Familial optic atrophy with negative electroretinograms. Arch Ophthalmol 1992; 110:640-645

Keywords: Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Genetic Disease

Financial Disclosures: The authors had no disclosures.

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Poster 155
Long-term structural changes of the anterior visual pathway after pituitary tumor resection

Fiona Costello[1], Won Hyung A Ryu[1], David Ben-Israel[1], Yves Starreveld[1]

[1]*University of Calgary, Calgary, Canada*

Introduction:
Optical coherence tomography has become a standard component in the neuro-ophthalmological assessment of patients with pituitary tumors. In particular, preoperative structural measurement of the anterior visual pathway has been shown to be predictive of early post-operative visual recovery in patients with compressive neuropathy. However, the course of long-term outcome remains heterogeneous with a subset of patients experiencing progressive dysfunction even after complete decompression of the optic apparatus. The purpose of this study was to characterize the long-term structural changes of the anterior visual pathway in patients who underwent pituitary tumor resection.

Methods:
22 patients (10F: 12M) with diagnosis of symptomatic pituitary macroadenomas underwent a neuro-ophthalmic evaluation and spectral-domain optical coherence tomography (OCT) testing pre-operatively, and up to 3 years after surgery. Retinal nerve fiber layer thickness (RNFLT) and ganglion cell layer thickness (GCLT) were compared between patients with normalized visual function versus persistent visual field deficits after surgery (mean deviation ≤ -5.0 decibels).

Results:
Preoperative RNFLT and GCLT between the two patient groups were significantly different with patients with persistent deficit having thinner RNFL and GCL (84.1um vs 71.8um; $p<0.01$, 72.1um vs 62.6um; $p<0.01$). There was progressive thinning of the RNFL in patients with persistent deficit at long-term follow-up (1-3 years postop) with trend towards significance (71.8um vs 65.2um; $p=0.06$). Furthermore, these patients had significant decrease in GCLT at long-term follow-up (62.6um vs 52.2um; $p=0.04$). Contrastingly, patients with normalized visual field function exhibited stable RNFLT and GCLT (84.1um vs 81.7um; $p=0.18$, 72.1um vs 70.9um; $p=0.29$ respectively).

Conclusions:
There are long-term structural changes seen in the anterior visual pathway in patients with ongoing visual dysfunction even after complete decompression of the optic apparatus. This argues for the notion of threshold effect in compressive neuropathy even after decompression where irreversible and progressive injury occur preventing functional recovery.

References: None.

Keywords: Tumors, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuroimaging

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Poster 156
Very Poor Visual Acuity in Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

Michael Dattilo[1], Tian Tian[1], Beau Bruce[1], Kannan Narayana[1], Jason Peragallo[1], Nancy Newman[1], Valerie Biousse[1]

[1]*Emory University, Atlanta, Georgia, USA*

Introduction:
Very poor visual acuity (VA) at presentation is unusual in NAION, and is usually suggestive of arteritic AION. In the IONDT, 34/420 (8%) had HM or worse VA (21 HM, 13 LP, and 0 NLP). In Hayreh's cohort, 34/237 (14%) had VA of CF or worse. Our goal was to report the frequency of very poor VA in NAION patients and to describe patient characteristics.

Methods:
Retrospective review of 151 consecutive NAION patients with detailed neuro-ophthalmologic evaluation seen at our institution between 07/14/2014-04/27/2016. Patients with HM or worse initial VA were included. Temporal arteritis and other causes of optic neuropathies were excluded in all patients.

Results:
In 17/151 (11%) NAION patients, very poor VA (2 NLP, 6 LP, 10 HM (one had HM VA OU from bilateral sequential NAION)) was documented (11 (65%) men; average age 63yo (<29-86yo); 14 (82%) white, 2 (12%) African-American, 1 (6%) Indian). All patients had a disc-at-risk and at least one vascular risk factor; 14 (82%) had ≥2 vascular risk factors. Eight had fundus photographs obtained within 30 days of onset; all had severe, pallorous optic disc edema. Ten (59%) had bilateral sequential NAION (3/10 with incidentally discovered previous NAION at the time of presentation) and 2 (12%) had recurrent NAION. Seven (41%) had a temporal artery biopsy. Oral or IV steroids were given to 3/7 patients with unilateral NAION, to 4/10 with bilateral sequential NAION after the first NAION and to 7/10 patients after the second NAION. Visual acuity at last follow-up ranged from 20/50 to light perception (LP) with VA 20/400 or better in 4/17 patients.

Conclusions:
11% of NAION patients had profound visual impairment, similar to previous large studies. The 8 patients with photographs had unusually severe disc edema at presentation. Bilateral sequential NAION was more common than in the IONDT.

References: 1. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. Arch Ophthalmol. 1996;114(11):1366-74 2. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: natural history of visual outcome. Ophthalmology. 2008;115(2):298-305 3. Sawle GV, James CB, Russell RW. The natural history of non-arteritic anterior ischaemic optic neuropathy. J Neurol Neurosurg Psychiatry. 1990;53(10):830-3 4. Preechawat P, Bruce BB, Newman NJ, Biousse V. Anterior ischemic optic neuropathy in patients younger than 50 years. Am J Ophthalmol, 2007. 144(6): 953-960 5. Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D, Dickersin K; Ischemic Optic Neuropathy Decompression Trial Research Group. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. Am J Ophthalmol. 2002;134(3):317-28

Keywords: Optic neuropathy

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Poster 157

Prediction of intracranial hemorrhagic events based on retinal microvascular abnormalities: a meta-analysis

Oana Dumitrascu[1], Cristina Valencia-Sanchez[1], Gyanendra Kumar[1]

[1]*Mayo Clinic Arizona, Phoenix, Arizona, USA*

Introduction:
Retinal microvascular abnormalities have been shown to be associated with intracranial hemorrhage (ICH) in several studies. The standardization of the retinal findings and the degree of the association remain unclear. Objective: To synthesize estimates of risk across cohort studies and to quantify the association of retinal microvascular signs with incident intracranial bleeding events.

Methods:
We systematically searched the Cochrane Library, PubMed, Scopus, Web of Science, and Ovid databases through September 30, 2016 for studies evaluating the effect of retinal microvascular signs on the risk of ICH. Data were abstracted using predefined criteria and then pooled using Mix 2.0 Pro (Biostat XL) software.

Results:
A total of 3 cohort studies including 4996 participants met inclusion criteria for the meta-analysis. Heterogeneity was significant (I2 = 91.5%; p<0.5) and studies were of good quality (based on Newcastle–Ottawa Scale). When compared with subjects without retinal vascular abnormalities, subjects with focal arteriolar narrowing (n= 4301; OR 5.57; 95% CI 1.43-21.71), arterio-venous nicking (n= 4896; OR 2.18; 95% CI 1.05-4.53) and retinal hemorrhages/ microaneurysms (n= 4895; OR 2.25; 95% CI 1.12-4.51) had significantly increased risk of incident ICH. The number of studies was too small for a statistical or funnel-plot evaluation of publication bias.

Conclusions:
Focal arteriolar narrowing was associated with the highest risk of ICH, followed by retinal hemorrhages/microaneurysms, and arterio-venous nicking. Prospective population-based studies should further investigate the temporal relationship.

References: None.

Keywords: Vascular disorders, Stroke Trauma, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 158
Decellularization of Porcine and Primate Optic Nerve Lamina

Lilangi Ediriwickrema[1], Rebecca Fawcett[2], Neil Miller[1], Steven Bernstein[2]

[1]Johns Hopkins University, Wilmer Eye Institute, Batimore, Maryland, USA, [2]University of Maryland School of Medicine, Department of Ophthalmology, Baltimore, Maryland, USA

Introduction:
The optic nerve lamina cribrosa is a mesh-like collagenous structure consisting of an extracellular matrix with varying porosity and glial cell distribution through which axons of retinal ganglion cells travel en route to the lateral geniculate nucleus. There has been significant interest in its structure with respect to its possible role in the pathophysiology of glaucomatous optic neuropathy. Our goal was to decellularize porcine and primate lamina to evaluate for a potential role as a three-dimensional scaffold for stem cell growth, regeneration, and delivery.

Methods:
Optic nerve lamina were dissected from porcine and primate cadaveric enucleations. The tissue specimen were embedded into a sugar moiety and subsequently sectioned into variable thicknesses using a cryotome. The specimens were then decellularized using a chemical detergent buffer (Tris-SDS-EDTA) over several pre-determined time-points. Histological analysis using Gömöri trichrome staining confirmed complete decellularization. Select decellularized scaffolds were then sterilized, seeded with either squamous cell carcinoma cells (SCC) or human neural progenitor cells, and maintained in stem cell culture.

Results:
Gömöri trichrome staining confirmed that porcine or primate optic nerve lamina sectioned at 50 µm, 100 µm, or 180 µm thicknesses were completely decellularized at 45 minutes, 1 hour, or 2 hours, respectively. Sterilized porcine laminar sections tolerated SCC and neural progenitor cell adhesion, three-dimensional growth, and survival in culture confirming biocompatibility.

Conclusions:
Chemical detergent buffer immersion can lead to complete decellularization of porcine and primate optic nerve lamina. These porous extracellular matrices may have a potential role as a scaffold for cellular growth and neural regeneration in treating optic neuropathy.

References: Radius RL, Gonzales M. Anatomy of the Lamina Cribrosa in Human Eyes. Arch Ophthalmol. 1981;99(12):2159-2162. doi:10.1001/archopht.1981.03930021035010 Morgan-Davies J, Taylor N, Hill AR, Aspinall P, O'Brien CJ, et al. Three dimensional analysis of the lamina cribrosa in glaucoma. Br J Ophthalmol. 2004 Oct; 88(10): 1299-1304. doi: 10.1136/bjo.2003.036020 Goldberg JL, Guido W, AGI Working Participants. Report on the National Eye Institute Audacious Goals Initiative: Regenerating the Optic Nerve. IOVS (2015), 1552-5783. Ouyang, H, Goldberg JL, Chen S, Li W, Xu GT, et al. Ocular Stem Cell Research from Basic Science to Clinical Application: A Report from Zhongshan Ophthalmic Center Ocular Stem Cell Symposium. International Journal of Molecular Sciences (2016), 17 (415).

Keywords: Optic neuropathy, Optic nerve trauma and treatment

Financial Disclosures: The authors had no disclosures.

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Poster 159
Multifocal visual evoked potentials in optic neuritis and multiple sclerosis: A review

Mathias Falck Schmidt[1], Jette Frederiksen[1], Gorm Phil-Jensen[1]

[1]Rigshospitalet - Glostrup, Copenhagen, Denmark

Introduction:
The purpose of this review is to present a thorough survey of the results obtained by mf-VEP in ON and MS patients including comparisons to other measurements of the visual system (e.g. ff-VEP, OCT, visual functions, MRI), ON and MS disease course and disability. The aim is to evaluate whether mf-VEP can be applied as a valuable method to detect visual pathway involvement in ON and MS and to monitor long term disease course.

Methods:
PubMed and EMBASE databases were consulted between 1st and 8th of October 2014 and again in 2016. Search terms were "Optic Neuritis AND multifocal visual evoked potential", "Multiple Sclerosis AND multifocal visual evoked potential". Review articles were excluded and every published trial of mf-VEP in MS or demyelinating disease was included in this paper. Furthermore, reference lists of the included articles were searched. Unpublished and ongoing trials were searched for on the https://clinicaltrials.gov/ webpage using the same search terms. In total 39 published studies including mf-VEP measurements were retrieved and results of these are discussed in this review.

Results:
Results obtained in ON and MS have generally shown good sensitivity in detecting abnormality. Good correlation is shown between mf-VEP and OCT, ff-VEP, MRI modalities (MTR, DTI), SAP and low-contrast-visual acuity. Compared to the ff-VEP the mf-VEP, in most studies, has shown superior sensitivity and specificity and especially small, peripheral lesions or lesions of the upper visual field seemed to be more readily detected on mf-VEP.

Conclusions:
In summary, the mf-VEP presents a compelling new method that may be incorporated as a diagnostic and prognostic marker in ON and MS and in monitoring disease course with regards to axonal loss, and de- and remyelination.

References: None.

Keywords: Demeylinating disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 160

Traumatic Brain Injury and Pediatric Ocular Trauma- Analysis of National Trauma Data Bank

Ryan Gise[1], David Poulsen[2], Yssra Soliman[3], Afshin Parsikia[4], Joyce Mbekeani[5]

[1]Department of Ophthalmology, Montefiore Medical Center and Albert Einstein COM, Bronx, New York, USA, [2]Department of Ophthalmology, Montefiore Medical Center/Albert Einstein COM, Bronx, New York, USA, [3]Albert Einstein College of Medicine, Bronx, New York, USA, [4]Department of Surgery, Jacobi Medical Center, Bronx, New York, USA, [5]Dept of Surgery, Jacobi Medical Center, Dept of Ophthalmology, Albert Einstein COM, Bronx, New York, USA

Introduction:
Traumatic brain injury (TBI) is a leading cause of pediatric disability and mortality. Compromised visual function from concomitant TBI and ocular trauma that may occur in major trauma further complicates recovery and rehabilitation and could negatively impact neuro-cognitive development. We aimed to evaluate epidemiological patterns of TBI in pediatric patients admitted with ocular injuries in the United States.

Methods:
The National Trauma Data Bank from 2008 to 2014 was used to retrospectively study pediatric patients (<21years) admitted with ocular trauma and TBI. Patients were identified using ICD-9 codes. Statistical analysis was performed with SPSS software. Variables were correlated using student t-test and Chi-squared analysis. Odds ratios (OR) were also calculated. Statistical significance was set at $p<0.05$.

Results:
32,173 (54.7%) of 58,765 pediatric patients admitted with ocular trauma were diagnosed with TBI. The mean age was 12.3yrs (SD=7). Males (68.8%) and were older (mean = 12.6yrs) than females (mean = 10.6yrs); $p<0.001$. Race distribution was Whites, 61.2%, Blacks, 16.1% and other, 28.8%. The southern region reported most cases, 36.4%. Mean injury severity score was "severe" 17 (SD=11.2) and mortality occurred in 5.1%. Frequent ocular injuries were contusion of eye/adnexa, 39.1% and orbital fractures, 35.8%. Visual pathway (VPI) and intracranial nerve injuries occurred in 7.1%. Of VPI, optic nerves were affected in 85.4%. Common mechanisms were motor vehicle-occupant (MVTO), 32.6% and struck by against (SBA), 12.6% and locations were street, 49.8% and home, 22.7%. The 0-3yrs group had greater odds of falls (OR=3.5; CI=3.3-3.8) and home location (OR=15.8; CI=14.8-16.8); $p<0.001$ and the 19-21yrs group, MVTO (OR=1.8; CI=1.7-1.9) and street location (OR=2.2; CI=2.1-2.3); $p<0.001$.

Conclusions:
In children, ocular trauma is frequently complicated by traumatic brain injury, resulting mostly from MVTO and SBA. Identified demographic, regional and mechanistic differences could be instrumental in developing preventative measures and policies aimed at reducing long-term disability and preserving life.

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Keywords: Pediatric neuro-ophthalmology, Optic neuropathy, Optic nerve trauma and treatment

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Poster 161
Physiologic Electrical Fields Direct Retina Ganglion Cell Neurite Growth

Kimberly Gokoffski[1], Xingyuan Jia[2], Min Zhao[2]

[1]USC Roski Eye Institute, Los Angeles, California, USA, [2]University of California Davis, Sacramento, California, USA

Introduction:
Restoration of vision in patients with advanced optic neuropathies such as glaucoma requires regenerating the optic nerve (ON). The current rate-limiting step to ON regeneration is directing axons of newly transplanted cells to grow out of the retina to their distant targets. Much of the current effort to address this problem aims at recapitulating the molecular neurotropic signals that directed ON growth during development. However, studies have shown that their presence alone is insufficient to support axon growth of transplanted RGCs. The body has naturally occurring electrical currents that have been shown to exert neurotropic effects on motor neurons and dorsal root ganglion cells. The effects of an electrical field (EF) on RGC growth, however, have never been tested before. Here, we demonstrate for the first time that RGC axons grow directionally towards the cathode when exposed to an EF.

Methods:
Retina was isolated from post-natal mice and cultured in an electrotaxis apparatus. Eighteen hours after plating, retina was exposed to various EF strengths. Time-lapsed microscopy was performed.

Results:
In the absence of an EF, RGC neurites demonstrated indiscriminate directional growth from the tissue edge. Retinal cultures that were exposed to an EF of 200mV/mm, however, showed marked asymmetry in neurite growth: 81.2% were directed at the cathode, while 4.8% and 14.1% were directed towards the anode or perpendicular to the field, respectively ($p<0.001$). EF does not affect the length or rate of RGC axon growth. Interestingly, RGC axons responded acutely to changes in EF polarity, suggesting that EFs exert direct neurotropic effects on neurite growth as opposed to controlling directional growth via secondary effects.

Conclusions:
The significance of this work lies in its potential to advance the field of ON regeneration. Application of exogenous cues such as electrical currents may be necessary to direct the growth of newly transplanted RGCs.

References: McCaig, C. D., Rajnicek, A. M., Song, B. & Zhao, M. Controlling cell behavior electrically: current views and future potential. Physiological reviews 85, 943-978, doi:10.1152/physrev.00020.2004 (2005). Venugopalan, P. et al. Transplanted neurons integrate into adult retinas and respond to light. Nat Commun 7, 10472, doi:10.1038/ncomms10472 (2016). Sun, L., Han, X. & He, S. Direction-selective circuitry in rat retina develops independently of GABAergic, cholinergic and action potential activity. PloS one 6, e19477.

Keywords: Optic neuropathy, Miscellaneous

Financial Disclosures: The authors had no disclosures.

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Poster 162
Assessing the Vitreopapillary Interface in Acute Nonarteritic Anterior Ischemic Optic Neuropathy

Sidney Gospe, III[1], M. Tariq Bhatti[1], Mays El-Dairi[1]

[1]*Duke University Medical Center, Durham, North Carolina, USA*

Introduction:
Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic neuropathy in adults over age 50. While NAION typically occurs in patients with risk factors for microvascular ischemia, some have suggested an important mechanistic role for vitreous traction on the optic nerve head (ONH). Parsa and Hoyt have proposed that NAION is a misnomer and purely a tractional phenomenon. To test this hypothesis, we retrospectively assessed the posterior vitreous face by optical coherence tomography (OCT) in patients during the acute phase of NAION.

Methods:
Subjects diagnosed with NAION at our institution between 2011 and 2014 were identified in a retrospective review of electronic medical records. Inclusion required documentation of a swollen ONH and OCT imaging of the vitreopapillary interface. Exclusion criteria included positive temporal artery biopsy or alternative explanations for ONH swelling.

Results:
Thirty-two eyes of 31 subjects (39 to 87 years of age) were included. Prior complete posterior vitreous detachment (PVD) was noted in 7 eyes (22%), while the posterior hyaloid remained attached in 25 (78%). OCT did not demonstrate significant vitreopapillary traction in any cases. Not surprisingly, the presence of PVD significantly correlated with age, as 7 of 8 (87.5%) eyes age 70 or older had pre-existing PVD, while only 1 of 24 (4%) eyes below 70 years did ($p<0.0001$). None of the 13 non-PVD eyes with follow-up OCT (1 month to 6 years) demonstrated a spontaneous interval PVD despite resolution of ONH swelling. Pre-existing PVD did not correlate with final visual outcome or mean deviation on automated perimetry, but showed a non-significant trend toward thicker retinal nerve fiber layer after swelling resolved ($p=0.063$).

Conclusions:
While vitreopapillary adhesion may potentially contribute to acute ONH ischemia in some patients, it is not required for NAION to occur and appears unrelated to visual outcome.

References: Parsa CF, Hoyt WF, Nonarteritic anterior ischemic optic neuropathy (NAION): a misnomer. Rearranging pieces of a puzzle to reveal a nonischemic papillopathy caused by vitreous separation, Ophthalmology 122(3):439-42, 2015.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 163
Papilledema from Compression of Intracranial Venous Sinuses by Dural Meningiomas

Alexander Hartmann[1], Amit Saindane[1], Beau Bruce[2], Nancy Newman[1], Valerie Biousse[1]

[1]Emory University, Atlanta, Georgia, USA, [2]Center for Disease Control, Atlanta, Georgia, USA

Introduction:
To describe neuro-ophthalmologic manifestations and management of intracranial dural sinus compression causing venous hypertension and papilledema. Chronic papilledema mimicking idiopathic intracranial hypertension (IIH) may result from venous hypertension from compression of an intracranial venous dural sinus by a neoplasm. The diagnosis is often missed and management remains challenging.

Methods:
Retrospective review of patients with increased intracranial pressure (ICP) secondary to compression of intracranial dural sinuses seen between 2012-2016 at our institution.

Results:
Nine patients with compression of an intracranial dural sinus and papilledema were identified (6 women, 3 men, mean age 46yo[28-80]; median BMI 29[24-33]). Median CSF-opening pressure was 28cmH2O[20-45]. All lesions were consistent with dural meningiomas involving the posterior superior sagittal sinus (3), or the dominant right transverse venous sinus (6). All 6 patients with right transverse sinus compression had a hypoplastic or stenotic left transverse sinus. Correct diagnosis was delayed in 5/9 patients (misdiagnosis of IIH in 4 [meningioma either missed on initial brain MRI (no MRV) or deemed to be too small to cause intracranial hypertension], and of venous thrombosis in 1 patient in whom the meningioma was missed on initial MRI). In 3 patients, delayed diagnosis resulted in profound visual loss from chronic papilledema. Treatments included combinations of acetazolamide (6), CSF-shunts (4), optic nerve sheath fenestration (1), surgical resection (2), radiation therapy (3), and endovascular venous stenting (1). Three patients also received anticoagulation for venous thrombosis secondary to compression of the venous sinus. Review of the literature revealed less than 20 similar cases described in detail and 138 undetailed cases.

Conclusions:
Meningiomas involving intracranial dural sinuses may cause venous hypertension and resultant intracranial hypertension with chronic papilledema and visual loss. Clinical presentations mimic IIH; careful review of brain MRI, ideally with MRV, is necessary in all presumed IIH patients. Treatment requires a multidisciplinary approach, often with multiple sequential interventions.

References: Mathiesen T, Pettersson-Segerlind J, Kihlström L, Ulfarsson E, Meningiomas Engaging Major Venous Sinuses, World Neurosurgery, 81(1):116-124, 2014. Mantovani A, Maio SD, Ferreira MJ, Sekhar LN. Management of Meningiomas Invading the Major Dural Venous Sinuses: Operative Technique, Results, and Potential Benefit for Higher Grade Tumors, World Neurosurgery, 2(3-4):455-467, 2014. Kim AW, Trobe JD, Syndrome simulating pseudotumor cerebri caused by partial transverse venous sinus obstruction in metastatic prostate cancer, American Journal of Ophthalmology, 129(2):254-256, 2000. Shah AH, Ivan ME, Komotar RJ, Pseudotumor-like syndrome and cerebrospinal fluid leak in meningiomas involving the posterior third of the superior sagittal sinus: report of 4 cases, Journal of Neurosurgery, 125(1):62-66, 2016.

Keywords: Tumors, Neuroimaging, High intracranial pressure/headache, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 164

Visual Outcome of Systemic Corticosteroids Treatment in Non-Arteritic Anterior Ischemic Optic Neuropathy

Ruth Huna-Baron[1], Guy Tam[2], Iris Ben-Bassat-Mizrachi[2], Alon Skaat[3]

[1]Eye Institute, Sheba Medical Center ,Sackler School Of Medicine Tel Aviv University, Ramat Gan, Israel, [2]Neuro-Ophthalmology unit, The Goldschleger Eye Institute, Sheba Medical Center, Ramat Gan, Israel, [3]Goldschleger Eye Institute Sheba Medical Center Tel-Hashomer, Ramat Gan, Israel

Introduction:
To date non arteritic anterior ischemic optic neuropathy (NAION) which is the most common acute optic neuropathy after the age 50 still lacks a proven effective accepted therapy. Recently a large retrospective non-randomized study suggested that systemic corticosteroid therapy given during the acute phase of NAION significantly improved visual acuity (VA) and visual fields (VF). Our purpose was to evaluate the visual and anatomical outcome of oral corticosteroids treatment in patients with NAION.

Methods:
We revised charts of 168 consecutive NAION patients seen at our clinic in 2013-2016 with at least 6 months of follow- up to find 7 NAION patients (9 eyes) treated during the acute phase with oral corticosteroids. The control group consisted of age and risk factor - matched cohort of 10 patients that received no treatment. Visual acuity, Humphrey automated visual field defects and retinal nerve fiber layer (RNFL) measured by Optical Coherence Tomography (OCT) of the affected eye were compared between groups at baseline and at end of follow-up.

Results:
VA at end of follow-up did not improve in either group (p =0.4 treated group, p = 0.09 control group). No improvement in VF mean deviation was found in treated patients (p=0.9) and untreated patients (p=0 .6). No difference was found in RNFL thickness between the groups. Complications occurred in two of the treated patients (29%).In one of them, steroid therapy had to be discontinued because of severe steroid induced depression. No complications developed in the control group.

Conclusions:
Systemic steroid treatment did not show any beneficial effect on visual outcome as well as on RNFL thickness when given during the acute phase of NAION in our small retrospective study. Since corticosteroids can cause serious adverse effects as in our patients this treatment for NAION seems unworthy.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 165

Dynamic contour tonometry to measure ocular pulse amplitude in patients with suspected giant cell arteritis

Edsel Ing[1], Felix Tyndel[2], Paul Ranalli[2], Lam Kay[2], Harleen Bedi[2], Brian Healy[3], Lucas Bachmann[4], Nurhan Torun[5]

[1]University of Toronto, Michael Garron (Toronto East General) Hospital, Toronto, Canada, [2]University of Toronto, Toronto, Canada, [3]Harvard School of Public Health, Boston, Massachusetts, USA, [4]Horton Center, Zurich, Switzerland, [5]Beth Israel Deaconess, Boston, Massachusetts, USA

Introduction:
Dynamic contour tonometry (DCT) provides a painless and quick measurement of ocular pulse amplitude (OPA), which can reflect ocular perfusion. Primary aim: to delineate the role of DCT in giant cell arteritis (GCA) suspects undergoing temporal artery biopsy (TABx). We hypothesize a diminished OPA in patients with positive TABx compared to patients with negative TABx. Secondary aim: to develop a logistic regression risk score for GCA using the a priori objective criteria of age, OPA, and C-reactive protein (CRP).

Methods:
Patients undergoing TABx were enrolled in this IRB-approved prospective validation study from June 2015 to present. The pre-steroid treatment CRP was obtained. The OPA measurement immediately preceded the TABx. A logistic regression model was fit with the TABx pathology result as the outcome and age, CRP and average OPA (avgOPA) between the two eyes as continuous predictors.

Results:
Fifteen of the 76 TABx were positive. The mean OPA was 2.8 +/- 1.01, and 2.50 +/-1.33 in patients with negative and positive TABx respectively. OPA less than 2.0 was in the lower 25th percentile of subjects with negative TABx. The use and time of initiation of steroids varied widely amongst the patients. Six patients did not have CRP drawn before the referring doctor started steroids. Seventy subjects had complete information for multivariate logistic regression. The estimated odds ratios were 1.000 (p=.993, 95%CI 0.934, 1.071) for age, 1.096 (p=.055, 95%CI 0.998, 1.204) for CRP, and 0.449 (p=.038, 95%CI 0.210, 0.958) for avgOPA. The area under the receiving operating curve was 0.8046.

Conclusions:
OPA was a statistically significant predictor of the TABx result, and CRP approached statistical significance. The risk score derived from the logistic regression coefficients will be refined as more patients are recruited. Further work is needed to determine if OPA can guide steroid dosing.

References: Knecht PB, Bachmann LM, Thiel MA, Landau K, Kaufmann C. Ocular pulse amplitude as a diagnostic adjunct in giant cell arteritis. Eye (Lond). 2015 Jul;29(7):860-5

Keywords: Optic neuropathy, Vascular disorders, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Grant Support: None.

Poster 166
Intracranial Arterial Compression of the Anterior Visual Pathway

Neeranjali Jain[1], Andrew Kam[1], Calum Chong[1], Katherine Francis[1], Allison Newey[2], Ashish Agar[1], Yashar Kalani[3], Ian Francis[1]

[1]Department of Ophthalmology, Prince of Wales Hospital, Sydney, Australia, [2]Department of Radiology, Royal North Shore Hospital, Sydney, Australia, [3]Division of Neurological Surgery, Barrow Neurological Institute., Phoenix, Arizona, USA

Introduction:
Intracranial blood vessels can compress adjacent cranial nerves, leading to disorders such as trigeminal and glossopharyngeal neuralgia, and hemifacial spasm. However, the occurrence of compressive damage by intracranial arteries of the Anterior Visual Pathway (AVP), consisting of the optic nerves, chiasm or optic tracts, is poorly recognized. This study aimed to determine whether vascular compression of the AVP could contribute to visual field defects, pupillary abnormalities affecting the AVP, and optic nerve head changes in patients without an identified cause of their visual dysfunction.

Methods:
33 patients (37-91 years) with intracranial artery-AVP compression, as demonstrated by magnetic resonance imaging, were identified by reviewing case records from an ophthalmology practice. Variables including demographics, as well as corrected distance visual acuity, visual fields, pupillary reactions and optic disc appearance were retrieved from the records.

Results:
AVP compression sites matched the visual deficits observed in 26 (79%) cases. The internal carotid arteries were involved in most cases of optic nerve compression (21/27: 78%), the anterior cerebral arteries were involved in most cases of chiasmal compression (7/8: 87%) and the posterior communicating artery compressed an optic tract in one case. Patients with relative afferent pupillary defects demonstrated either compression of ipsilateral AVP structures (n=4) or bilateral compression of optic nerves (n=4).

Conclusions:
AVP compression by intracranial arteries may be a causative factor in patients with unexplained visual field defects or pupil abnormalities. AVP compression from the optic nerve through to the optic tract may contribute to these phenomena. As this entity may be confused with normal tension glaucoma, investigation of possible vascular compression with MRI could be considered in patients who have features which are atypical of normal tension glaucoma.

References: None.

Keywords: Vascular disorders, Neuroimaging

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Grant Support: None.

Poster 167

Utility of Spectral Domain OCT (SD-OCT) to distinguish between Papilledema and Pseudopapilledema

Imran Jivraj[1], Cesar Alfaro Cruz[2], Maxwell Pistilli[2], Anita Kohli[3], Tomas Aleman[3], Grant Liu[4], Kenneth Shindler[3], Robert Avery[4], Mona Garvin[5], Faisal Althekair[6], Ahmara Ross[3], Madhura Tamhankar[3]

[1]University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [3]The Scheie Eye Institute, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [4]Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [5]University of Iowa, Iowa City, Iowa, USA, [6]Massachusetts General Hospital, Boston, Massachusetts, USA

Introduction:

Differences in SD-OCT measurements between patients with papilledema and pseudopapilledema have been described (1-5). The sensitivity and specificity of SD-OCT to detect papilledema among patients with optic disc elevation were studied prospectively.

Methods:

Adult patients (n=34) with optic disc elevation were enrolled in a prospective longitudinal study. Independent assessment of fundus photographic change in optic disc elevation was diagnostic of papilledema. SD-OCT was used to measure peripapillary retinal nerve fiber layer (pRNFL) and paracentral ganglion cell–to-inner plexiform layer (GCL-IPL) thicknesses at baseline and within six months of follow-up using proprietary and 3D segmentation software.

Results:

Sixteen patients (47.1%) were diagnosed with papilledema and 18 (52.9%) with pseudopapilledema. Patients with papilledema had greater baseline mean pRNFL thickness (219.0 vs 108.0µm, p<0.001) and greater change in pRNFL (ΔpRNFL) at six months (-100.5 vs. -11.0µm, p<0.001). In patients with mild elevation (Frisen Grades 1 and 2), both baseline pRNFL (137.0 vs 108µm, p=0.03) and ΔpRNFL (-46.5 vs -11.0µm, p=0.001) remained significantly greater among those with papilledema. Mean GCL-IPL thickness was similar at baseline between the two subgroups but there was a small reduction in GCL-IPL thickness among patients with papilledema (-2.4 vs -0.6µm, p<0.001). Mean baseline pRNFL ≥181µm and ΔpRNFL ≥40µm had 100% specificity to exclude pseudopapilledema. A ≥13% ΔpRNFL had a sensitivity of 94% and specificity of 72% for detecting papilledema.

Conclusions:

Mean baseline pRFNL and ΔpRNFL were significantly greater among patients with papilledema, and remained significantly greater when patients with mild disc elevation were separately analysed. A 13% ΔpRNFL was highly sensitive for papilledema but moderately specific. 28% of patients demonstrated >13% ΔpRNFL in the absence of photographic change; these patients may have had papilledema but photographic change was not observed within the study interval. Baseline and longitudinal change in SD-OCT parameters may be useful in the diagnosis of papilledema.

References: 1. OCT Sub-Study for NORDIC IIH Study Group. Papilledema Outcomes from the Optical Coherence Tomography Substudy of the Idiopathic Intracranial Hypertension Treatment Trial. Ophthalmology. 2015;122(9):1939-45 e2. 2. OCT Sub-Study for NORDIC IIH Study Group. Baseline OCT measurements in the idiopathic intracranial hypertension treatment trial, part II: correlations and relationship to clinical features. Invest Ophthalmol Vis Sci. 2014;55(12):8173-9. 3. Fard MA, Fakhree S, Abdi P, et al. Quantification of peripapillary total retinal volume in pseudopapilledema and mild papilledema using spectral-domain optical coherence tomography. Am J Ophthalmol. 2014;158(1):136-43. 4. Skau M, Yri H, Sander B, et al. Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension. Graefes Arch Clin Exp Ophthalmol. 2013;251(2):567-74. 5. Wang JK, Kardon RH, Kupersmith MJ, Garvin MK. Automated quantification of volumetric optic disc swelling in papilledema using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(7):4069-75.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy, High intracranial pressure/headache, Pseudotumor Cerebri

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Grant Support: None.

Poster 168
Brightness comparison testing quantification and relation with afferent pupillary defects

Emely Karam[1]

[1]*Centro Medico Docente la Trinidad Unidad Oftalmológica de Caracas, Caracas, Venezuela*

Introduction:
To quantify the brightness comparison test with neutral density filters and determine the relation with afferent pupillary defect (RAPD)

Methods:
The subjective brightness test was doing in 57 patients with unilateral ischemic optic neuropathy (16) , optic neuritis (25), traumatic optic neuropathy (3) and compressive optic neuropathy (13). After it, a neutral density filter bar was use to reduced the brigtness light in the best eye in order to simulate similar effect int the affected eye. The "swinging flashlight test" was used to diagnose RAPD and the degree of which was quantified by bar of neutral density .

Results:
The analysis of comparison between objective and subjective britghness test the mean were: for the group of 0.3 Uds log of density filter the subjective test was 90 % (7 cases). For the group of 0.6 Uds log the mean was 84% (18 patientes); in 0.9 uds/log group the mean was 77% (7 patients). For the group of 1.2 Uds log the mean was 45% (6 patients); for the1.5 uds log group, the mean was 26% (5 patients) and for 1.8 uds log the mean was 25% (14 patients). In the analysis of patients with RAPD a high correlation was found when comparing with brightness comparation test measurment in both cases with bar of neutral density. This was statistically significant ($p = <0.001$)

Conclusions:
Brightness comparison testing quantification is a very simple and objective test to monitor the course of patient's with neuropathy and also could be a indirect method to corroborated the RAPD

References: Danesh-Meyer HV, Papchenko TL, Savino PJ, Gamble GD. Brightness sensitivity and color perception as predictors of relativeafferent pupillary defect. Invest Ophthalmol Vis Sci;48(8):3616-21,2007 Browning DJ1, Buckley EG. Reliability of brightness comparison testing in predicting afferent pupillary defects. Arch Ophthalmol.106(3):341-3,1988

Keywords: Optic neuropathy, Pupils Retina, Non-organic visual disorders, Miscellaneous, Orbit/ocular pathology

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Grant Support: None.

Poster 169
Transcorneal Electrical Stimulation in Optic Neuropathies

Umur Kayabasi[1]

[1]*Uskudar University, D- NO Visual Treatment Center, Istanbul, Turkey*

Introduction:
Aim was to achieve improvement in vision and visual fields in optic neuropathies by transcorneal electrical stimulation (TES) .

Methods:
20 patients with non-arteritic anterior ischemic optic neuropathy and 10 patients with traumatic optic neuropathy were stimulated 40 minutes per day for 10 consecutive days by the TES device. Patients with optic neuropathy were treated at least 2 months after the acute event.

Results:
In both groups, improvement in vision and visual fields was achieved. The average visual acuity improvement was 2 Snellen lines. Visual field improvements after 10 days of TES were documented. Expansion of fields reached approximately 25 percent of the initial result. The change in Mean Deviations was found to be highly significant. (p: 007)

Conclusions:
TES can be considered as a safe and effective treatment in certain optic neuropathies.

References: None.

Keywords: Optic nerve trauma and treatment, Optic neuropathy, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 170

Long-term Change of Retinal Nerve Fiber Layer and Ganglion Cell Layer in Traumatic Optic Neuropathy

Dae Hyun Kim[1], Ji Seong Jeong[2], Tae Jin Kim[1]

[1]Chosun University Hospital, Gwangju, Korea, Republic of, [2]Armed Force HamPyung Hospital, HamPyung, Korea, Republic of

Introduction:

In this study, long-term changes of peripapillary retinal nerve fiber layer (cpRNFL) thickness and ganglion cell-Inner plexiform layer (GCIPL) thickness in traumatic optic neuropathy (TON) were investigated.

Methods:

A prospective, comparative study of eleven patients who were diagnosed with unilateral TON was completed to evaluate changes of cpRNFL and GCIPL thickness through the use of spectral-domain optical coherence tomography (SD-OCT). The thickness of each retinal layer in the affected eyes was compared with that of the unaffected eyes. These measurements were obtained sequentially by acute presentation (within 7days) and at 1, 3, 6, and 12 months after the trauma.

Results:

All eleven patients showed progressive reduction of both cpRNFL and GCIPL thickness. At acute presentation and at 1,3,6, and 12 months, the mean cpRNFL thickness was 95.36 ㎛, 84,27 ㎛, 61.18 ㎛, 57.36 ㎛, and 52.18 ㎛, respectively, and the GCIPL thickness was 77.64 ㎛, 57.91 ㎛, 56 ㎛, 54.36 ㎛, and 52 ㎛, respectively. There was no significant difference in the mean cpRNFL thickness in the TON eyes compared with contralateral unaffected eyes at acute presentation and at 1month. (P=1, P=0.11). On the other hand, there was significant thinning of the mean cpRNFL thickness in the TON eyes compared with contralateral eyes was observed at 3, 6, and 12months (all P<0.01). The mean GCIPL thickness in the TON eyes compared with contralateral eyes were not different at acute presentation(P=1). But there was a significant thinning of the mean GCIPL thickness in the TON eyes compared with contralateral eyes at 1, 3, 6, and 12 months (all P<0.01).

Conclusions:

In TON, the thinning of GCIPL thickness was observed 1month after trauma, whereas the cpRNFL thickness was observed at 3 months. From this study we found that GCIPL loss occurs faster than cpRNFL thinning in TON.

References: None.

Keywords: Optic nerve trauma and treatment

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 171
Value of electrophysiology tests in the traumatic optic neuropathy

Kun Hae Kim[1], Ungsoo Kim[2]

[1]Kim's Eye Hospital, Seoul, Korea, Republic of, [2]Kim's Eye Hospital, Konyang University, Seoul, Korea, Republic of

Introduction:
To study correlation between electrophysiologic examinations which evaluate visual functions with optical coherence tomography (OCT), an anatomical evaluation in patients with traumatic optic neuropathy.

Methods:
Retrospective, observational case series study. Twenty eyes from patients diagnosed with traumatic optic neuropathy were included. Basic ophthalmologic examinations were performed. Pattern electroretinogram (ERG) (P50 amplitude, N95 amplitude and N95/P50 ratio) and pattern visual evoked potential (VEP) (P100 amplitude and latency) were analyzed and compared with the thickness of peripapillary retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer complex measured with OCT.

Results:
20 patients (17 male, 3 female) were evaluated. All parameters including P50 amplitude, N95 amplitude, N95/P50 ratio, P100 amplitude and P100 latency changed in the traumatic eye. When it comes to pattern ERG with visual acuity, N95/P50 ratio showed the significant correlation ($r=0.517$ $p=.028$). Although temporal RNFL thickness had a significant correlation with P100 amplitude of pattern VEP ($r=-0.930$, $P<0.001$), pattern ERG did not show a correlation with OCT. In the patients with no detectable pattern VEP, pattern ERG could be obtained in 7 out of 8 patients.

Conclusions:
In patients with traumatic optic neuropathy, the pattern ERG may be a helpful alternative to pattern VEPs. ERG shows retinal function whereas VEP may reflect any abnormalities that affect visual pathway including visual cortex in the brain. Also in cases of flat VEP signals, results of ERG tend to achieve viable wave forms.

References: None.

Keywords: Optic neuropathy, Optic nerve trauma and treatment

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 172
Primary Optic Neuropathy In Behcet's Disease

Chuntao Lai[1], Qinglin Yang[1], Jiawei Wang[1], Lin Sun[1], Qian Wang[1], Lei Liu[1], Qinglin Chang[2], Xuehui Shi[3], Shilei Cui[1]

[1]Department of Neurology, Beijing Tongren Hospital, Capital Medical University, Beijing, China, [2]Department of Radiology, Beijing Tongren Hospital, Capital Medical University, Beijing, China, [3]Ophthalmology Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Introduction:
To describe the clinical features and MRI findings of primary optic neuropathy in Behcet's disease (BD).

Methods:
Observational study. Fifty-seven consecutive patients seen in a hospital-based neurology department between June 1, 2015 and September 31, 2016, with optic nerve involvement who met the international criteria for the diagnosis of BD were prospectively included. Ten previously patients published with optic perineuritis in BD were included in this study. Patients whose visual loss was caused by retinal vasculitis or with positive AQP4-Ab were excluded. Contrast –enhanced MRI of the optic nerves was performed on each patient. Their medical records and optic nerve MRI data were reviewed and evaluated.

Results:
A total of sixty-seven patients（46 female/21 male= 2.2/1） were identified. The age of onset of visual loss ranged from 14 to 75 years (mean, 37 years). Fifty patients (75%) presented with unilateral onset. Fifty-four (64%) of 84 affected eyes had severe visual loss (≦20/200). In 75 eyes with MRI changes on either side, 56 eyes (75%) showed significant perineural enhancement around the optic nerve, 33 eyes（44%, Pearson tests, p = 0.000） demonstrated increased signal within the optic nerve (31 eyes) or optic nerve head enhancement (2 eyes).

Conclusions:
Primary optic neuropathy in BD occurs more often in females and often presents with severe, unilateral visual loss. Perineural enhancement around the optic nerve is a distinct MRI feature.

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Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 173
Anatomical Correlates of Visual Field Defects in Patients with Optic Disc Drusen using EDI-OCT

Lasse Malmqvist[1], Anne-Sofie Lindberg[2], Vedrana Dahl[2], Thomas Jørgensen[2], Steffen Hamann[3]

[1]Department of Ophthalmology, Rigshospitalet, Denmark, 2600 Glostrup, Denmark, [2]DTU Compute, Technical University of Denmark, Lyngby, Denmark, [3]Department of Ophthalmology, Rigshospitalet, Copenhagen, Denmark

Introduction:
Optic disc drusen (ODD) are found in up to 2.4% of the population and are known to cause visual field defects. The purpose of the current study was to investigate how quantitatively estimated volume and anatomical location of ODD influence degree of visual field defects.

Methods:
Anatomical location, volume of ODD, and peripapillary retinal nerve fiber layer (RNFL) thickness was assessed in 37 ODD patients using enhanced depth imaging optical coherence tomography (EDI-OCT). ODD volume was calculated by manual segmentation of ODD in 97 B-scans per eye. The weighted anatomical location of ODD was calculated using the distance from the level of Bruch's membrane and the volume of the individual ODD. Anatomical characteristics were correlated with optic nerve function using automated perimetric mean deviation (MD).

Results:
Average MD was -6.8 dB (± 6.3 dB). Mean peripapillary RNFL thickness was 77.1 µm (± 23.6 µm), mean ODD volume was 0.32 mm3 (± 0.28 mm3), and mean weighted location of ODD was 226 µm (± 150 µm) above the level of Bruch's membrane. In a multivariate regression analysis a worsening of MD was significantly correlated with larger ODD volume (R^2=0.49, P<0.0001). No correlation was found between MD and weighted location. RNFL decreased significantly with larger ODD volume (R^2=0.43, P<0.0001).

Conclusions:
The volume of ODD is the most important anatomical parameter to influence the degree of visual field defects. No correlation was found between anatomical ODD location and degree of visual field defects.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 174

Elevated VEGF and reduced IL-2 in patients with acute non-arteritic anterior ischemic optic neuropathy (NAION)

Jonathan Micieli[1], Cindy Lam[1], Kinda Najem[2], Edward Margolin[1]

[1]Department of Ophthalmology and Vision Science, University of Toronto, Canada, Toronto, Canada, [2]Department of Ophthalmology, Université de Montréal, Canada, Montreal, Canada

Introduction:

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in older adults, which has no established treatment. It remains unknown how the intraocular cytokine milieu is altered in the acute phase of the disease, which has implications for the design of future therapies and diagnostic testing. The goal of this study was to measure and compare the cytokine concentrations in the aqueous humor of patients with acute NAION and normal age-related cataract controls.

Methods:

In this prospective observation study, aqueous humor samples were obtained in 10 patients with acute NAION (within 14 days of symptom onset) and 15 control patients with age-related cataract. The levels of 6 cytokines [vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-2, IL-6, and IL-8] were determined using a multiplex bead immunoassay. The clinical characteristics of patients were also collected for correlation analysis.

Results:

The mean concentration of VEGF (94.1 + 40.4 pg/mL) was significantly higher in the NAION group compared to the cataract controls (52.2 + 20.8 pg/mL; p = 0.010) and the mean concentration of IL-2 (5.56 + 1.27 pg/mL) was significantly lower in the NAION group than in the cataract controls (16.6 + 14.0 pg/mL; p = 0.002). There were no differences in the concentration of TNF-α, IL-1β IL-6 and IL-8. There was a strong negative correlation between the VEGF concentration and the peripapillary RNFL thickness at presentation (r = -0.657, p = 0.055). There was no significant correlation between the RNFL thickness and any other cytokines, the mean deviation on 24-2 Humphrey visual fields, or the duration of vision loss.

Conclusions:

Acute NAION is associated with increased intraocular VEGF and a decreased IL-2. This has implications for future therapeutic interventions and diagnostic testing in patients with this acute optic neuropathy.

References: None.

Keywords: Optic neuropathy, Vascular disorders

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Poster 175

Multifocal Visual Evoked Potential in Temporal Hemianopia from Pituitary Tumors. Correlation with Perimetry and OCT

MÁRIO LUIZ MONTEIRO[1], RAFAEL SOUSA[1], Maria Oyamada[1], Leonardo Cunha[2]

[1]UNIVERSITY OF SÃO PAULO MEDICAL SCHOOL, SÃO PAULO, Brazil, [2]Federal University of Juiz de Fora; University of São Paulo Medical School, Juiz de Fora, Brazil

Introduction:
The purpose of this study was to compare multifocal visual evoked potential (mfVEP) measurements in eyes with temporal hemianopia and chiasmal compression from pituitary tumors with those of normal controls. We also wanted to assess the relationship between mfVEP, standard automated perimetry (SAP) and fourier domain-optical coherence tomography (fd-OCT).

Methods:
Twenty-seven eyes from 21 patients with pituitary tumors and permanent temporal visual field (VF) defects from chiasmal compression and 43 eyes from 23 healthy subjects underwent mfVEP, SAP and fd-OCT macular and retinal nerve fiber layer (RNFL) thickness measurements. VF loss was estimated in four quadrants and each half of both the 24-2 and 10-2 strategy test points. mfVEP and OCT macular measurements were averaged for each quadrant and half of the central measured area, while RNFL thickness was determined for sectors around the optic disc. The two groups were compared. Agreement and correlations between mfVEP, VF and OCT findings were verified.

Results:
mfVEP P1 and N2 amplitude parameters of temporal measurements were significantly smaller in patients than controls. No significant difference was observed in amplitude parameters from the nasal measurements. A significant correlation was found between mfVEP amplitude parameters and temporal VF loss as well as with corresponding OCT-measured macular and RNFL thickness parameters

Conclusions:
mfVEP amplitude parameters were able to differentiate eyes with temporal hemianopia from controls and were significantly correlated with VF and OCT findings. These data suggest that it is a useful technology for detecting visual abnormalities in patients with chiasmal compression

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy, Perimetry, Miscellaneous, Visual fields

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Poster 176
Dalfampridine in Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

Mark Moster[1], Robert Sergott[1], Benjamin Leiby[2]

[1]Wills Eye Hospital and Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [2]Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Introduction:
Dalfampridine improves walking speed in MS patients. There is some evidence of visual improvement in MS and improved motor function in early stroke studies. We hypothesized that patients with chronic stable deficits after NAION will have improved visual function with the administration of dalfampridine. Therefore, we performed a pilot clinical trial to determine whether this was true.

Methods:
Patients with NAION were enrolled at least 6 months after onset of NAION. This pilot study employed a double masked crossover design. Patients were randomized to begin with a 2 weeks course of either dalfampridine 10 mg bid orally or 2 weeks of placebo (Period 1). This was followed by a 2 week washout period with no treatment, followed by 2 weeks with the alternative treatment (Period 2).

Results:
The primary outcome of the study was visual acuity (VA). During treatment with drug, VA improved on average by 0.10 logMAR(Diff=-0.10 95% CI:-0.22 to 0.01). By contrast, there was no evidence of change in logMAR under placebo (Diff=0.01 95% CI:-0.10 to 0.13). There was no significant difference between treatments (Drug-Placebo: -0.12 (-0.28, 0.04); p=0.1504). Seven patients did show improvement in VA of 0.1 logMAR or more on drug and not placebo, and 5 patients showed improvement of VA of 0.3 logMar or more on drug and not placebo.

Conclusions:
This study failed to find a statistically significant benefit of dalfampridine in NAION, an infarct in the optic nerve. However, 7 patients showed improvement in VA of 0.1 logMAR or more on drug and not placebo, and 5 patients showed improvement of VA of 0.3 logMar or more on drug and not placebo. This suggests a possible subgroup of "responders" similar to the findings of dalfampridine in MS. A larger and perhaps longer clinical trial might clarify whether dalfampridine is beneficial for a subgroup of NAION patients.

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Keywords: Optic neuropathy, Vascular disorders

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Poster 177
Hereditary optic neuropathies in childhood

Christophe Orssaud[1], Matthieu Robert[2], Dominique Bremond Gignac[3]

[1]HEGP UF of Ophthalmology, Paris, France, Metropolitan, [2]Hôpital Necker Enfants Malades, Paris, France, [3]Hôpital Necker Enfants Malades / OPHTARA, Paris, France

Introduction:
Knowledge of the genetic mechanisms underlying hereditary optic neuropathies has increased over the past two decades. Identified genes are mainly related to forms that begin after adolescence. However, hereditary optic neuropathies can begin from early childhood and may then exhibit specific clinical features. We report a series of patients with early-onset hereditary optic neuropathies to determine their clinical and genetic characteristics.

Methods:
Patients with hereditary optic neuropathy with an onset before the age of 14 were identified. Presentation at onset, evolution of visual acuity, fundus characteristics, visual field and OCT when available were analyzed. Systemic associations were looked for.

Results:
Thirty seven patients were included. Leber hereditary optic neuropathy was confirmed in 12 cases, Wolfram syndrome in 8, dominant optic atrophy in 12. In 5 patients, including two siblings, no gene could be identified. In a group of 20 patients, the mean visual acuity was 0.86 (+/- 0.31) LogMAR at the age of 15 (or at his last measurement if the patient was younger). Complete optic atrophy was usual at the end of adolescence. Apart from abnormalities associated with Wolfram syndrome, deafness and cardiac abnormalities were observed in 6 patients.

Conclusions:
Although most hereditary optic neuropathies begin after adolescence, onset before the age of 14 is not exceptional. It account for 28.1% of all our hereditary optic neuropathies. Early visual impairment is expected in Wolfram syndrome. But Leber's hereditary optic neuropathy and dominant optic atrophy were also frequent diagnosis in this population. They each represent 1/3 of our series. Functional prognosis and clinical and paraclinic abnormalities are as severe as in forms with a later onset. Visual acuity is usually severely impaired at the end of adolescence, even in cases of dominant optic atrophy or Wolfram syndrome. Central scotoma was always observed. Apart from Wolfram's syndrome, early-onset neuropathies were frequently isolated.

References: None.

Keywords: Optic neuropathy, Genetic Disease, Pediatric neuro-ophthalmology

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Poster 178
Clinical profile of Pediatric Optic Neuritis - Data from the Indian Sub continent

Preeti Patil Chhablani[1], Akshay Badakere[1]

[1]L V Prasad Eye Institute, Hyderabad, Telangana, India

Introduction:
Pediatric Optic Neuritis is distinctly different from that in adults however there is a lack of data about this entity. Also, we know that adult optic neuritis also has shown significant racial and regional differences. However, there is scant data from the Indian sub continent on optic neuritis in children. This study aims to describe the clinical profile and visual prognosis in bilateral pediatric optic neuritis presenting to a tertiary care eye institute in India.

Methods:
A retrospective review of all patients under the age of 18 years diagnosed to have bilateral optic neuritis during the period from January 2010 to December 2014 was done.The main outcome measure studied was visual acuity at final follow up. Possible factors responsible for lack of visual recovery and underlying systemic conditions were analyzed.

Results:
A total of 44 patients (51% females) were included. Mean age was 12.3 years. Presenting vision ranged from 20/40 to NLP with 63 % having less than 20/200 vision. 47.7% had disc edema at presentation and 9 % has some degree of optic disc pallor at presentation. All patients were treated with intravenous methyl prednisolone. 65% recovered to a final acuity of better than 20/50. Patients with disc edema fared better than those with pallor. Time to presentation negatively corelated with the final visual outcome as did age at presentation. Younger age at presentation and those who presented late to the clinic had poorer outcomes. Baseline visual field changes and MRI findings did not affect the final visual acuity.

Conclusions:
In children presenting with bilateral optic neuritis, prompt treatment with intravenous steroids can have a favourable outcome.

References: None.

Keywords: Optic neuropathy, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 179
METHANOL TOXICITY , BANGLADESH PERSPECTIVE

Dr. Sarwat Rahman[1]

[1]*Bangladesh Eye Hospital Ltd, Dhaka, Bangladesh*

Introduction:
Methanol intoxication may often cause mortality and ocular morbidity. Irreversible visual loss may occur with in hours to days after ingestion. If treatment is delayed beyond the first hours, permanent damage to optic nerve pathways may occur. We report on some cases of methanol induced blindness treated with steroids and vitamin B-1.

Methods:
Patients attending the neuro-ophthalmic clinic in our hospital between December 2012 to January 2015

Results:
All were male between 25 to 65 years . They came with sudden visual loss after ingestion of huge amount of local alcohol, most of the patient came from the different part of the country after treating in primary healthcare center. Patient came to our clinic as soon as 12 hours to 21 days after ingestion . all the patient irrespective of time of presentation were treated with Intravenous methyl prednisolone 1gm in 500 ml ringer lactate slowly over 2 hours followed by oral prednisolone 1mg/kg for 5days then tapered in 4 weeks. Intramascular hydroxycobalamine 1000 ml twice weekly for 3 weeks and oral pentoxyphyline (400mg) daily for 6 weeks. Presentation within 12 hours was also treated in ICU for metabolic acidosis. For the rest of the case treatment with ethanol or haemodialysis were too late to be effective as the patients acid base balance was normal.

Conclusions:
Combination of steroied and vitamine B was highly effective in treating severe methanol optic neuropathy . whether using only one of the drugs might be sufficient or not but as the risk of permanent blindness is high , we use this combination in the event of methanol intoxication.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 180

Optic Nerve Head Edema (ONHE) Among Patients Presenting to Emergency Department In The FOTO-ED Study

Virender Sachdeva[1], Caroline Vasseneix[1], Rabih Hage[1], Samuel Bidot[1], Lindsay Clough[2], David Wright[3], Beau Bruce[4], Valerie Biousse[5], Nancy Newman[6]

[1]Neuro-ophthalmology Unit, Department of Ophthalmology, Emory University, Atlanta, Georgia, USA, [2]Emory University School of Medicine, Altanta, Georgia, USA, [3]Department of Emergency Medicine, Emory University, Atlanta, Georgia, USA, [4]Department Ophthalmology, Neurology and Epidemiology, Emory University, Atlanta, Georgia, USA, [5]Department of Ophthalmology and Neurology, Emory University, Atlanta, Georgia, USA, [6]Department of Ophthalmology, Neurology and Neurological Surgery, Emory University, Atlanta, Georgia, USA

Introduction:

The FOTO-ED study[1-3] showed that non-mydriatic retinal photography in the emergency department (ED) is feasible and may improve patient care and outcomes when systematically performed in patients with a chief complaint of headache, neurologic deficit, visual loss, or elevated blood pressure (BP). Finding ONHE is particularly important in this patient population[4,5]. The purpose of this study was to describe the characteristics of the patients diagnosed with ONHE in FOTO-ED phases.

Methods:

Subgroup analysis of patients diagnosed with ONHE in all 3 phases of the prospective FOTO-ED study. The ONHE subgroup was compared to the non-ONHE group using logistic regression.

Results:

The FOTO-ED studies included 1429 patients, among whom 36 (2.5%, 95% CI:1.8-3.5%) had ONHE [median age, 31 (IQR:27-40), women, 71.4%, African-Americans, 77.8%]. ONHE was bilateral in 26/36 and unilateral in 10/36 patients. Chief complaints included headaches (18/36), acute visual deficit (10/36), acute neurological deficit (4/36), elevated BP (2/36), both headaches and acute visual deficit (2/36). Final diagnoses were IIH (18/36), optic neuritis (3/36), CSF shunt malfunction/infection (3/36); 2 each with brain tumor, non-arteritic ischemic optic neuropathy, cerebral venous sinus thrombosis, and malignant hypertension; and 1 each with meningitis, cerebral infarction, neurosarcoidosis, and retinopathy. 15/36 patients were sent to the ED with a diagnosis of ONHE already made by the referring physician; fundus photographs were the first to establish ONHE in 21/36 (58%) while in the ED; the ED providers identified the presence of ONHE in only 5/21 (23.8%) of these patients. Knowledge of ONHE led to a change in final diagnosis for 10/36 patients.

Conclusions:

One in 40 patients (2.5%) presenting to the ED with a chief complaint of headache, neurologic deficit, visual loss, or elevated BP had ONHE. The identification of ONHE altered the patient disposition and contributed to the final diagnosis, confirming the importance of funduscopic examination in the ED.

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Keywords: Optic neuropathy, High intracranial pressure/headache

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Poster 181

Patients with supratentorial neoplasms have increased IOP but similar optic nerves compared with control subjects

Zainab Shirazi[1], Judy Chen[1], Martin Nicholas[1], Heather Moss[2]

[1]University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA, [2]Stanford University School of Medicine, Stanford, California, USA

Introduction:

Patients with malignant brain tumors(MBT) are at risk for papilledema due to elevated intracranial pressure and glaucoma due to elevation of intra-ocular pressure(IOP) related to corticosteroid treatment. The purpose of this study was to establish the prevalence of these secondary optic neuropathies in patients with MBT.

Methods:

Adult subjects with supratentorial MBT sparing the optic nerves, chiasm and tracts(n=32) and control subjects(n=24) of similar age underwent SLO and OCT imaging of the optic nerve heads and peripapillary retinal nerve fiber layer(RNFL)(Heidelberg Spectralis) to screen for papilledema and glaucomatous optic neuropathy. IOP assessed for glaucoma risk. Pinhole visual acuity(VA) measured visual function. Vision specific quality of life(National Eye Institute Visual Functioning Questionnaire(VFQ-25)) and symptoms(MD Anderson Symptom Inventory-Brain Tumor(MDASI-BT)) were assessed.

Results:

Neither SLO nor OCT images suggested papilledema in any subject. Average RNFL did not differ between groups(p=0.91,generalized estimating equations(GEE)). IOP was higher in MBT than control subjects(7.3mm Hg,CI[4.3, 10.3],p24mmHg). IOP was neither associated with optic nerve cupping nor RNFL thinning. VA was worse in MBT subjects (p<0.0005,GEE) with 6/31(19.4%) MBT and no control subjects having best VA worse than 20/40. 11/32(34.4%) MBT versus 1/24(4.2%) control subjects had VFQ25<93.45(p=0.008, Fisher's exact). 17/32(53%) MBT versus 4/23(17%) control subjects reported visual symptoms on the MDASI-BT(p=0.007,Fisher's exact). Survey scores were neither associated with VA nor OCT measures.

Conclusions:

In this cross-sectional study of 32 adults with supratentorial MBT not affecting the optic nerves, no cases of papilledema were detected. Though IOP was elevated in brain tumor patients there was no evidence of associated glaucomatous optic neuropathy. Though we find that adult patients with supratentorial MBT are more likely to report visual symptoms and diminished vision specific quality of life than normal subjects, secondary optic neuropathies do not account for this.

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Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Tumors

Financial Disclosures: The authors had no disclosures.

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Poster 182

Abnormal retinal ganglion cell physiology in mice with neurofibromatosis, optic pathway gliomas, and visual loss

Steven Stasheff[1]

[1]*Children's National Health System & National Eye Institute, Bethesda, Maryland, USA*

Introduction:
A longstanding mystery complicates the care of patients with a common childhood neurologic disease causing severe visual loss, neurofibromatosis type 1 (NF1). Namely, among the ~20% of young children with NF1 who develop optic pathway gliomas (OPGs), the degree of visual loss or recovery often is not readily predicted by tumor characteristics or treatment response. We investigated whether disruptions of retinal ganglion cell (RGC) physiology might help explain this striking disparity.

Methods:
We used in vitro multielectrode recording to sample spontaneous activity and responses of individual RGCs to broad illumination, in retinas isolated from transgenic mice with inducible knockout of the neurofibromin (Nf1) gene selectively in glial precursor cells: Nf1-hGFAP-CKO (or NF1-OPG) mice. These mice typically develop prominent OPGs by 4-6 months of age, so we recorded RGC activity at this stage of OPG development. We performed histologic analysis of the number and types of surviving axons in the optic nerves of the same retinas.

Results:
A lower number of active RGCs per retina were detected in NF1-OPG mice than in littermate controls. In addition, surviving RGCs on average exhibited a higher spontaneous discharge rate but less vigorous responses to the onset or offset of moderately intense full field illumination.

Conclusions:
The discovered abnormalities in RGC function suggest that OPGs may disrupt the integrity of the "message" the retina sends the brain about the visual world prior to the loss of RGCs themselves. More detailed analysis of particular RGC types susceptible to this degradation of neural signaling, the developmental stages at which such critical changes take place, and the corresponding characteristics of optic pathway gliomas that most reliably predict visual loss. Ideally, these principles can be readily translated to clinical testing that predicts and detects visual dysfunction earlier than current methods.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Higher visual functions, Pediatric neuro-ophthalmology, Optic neuropathy

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Poster 183
Overdiagnosis of optic neuritis

Leanne Stunkel[1], Gregory Van Stavern[2], Nathan Kung[2], Collin McClelland[3]

[1]Washington University School of Medicine in St. Louis Department of Neurology, St. Louis, Missouri, USA, [2]Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA, [3]University of Minnesota, Minneapolis, Minnesota, USA

Introduction:
This is a study to assess the incidence of, and characterize factors contributing to, overdiagnosis of optic neuritis in patients seen by neuro-ophthalmology at one tertiary care center. Accurate diagnosis of optic neuritis facilitates appropriate work-up, early diagnosis of multiple sclerosis, and access to follow-up. Alternative diagnoses may be mistaken for optic neuritis, leading to unnecessary MRIs, lumbar punctures (LPs), treatments, loss of time, and expense.

Methods:
New patient encounters between January 2014 and October 2016 were retrospectively reviewed to identify patients referred with a diagnosis of optic neuritis. Definite diagnosis was determined by experienced neuro-ophthalmologists. For cases found not to have optic neuritis, the Diagnosis Error Evaluation and Research (DEER) taxonomy tool was applied to identify the type of diagnostic error.

Results:
122 patients were referred for optic neuritis during the study period. 50 (41%) were confirmed to have optic neuritis. 72 (59%) patients had an alternative diagnosis. The most common were headache and eye pain, functional visual loss, non-arteritic anterior ischemic optic neuropathy (NAION), and other optic neuropathies. The most common diagnostic errors were in eliciting or interpreting critical elements of history; 24 of 72 (33%). The second most common were errors weighing or considering alternative diagnoses; 23 of 72 (32%). The next most common were errors weighing or interpreting physical exam findings; 15 of 72 (21%). Other errors were due to misinterpretation of diagnostic tests; 10 of 72 (14%). In patients who did not have optic neuritis, 12 (17%) had negative MRI results preceding the referral. 8 (7%) inappropriately received IV steroids. 12 (17%) had received LP.

Conclusions:
Optic neuritis was overdiagnosed in 59% of patients referred, prompting unnecessary and costly diagnostic tests, procedures, and treatments. The most common errors were overreliance on a single item of history and failure to consider alternative diagnoses.

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Keywords: Optic neuropathy, Neuroimaging, Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Non-organic visual disorders

Financial Disclosures: The authors had no disclosures.

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Poster 184
Vaccines and Optic Neuritis: a systematic review

Mia Topsøe Mailand[1], Jette Lautrup Frederiksen[2]

[1]University of Copenhagen, Copenhagen, Denmark, [2]Department of Neurology and University of Copenhagen, Glostrup, Denmark

Introduction:
Vaccinations is often the most effective tool against some disease known to mankind. Case reports of optic neuritis following vaccination can lead to distrust in the safety of vaccines. Therefore it is important to gather existing knowledge on vaccines and optic neuritis in order to not confuse temporal and causal relations. This study is a literature review on the role of vaccines regarding the risk of developing optic neuritis.

Methods:
A systematic literature review on the database PubMed using the Mesh terms: ”vaccination”/”immunization”/”vaccines” and ”optic neuritis”. Relevant studies and reviews were included, single case stories were excluded.

Results:
Thirteen relevant studies and three reviews on vaccination and ON were identified.

Conclusions:
The summarized results of the studies did not raise sufficient evidence to back up a positive association between optic neuritis and vaccination against HBV, HAV, HPV, MMR, influenza, variola, varicella, diphtheria, tetanus, pertussis, anthrax, meningococcal, pneumococcal or typhoid. However, since the number of identified studies of vaccines and optic neuritis was limited, a complete exclusion of causation cannot be made.

References: None.

Keywords: Demeylinating disease, Optic neuropathy

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Poster 185

Optic Neuritis Associated with Anti-Myelin-Oligodendrocyte Glycoprotein Antibodies: a Case Series

Emilie Tournaire-Marques[1], Cecile Dulau[2], Camille Seguy[1], Marie-Noëlle Delyfer[1], Jean-François Korobelnik[1], Marie-Bénédicte Rougier[1]

[1]Ophthalmology, 33000 Bordeaux, France, [2]Neurology, Bordeaux, France

Introduction:

Optic neuritis associated with antibodies against myelin-oligodendrocyte glycoprotein (MOG) is a sight threatened disease recently identified. The goal of this study was to describe the clinical features, the MRI findings and the response to steroid therapies in a series of patients suffering from an optic neuritis associated with MOG antibodies.

Methods:

Between February 2015 and July 2016, we consecutively enrolled 7 patients with optic neuritis and positive MOG antibodies with negative anti aquaporin-4 antibodies. We retrospectively reviewed the clinical symptoms, cerebrospinal fluid (CSF) data, and MRI findings of these patients.

Results:

2 women and 5 men were enrolled. Mean age was 41 years (16-61 yo). All patients presented an unilateral painful sub-acute visual loss. In 5 patients visual acuity was less than 20/200. Fundus examination showed an optic nerve swelling in 5 patients, and the 2 others presented a bilateral optic nerve atrophy. In all patients the neurological examination was normal. When available (5 patients), the CSF analysis demonstrated the absence of oligoclonal band. Brain MRI demonstrated an abnormal T2 hyperintensity and enhancement involving the optic nerve in all patients, and in 6 patients the lesion extended from the orbit to the chiasma. The treatment consisted in intravenous methylprednisolone. Plasmapheresis therapy was performed in 2 patients. Visual acuity improved in 6 patients. During the study, a relapse occurred in the same eye in 2 patients, and in the other eye in 4 patients. Rituximab was introduced in 5 patients. No recurrence was observed in any patient treated with rituximab.

Conclusions:

Anti-MOG optic neuritis is a severe entity which must be identified very quickly in order to avoid the contralateral damage and a potential blindness. The clinical symptoms, CSF and MRI data differ from those encountered in multiple sclerosis. Anti-MOG antibodies must be systematically measured in case of atypical and/or relapsing optic neuritis.

References: None.

Keywords: Demeylinating disease, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 186
Pediatric Leber Hereditary Optic Neuropathy (LHON): A Literature Review

Scott Uretsky[1], Sabrina Bentobji[1], Isabelle Pengue Koyi[1], Nancy Newman[2]

[1]GenSight Biologics, Paris, France, [2]Dept. of Ophthalmology, Neurology & Neurological Surgery, Emory University, Atlanta, Georgia, USA

Introduction:
Visual prognosis in LHON is dependent on the primary causative mtDNA mutation and the age at onset of vision loss. Pediatric LHON patients are reported to have a better visual prognosis with decreasing age at onset. This impacts the risk-benefit assessment when determining appropriate inclusion criteria for therapeutic trials. We reviewed the literature to determine age-specific visual prognosis in pediatric LHON patients.

Methods:
A literature search was performed of all English-language articles on LHON that included information on patient age at onset. Articles included were limited to those reporting molecular diagnoses with one exception (van Senus 1963). Pertinent features collected included age at onset and final visual outcomes. Analyses were focused on the most common G11778A ND4 mutation.

Results:
ND4 LHON is not uncommon in patients <18 years, representing 21-40% of reported cohorts. 15-17-year-olds represent the majority of the pediatric ND4 LHON patients (11-30% of all patients) and visual prognosis at this age is identical to those aged ≥18 years. There is limited data regarding prognosis in those aged 12-14 years. Pediatric ND4 LHON patients ≤12 years (and especially those <10 years) have a better visual prognosis and often present with a slowly progressive form of visual loss, the latter having a better prognosis than the acute onset form. Even those patients <10 years with acute bilateral loss have high rates of spontaneous recovery.

Conclusions:
Pediatric ND4 patients ≤12 years-old have better visual outcomes compared to older patients. Exclusion of this age group from trials of experimental therapies is appropriate until establishment of clear risk-benefit profiles. Additional data is needed for the 12-14-year-old group. Patients >15 years-old share the same visual prognosis as adults, as acknowledged by the recent regulatory approval for their inclusion in the RESCUE and REVERSE ND4 LHON gene therapy trials.

References: None.

Keywords: Genetic Disease, Pediatric neuro-ophthalmology, Optic neuropathy

Financial Disclosures: GenSight Biologics (Sponsor) Employee

Grant Support: None.

Poster 187

Characteristics And Visual Outcome Of Neuromyelitis Optica Spectrum Disorder-Related Optic Neuritis:Comparison Between Thais And Americans

Kavin Vanikieti[1], Anuchit Poonyathalang[1], Panitha Jindahra[1], Peggy Bouzika[2], Joseph Rizzo[2], Dean Cestari[2]

[1]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [2]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, USA

Introduction:
Neuromyelitis optica spectrum disorder (NMOSD) is more common in Asian population. Few studies have examined the features of optic neuritis (ON) within NMOSD in different racial populations. We compared the clinical characteristics and long-term visual outcome of patients with NMOSD-related ON between a Thai and an American cohort.

Methods:
Medical records of 16 consecutive patients with NMOSD-related ON seen at a single American tertiary referral center between 2006-2015 were reviewed and compared with those of 16 consecutive patients seen at a single Thai tertiary referral center between 2010-2016. This represented the total number of NMOSD-related ON patients seen during that time. Data collected included gender, race, age of ON onset, and visual acuity and visual fields. Aquaporin 4 (AQP4) antibody seropositivity was also recorded.

Results:
All patients within the Thai cohort were Asians, while the American cohort consisted of 12 Caucasians, 2 Hispanics, 1 Asian and 1 Black patient. ON occurred in 21 eyes, with a total of 19 episodes in the Thai cohort, while 26 eyes were affected with a total of 25 episodes in the American cohort. AQP4-antibody was positive in all patients except for 2 American patients. There was no difference between the two cohorts with respect to gender ratio, age of ON onset, development of swollen optic disc, initial visual acuity and visual fields, presence of pain and laterality in each episode, anterior visual pathway segment involvement based on neuroimaging findings, mean time from symptom development to acute treatment, final visual acuity and visual fields. Azathioprine was the most common immunosuppressive treatment (75%) used among Thai patients in contrast with rituximab (62.5%), which was preferred among American patients.

Conclusions:
Despite the rarity of NMOSD-related ON among the predominantly Caucasian American population, the clinical characteristics and long-term visual outcome were not statistically different from those observed in the Thai population.

References: None.

Keywords: Demeylinating disease, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 188

Evaluation of cardiovascular risk factors in incidence and progress of non-arteritic anterior ischemic optic neuropathy

Haiyan Wang[1], Yusheng Wang[1], Fang Du[2]

[1]department of ophthalmology, xijing hospital, xi'an, China, [2]department of Neurology,xijing hospital, xi'an, China

Introduction:
This study aim to evaluate whether cardiovascular risk factors could influence the incidence and severity of non-arteritic anterior ischemic optic neuropathy (NAION).

Methods:
A total of 74 eyes (74 patients) newly diagnosed with NAION and 74 matched participants (as control) were included. Cardiovascular risk factors including the level of blood homocysteine (HCY), lipid, hemagglutination, folic acid and vitamin B12 were measured. Carotid doppler ultrasound was performed to evaluate the hemodynamic parameters and atherosclerosis. The difference in cardiovascular risk factors and abnormality of carotid were compared between NAION patients and non-NAION controls, and were assessed whether they have effect on severity of visual field defect.

Results:
Compared to controls, increased level of HCY (22.5±15.4 vs 11.1±8.2 umol/L, P0.05) were presented as well as level of folic acid(P>0.05), hemagglutination(P>0.05) and abnormality of carotid(P>0.05). The average of mean deviation (MD) of visual field was 16.6±7.5 dB in NAION patients. None of above was risk factors of MD by multiple lineal regression analysis.

Conclusions:
Hyperhomocysteinemia, hyperlipemia and reduced blood vitamin B12 were risk factors of incidence of NAION, however, they have no relationship with severity of visual field defect of NAION.

References: None.

Keywords: Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 189

Preliminary Baseline Characteristics of Patients with LHON Enrolled in RESCUE and REVERSE Gene Therapy Trials

Patrick Yu-Wai-Man[1], Nancy Newman[2], Robert Sergott[3], Molly Scannell Bryan[4], Valerio Carelli[5], Thomas Klopstock[6], Mark Moster[7], Alfredo Sadun[8], Jose-Alain Sahel[9], Catherine Vignal[10], Scott Uretsky[11]

[1]Wellcome Trust Centre Newcastle Eye Centre Moorfields Eye Hospital UCL, Newcastle upon Tyne, United Kingdom, [2]Dept. of Ophthalmology, Neurology and Neurological Surgery Emory University, Atlanta, Georgia, USA, [3]Neuro-Ophthalmology Service, Wills Eye Hospital, and Optic Nerve Research Center, Philadelphia, Pennsylvania, USA, [4]Optic Nerve Research Center and University of Illinois at Chicago, Chicago, Illinois, USA, [5]IRCCS Institute of Neurological Sciences; Unit of Neurology, University of Bologna, Bologna, Italy, [6]Dept. of Neurology, Friedrich-Baur-Institute, Munich, Germany, [7]Neuro-Ophthalmology, Wills Eye Hospital,Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [8]Doheny Eye Institute and Department of Ophthalmology, UCLA, Los Angeles, Los Angeles, California, USA, [9]Sorbonne Universités IDV CHNO Fondation Rothschild Dept of Ophtho Univ of Pittsburgh, Paris, France, [10]CHNO des Quinze-Vingts and Fondation Rothschild, Paris, France, [11]GenSight Biologics, Paris, France

Introduction:

RESCUE (NCT02652767) and REVERSE (NCT02652780) are Phase III, randomized, double-masked, sham-controlled trials of rAAV2/2-ND4, an intravitreally-injected gene therapy vector for the treatment of ND4 LHON. RESCUE patients have vision loss for ≤6 months and REVERSE patients from >6 months to 1-year.

Methods:

Inclusion criteria included age ≥15-years, presence of the G11778A-ND4 mutation and at least CF vision. Concurrent idebenone use was prohibited. We compared baseline characteristics of the first consecutively-recruited 10 RESCUE and 11 REVERSE patients.

Results:

16/21 were men (RESCUE 8/10, REVERSE 8/11). Mean (range) age (years): RESCUE 39.4 (20-69); REVERSE 36.2 (20-64); (p=0.7312). Mean (range) vision loss duration (days) for all eyes: RESCUE 128 (0-179); REVERSE 294.9 (184-364); p<0.0001. 5/21 patients had simultaneous onset. Two eyes had >20/20 vision at baseline in RESCUE; all eyes were <20/400 in REVERSE.   Mean (range) LogMAR at baseline for all eyes: RESCUE 1.109 (-0.2-2.11); REVERSE 1.696 (1-2.26). For best-/worst-seeing eyes: RESCUE: best 0.78 (-0.2-1.5), worst 1.438 (0.6-2.11); REVERSE best 1.586 (1-2.16), worst 1.806 (1.5-2.26). Combining all eyes of RESCUE/REVERSE patients revealed a significant positive correlation (squarerootR2=0.571) between vision loss duration and baseline LogMAR (p<0.0001). Of 82 baseline HVF, 34% were reliable; mean MD was -12.2 (RESCUE) and -27.8 (REVERSE); p=0.0002. Mean (SD) total macular volume (mm3) was smaller in REVERSE (7.7 (0.3) vs. 8.5 (0.4); p< 0.0001) driven by thinning of the RNFL and GCL. A statistically significant relationship existed between retinal metrics and vision, with decreases in RNFL and GCL associated with worse vision (RNFL: p=0.0005; GCL: p=0.0004).

Conclusions:

In these preliminary analyses, no age/gender differences were seen between the studies, but there were clinically significant differences in baseline LogMAR for all and best-/worst-seeing eyes, with the expected positive correlation between vision loss duration and worse baseline visual acuities. REVERSE patients demonstrated thinner RNFL, GCL and macular volumes and worse acuity at baseline.

References: None.

Keywords: Genetic Disease, Optic neuropathy

Financial Disclosures: Consultant for GenSight Biologics

Grant Support: None.

Poster 190

Spontaneous Recovery of Quality of Life in Leber Hereditary Optic Neuropathy with G11778A Mutation

Xiaojun Zhang[1], Shilei Cui[1], Hanqiu Jiang[1], Jingting Peng[1]

[1]Beijing Tongren Hospital, Capital Medical University, Beijing, China

Introduction:

Leber hereditary optic neuropathy(LHON) is characterized by progressive bilateral central vision loss leading to impaired vision related quality of life. The aim of this study is to evaluate the natural history of vision related function in daily living activities.

Methods:

Genetically confirmed LHON patients with G11778A mutation were prospectively evaluated with Visual Function Index 14 Questionnaire (VF-14) at 6 months, 1-year, and 3-year follow-up time-points after the involvement of the second eye.

Results:

Fifty-five LHON patients with G11778A mutation were included, with mean age of 16.3years (SD 6.1,range 10–38 years). The mean VF-14 scores at 6months, 1-year and 3-year follow-up was 18.0 (SD 19.2, range 0.0−85.4), 19.9 (SD 20.0, range 0.0−85.4) and 20.7 (SD 20.2, range 0.0–85.4) respectively, which showed statistically significant improvement comparing 6-months with 1-year and 1-year with 3-year followup($P<0.001$, $P<0.001$). The items that were significantly improved at 1-year compared with the 6 months follow-up included seeing steps or curbs or stairs ($p<0.01$), doing handiwork ($p<0.05$), playing sports ($p<0.05$), cooking ($p<0.01$), and watching television ($p<0.05$). At 3-year follow-up, only scores for cooking ($p<0.05$) and watching television ($p<0.05$) further significantly improved compared to those at 1-year follow-up. The three items that did not show significant improvement during 3 years of follow up were reading small print, reading a newspaper or book, and reading signs.

Conclusions:

Although permanent central visual loss is the main clinical feature of LHON patients with the G11778A mutation, some vision related function of daily living activities, such as seeing curbs or stairs, cooking, watching television and playing sports, showed spontaneous improvement over time. Functions requiring more central vision such as reading small print, newspaper or book and signs remained the most difficult tasks of daily living for LHON patients with G11778A mutation.

References: 1. Kirkman MA, Korsten A, Leonhardt M, Dimitriadis K, De Coo IF, et al. Quality of life in patients with Leber hereditary optic neuropathy. Invest Ophthalmol Vis Sci. 2009;50:3112–3115. 2. Lam BL, Feuer WJ, Schiffman JC, Porciatti V, Vandenbroucke R, et al. Trial end points and natural history in patients with G11778A Leber hereditary optic neuropathy: preparation for gene therapy clinical trial. JAMA Ophthalmol. 2014;132:428–436.

Keywords: Optic neuropathy, Genetic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 191
National-wide, Multiple-center Optic Neuritis Study in Mainland China

Xiaojun Zhang[1], Jingting Peng[2], Shihui Wei[3], Yonghua Hu[4], China Optic Neuritis study Group China Optic Neuritis study Group[5]

[1]Beijing Tongren Hospital, Capital Medical University, Beijing, China, [2]Department of Neurology, Beijing Tongren Hosipital, Capital Medical University, Beijing, China, [3]Department of ophthalmology, The General Hospital of People's Liberation Army, Beijing, China, [4]School of Public Health, Peking University, Beijing, China, [5]The General Hospital of People's Liberation Army, Beijing, China

Introduction:
Single-center, small sample studies of optic neuritis (ON) provided inconsistent results about clinical features and etiological types of optic neuritis (ON) in Mainland China.

Methods:
ON cases were collected both retrospectively and prospectively in 21 university hospital centers throughout Mainland China from 2010 to 2013. Demographic features were summarized and the etiological types of ON were classified according to current concept and revised criteria.

Results:
2305 ON included cases were referred from all 31 provinces/autonomous regions in Mainland China, of which 63.5% were female. Age ranged 2-86 years with a mean of 35.8 years. Brain, spinal MRI, AQP4-IgG and lumbar puncture were performed in 1605(69.6%), 471 cases (20.4%), 266 (11.5%) and 368 (16.0%) cases respectively. Syphilis, HIV infection and ANA were screened in 1882(81.6%), 1886(81.8%) and 1481(64.3%) cases respectively. 95 cases (4.1%) cases met the revised diagnostic criteria of MS were classified as MS-ON . 242 (10.5%) cases met diagnostic criteria for neuromyelitis optica spectrum disorders (NMOSD) were classified as NMOSD-ON. 198 (9.7%) were classified as autoimmune ON(A-ON) either due to ANA positivity(167 cases) or comorbid systemic vasculitis (6 cases of SLE and 25 cases of Sjogren syndrome). Infectious ON was identified on 38 cases (1.6%) including 33 cases of syphilitic ON, 2 cases with acute HIV infection and 3 cases of tuberculosis meningitis. Rare conditions associated with ON included Bechet disease, Ankylosing spondylitis, rheumatoid arthritis, Wegner granulomatosis and sarcoidosis. The remaining 1715 cases (74.4%) were classified as isolated idiopathic ON (I-ION), of which 12.7% still had visual acuity remain at 20/200 or worse at 3 months follow-up.

Conclusions:
With limited accessibility of AQP4-Ab and spinal cord MRI, NMOSD-ON was still found much more common than MS-ON. Relatively common autoimmune ON and poor visual recovery in isolated ON further suggested their close correlation with NMOSD.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

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Poster 192
Postural Instability in Children with Amblyopia and Strabismus Only without Amblyopia

Anat Bachar Zipori[1], Sharon Cushing[2], Linda Colpa[3], Karen Gordon[4], Agnes Wong[1]

[1]Department of Ophthalmology and Vision Sciences, Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada, Canada, [2]Department of Otolaryngology – Head and Neck Surgery, Hospital for Sick Children, Toronto, Canada, [3]Eye Movement and Vision Neuroscience Laboratory, Hospital for Sick Children, Toronto, Canada, [4]Archie's Cochlear Implant Laboratory, Hospital for Sick Children, Toronto, Canada

Introduction:
Vision plays an important role in controlling posture and balance. Reduced postural control has been reported in children with strabismus only, but not much have been reported specifically in amblyopia. The purpose of this study is to investigate whether children with amblyopia have reduced balance compared to children with strabismus only without amblyopia and healthy controls.

Methods:
Fifty-six participants were included: 15 patients with unilateral amblyopia from strabismus, anisometropia, or mixed mechanism (mean age 8.5 ±2.0 SD, females 60%), 19 with strabismus only without amblyopia (mean age 10.5±3.5 SD, females 36.8%), and 22 healthy controls (mean age 10.6 ±3.2 SD, females 27.3%). The primary outcome was the balance subtest score of the Bruininks-Oseretsky Test of Motor Proficiency 2 (BOT2).

Results:
Mean age and gender frequency were not statistically significant among the groups (age p=0.120, gender p=0.350). The mean age- and gender-adjusted BOT2 Balance Scores were substantially reduced in the amblyopia group (mean score 9.0 ± 3.0) and the strabismus only without amblyopia group (mean score 8.6± 2.4 SD) compared to healthy controls (mean score 18.9 ± 4.1) (p< 0.0001), but no statistical difference was demonstrated between the patients' groups.

Conclusions:
Our findings suggest that normal vision plays an important role in the development and maintenance of balance control. Amblyopia does not only affect vision, balance is also reduced when normal binocular vision is disrupted in childhood.

References: None.

Keywords: Vestibular, Ocular Motility, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 193
Papilledema caused by non-ocular disease

Fang Du[1], Haiyan Wang[2]

[1]Department of Neurology, Xijing hospital, xi'an, China, [2]department of ophthalmology, xi'an, China

Introduction:
The study aims to investigate characteristics and causes of papilledema caused by non-ocular disease.

Methods:
Consecutive outpatients with papilledema were included in this study, which were excluded with uveitis, scleritis, retinal vein occlusion, optic neuritis, non-arteritic anterior ischemic optic neuropathy, diabetic neuropathy and chronic low intraocular pressure. All patients were examined by visual field, MRI, blood test, blood pressure, blood glucose and cerebrospinal fluid (CSF) test. The characteristics and composition of entities were investigated and visual function was evaluated.

Results:
A total of 67 cases (124 eyes) of 25 male and 42 female were included in this study, 10 cases were unilateral and 57 cases were bilateral. The mean age was 41.7. Of all, 24 cases were with benign intracranial hypertension, 14 with intracranial tumor, 10 with thrombosis of intracranial venous sinus, 4 with progressive glomerulonephritis, , 3 with leukemia, 3 with intraorbital tumor, 2 with meningitis, 2 with cerebral cysticercosis, 2 with antiphospholipid syndrome, 1 with intracranial abscess, 1 with mycotic infection in paranasal sinuses, 1 with idiopathic papilledema. Of all, 47 cases primarily presented with ocular symptoms and 95.1% cases reported with ocular symptoms. The best corrected visual acuity was from non-light perception to 1.0. Visual field test were performed in 91 eyes, with most common visual field lesion was the enlargement of the blind spot(36.2%) and general constriction(27.4%).

Conclusions:
In addition to intraocular disease, intraccranial and systemic disease can also induce papilledema, of all cases in this study, benign intracranial hypertension, intracranial tumor and thrombosis of intracranial venous sinus may be most common causes.

References: None.

Keywords: High intracranial pressure/headache, Pseudotumor Cerebri, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 194
Long-term visual outcome in children with cortical visual impairment (CVI)

Swati Handa[1], Seyed Ehsan Saffari[2], Mark Borchert[3]

[1]KK Women's and Children's Hospital, Sinagpore, Singapore, [2]Duke-NUS Medical School, Singapore, Singapore, [3]The Vision Center at Childrens Hospital Los Angeles, Los Angeles, California, USA

Introduction:
Determine the factors affecting lack of visual improvement in children with CVI

Methods:
Case records of all children born before 2010 with at least 4 follow up visits for CVI were reviewed retrospectively. Information on etiology of CVI, age at presentation, age at primary insult, age of onset of seizures, duration of seizures, frequency of seizures at the last follow up (≤ 2 or > 2 seizures per week), visual acuity (VA) at presentation and follow up visits, duration of follow-up, associated neurological and ophthalmological problems was recorded. VA was assessed qualitatively in 6 grades. Improvement in qualitative VA was noted as the difference between the grades of VA at presentation and the last follow-up visit. The outcome was calculated as a ratio of actual improvement to potential improvement in grades of qualitative VA. Multivariable analysis determined factors affecting lack of vision improvement in all children and in various etiological groups.

Results:
53 children with CVI presented at median age 13.6 months (range 2.9 – 76.4 months) and were followed up for a median duration of 5.8 years (1.1 – 16.3 years). CVI resulted from CNS malformation, hypoxic or inflammatory injury, seizures and combined causes in 9.4%, 15.1%, 24.5% and 51.0% children, respectively. Vision improvement was noted in 83% children. Lack of VA improvement was associated with older age at presentation in the whole cohort (Estimate ± SD, -0.006 ± 0.002; p = 0.039), hypoxic (-0.011± 0.004; p = 0.019), seizure (-0.007 ± 0.003; p = 0.024) and combined (-0.010 ± 0.004; p = 0.020) groups after adjusting for various factors. None of the other investigated variables were associated with lack of VA improvement.

Conclusions:
Most of the children with CVI showed improvement in vision. Older age at presentation was associated with lack of improvement in children with CVI.

References: None.

Keywords: Pediatric neuro-ophthalmology, Higher Visual Cortical functions

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 195
New Methods for Quantification of Visual Photosensitivity Threshold and Symptoms

Byron Lam[1], Jennifer Verriotto[1], Alex Gonzalez[1], Mariela Aguilar[1], Cornelis Rowaan[1], William Feuer[1], Jean-Marie Parel[1]

[1]*Bascom Palmer Eye Institute, University of Miami, Miami, Florida, USA*

Introduction:
Visual photosensitivity is a common subjective symptom found in many conditions including ocular disorders and neurological disorders such as achromatopsia, migraine and traumatic brain injury. We aimed to develop two novel reproducible quantitative assessments of visual photosensitivity.

Methods:
We designed and built the Ocular Photosensitivity Analyzer (OPA), a fully automated instrument with computer-generated voice to determine light intensity visual photosensitivity threshold (VPT) and developed the Visual Light Sensitivity Questionnaire-8 (VLSA-8), an eight-question survey to assess the presence and severity of photosensitivity symptoms. We evaluated the test-retest variability and obtained normative values of these two approaches in 35 healthy normal subjects, distributed evenly over 5 age groups from 8 to 60 years. Each subject underwent 2 test sessions, each with VLSQ-8, eye examination, and OPA, four weeks apart, between April 2015 and June 2016.

Results:
Log-transformed VPTs (log10 lux) and VLSQ-8 results were highly reproducible between the two sessions (VPT ICC=0.86(95%CI=0.71-0.93, binocular testing, VLSQ-items ICC range=0.53-0.87). No consistent significant differences in VPTs were found with monocular ($p=0.053$, session 1) or binocular testing ($p=0.26$). Subjects in age group >30-40 years had significant higher VPTs than other age groups ($p\leq0.011$) except when compared to the >40-50 age group ($p=0.11$). Photosensitivity symptoms assessed by the VLSQ-8 were generally low and highly reproducible with ≥88% of responses between the 2 sessions being within one category of each other.

Conclusions:
The VPT from the automated OPA and the VLSQ-8 evaluation of photosensitivity symptoms are sensitive, reproducible, quantitative measures that assess different aspects of photosensitivity. The new approaches are potential measures to characterize disease severity, monitor disease progression, and evaluate treatment efficacy.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Higher visual functions

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Poster 196
Marc Chagall's Presumably Synesthetic Character

Avinoam Safran[1], Nicolae Sanda[2], José-Alain Sahel[3]

[1]Institut de la Vision, Sorbonne Universités - Paris 6, Paris, France, [2]Institut de la Vision, Paris, France, [3]Institut de la Vision, Sorbonne Universités - Paris 6, Collège de France, Paris, France

Introduction:
Marc Chagall's (1887-1985) work is a poignant, poetic evocation of Jewish life in his native East European town, and an ode to love. Surprisingly, in a number of his paintings Chagall depicted faces of central characters in most unusual colors, such as green or blue. We assume that this feature expresses a form of personality-color synesthesia. In this variant of developmental synesthesia, viewing known faces elicit emotionally mediated color percepts that in some occasions present with colored faces or bodies. To better understand that feature, we investigated Chagall's paintings and writings.

Methods:
We explored the 1020 Chagall's pictures collected in the WikiArt database, and analyzed painter's auto-biographical writings

Results:
Over seven decades, Marc Chagall repeatedly depicted faces of essential characters of his paintings in, sometimes strikingly intense, green or blue, and less frequently in red or yellow. Colors were apparently selected based on the kind of emotional valence evoked by the depicted character. Moreover, we found in his writings explicit indications that the painter experienced color synesthetic percepts, although he apparently did not comprehend the nature of these phenomena.

Conclusions:
The painter apparently experienced a form of personality-color synesthesia. The assumption is strongly supported by his autobiographical writings. Chagall's artworks most probably provide us with invaluable insights into perceptual phenomena of synesthesia. The significance of that condition is commonly underestimated. In addition, similarly to people with Charles Bonnet Syndrome, individuals affected by synesthesia are often afraid to report their perceptual experiences, fearing to be considered as insane, and they need to be reassured. Presumed synesthetic features in Chagall's depictions do not detract in any way from these artwork exceptional value

References: Safran, AB, Sanda, N. Color synesthesia. Insight into perception, emotion, and consciousness. Curr Opin Neurol. 2015 Feb;28(1):36-44. doi: 10.1097/WCO.0000000000000169.

Keywords: Higher visual functions, Higher Visual Cortical functions, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 197
Brain plasticity in central and peripheral visual field loss

Nicolae SANDA[1], Norman SABBAH[2], Leonardo CERLIANI[3], Colas AUTHIE[2], Amir AMEDI[4], Christophe HABAS[5], José-Alain SAHEL[2], Michel Thiebaut de Schotten[3], Avinoam SAFRAN[2]

[1]Institut de la Vision/ Hôpital Foch, 75013, France, [2]Institut de la Vision, Paris, France, [3]Institut du cerveau et de la moelle, Paris, France, [4]The Hebrew University of Jerusalem, Jerusalem, Israel, [5]Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France

Introduction:
Disorders specifically affecting central and peripheral vision represent invaluable models to study how brain adapts to visual deafferentation. We explored functional and structural changes subsequent to the loss of central or peripheral vision.

Methods:
In twelve Stargardt macular dystrophy (SMD), twelve retinitis pigmentosa tunnel vision (RPTV) and fourteen normally sighted subjects we assessed the resting-state functional connectivity of central and peripheral V1 and extracted the cortical thickness (CoTks) and resting-state cortical entropy (rs-CoEn) for the cytoarchitectonic regions of the occipital lobe.

Results:
Compared to normally sighted, afferented central and peripheral EVC enhance their functional connectivity with several areas involved in visual processing, whereas deafferented central and peripheral EVC increase their functional connectivity with more remote regions. The connectivity pattern of afferented EVC indicates adaptive changes that could enhance the visual processing capacity while the connectivity pattern of deafferented EVC may reflect these regions participation in high-order mechanisms. When compared to controls, both groups with visual loss exhibited decreased CoTks in dorsal area V3d and increased rs-CoEn in area LO-2. Peripheral visual field loss also showed a specific CoTks decrease in area hOc4v. Central visual field loss presented with a relative increase in CoTks in dorsal region hOc5/ V5-hMT+ and increased rs-CoEn in the ventral region FG1 of the fusiform gyrus, both regions having a processing predilection for peripheral visual field information.

Conclusions:
Current results revealed biomarkers of brain plasticity following central and peripheral visual field defects.Characterizing and understanding plastic changes induced by visual loss is essential for any attempt to develop efficient strategies of rehabilitation.

References: None.

Keywords: Neuroimaging, Higher Visual Cortical functions

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 198
CSF Total Protein Level in Patients with Idiopathic Intracranial Hypertension (IIH)

Damian Berezovsky[1], Caroline Vasseneix[1], Beau Bruce[1], Nancy Newman[1], Valerie Biousse[1]

[1]*Emory University, Atlanta, Georgia, USA*

Introduction:
By definition, CSF is normal in IIH.[1] Low CSF total protein has been reported in IIH with conflicting reports about whether there is a linear association between CSF-protein and CSF opening pressure (CSF-OP).[2-4] Our aim was to evaluate the relationship between CSF-protein and CSF-OP in IIH, and to explore the effect of age, gender, race, BMI and HVF mean deviation (HVFMD) on CSF-protein.

Methods:
Retrospective review of all IIH patients seen between 01/01/1989-05/20/2016. Demographics, CSF-OP, CSF contents, and HVFMD (at first and last evaluation) were collected. Linear regression of CSF-protein controlling for CSF-OP was performed on BMI (>40 kg/m2 vs. lower), age (pre-pubertal 0-13, pubertal 13-18, adult 18+), gender, race, and HVFMD.

Results:
284 IIH patients had complete CSF results available (13 pre-pubertal, 37 post-pubertal, 234 adults). Mean CSF-protein level was 3.4 mg/dL higher for post-pubertal and 2.6 mg/dL higher for adults compared to pre-pubertal patients controlling for CSF-OP (p=0.67). Mean CSF-protein was 9.0 mg/dL higher for men than women controlling for CSF-OP (p=0.0008). Mean CSF-protein level was 4.8 mg/dL higher for whites compared to blacks controlling for CSF-OP (p=0.005). IIH patients with BMI >40 had CSF-protein levels 0.19 mg/dL lower than those with lower BMIs controlling for CSF-OP (p=0.93). There was a 0.26 mg/dL decrease in CSF-protein per 1 dB greater HVFMD at last visit controlling for CSF-OP (p=0.048). Multivariable analysis found that CSF-OP (p=0.003), gender (p=0.0009), race (p=0.04) and HVFMD (last visit, worst eye, p=0.02) remained independently associated with CSF-protein. There was no effect measure modification of the protein CSF-OP association by the variables considered.

Conclusions:
There was a negative association between CSF-protein and CSF-OP. After controlling for CSF-OP, CSF-protein was higher in whites and in men, but was unaffected by age and BMI. Higher CSF-protein levels were also associated with lower (worse) HVFMD at last visit.

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Keywords: Pseudotumor Cerebri, High intracranial pressure/headache, Visual fields

Financial Disclosures: The authors had no disclosures.

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Poster 199
Anemia and IIH: A retrospective study

Shauna Berry[1], Ama Sadaka[1], Obadah Nakawah[2]

[1]Houston Methodist Hospital, Houston, Texas, USA, [2]Houston Methodist, Houston, Texas, USA

Introduction:
Little is known about the relationship between anemia and idiopathic intracranial hypertension (IIH). Although both are relatively common disorders in women of childbearing age, only few case reports and small case series in the literature supports their association. The study aims to determine the prevalence of anemia in patients with IIH and to elucidate the relationship between anemia and IIH.

Methods:
This is a retrospective chart review study of IIH patients who were referred to our Neuro-Ophthalmology clinic between 1/1/2016 and 12/31/2016. Patients with anemia (defined as Hgb of < 12 mg/dl in woman or < 13 mg/dl in men) and definite IIH (using the modified Dandy criteria) will be included in this study. Those with secondary causes of intracranial hypertension, including cerebral venous thrombosis and intracranial masses, will be excluded.

Results:
Data analysis is in progress and will be complete prior to NANOS

Conclusions:
Data analysis in progress.

References: None.

Keywords: High intracranial pressure/headache, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 200
Underestimation of vision loss with idiopathic intracranial hypertension

Mark Breazzano[1], Shikha Chaganti[2], Katrina Nelson[2], Bennett Landman[2], Patrick Lavin[3], Louise Mawn[4]

[1]Department of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Nashville, Tennessee, USA, [2]Departments of Computer Science and Electrical Engineering, Vanderbilt University, Nashville, Tennessee, USA, [3]Departments of Neurology and Ophthalmology, Vanderbilt Eye Institute, Nashville, Tennessee, USA, [4]Departments of Neurological Surgery and Ophthalmology, Vanderbilt Eye Institute, Nashville, Tennessee, USA

Introduction:
We sought to correlate clinical findings of vision loss with anatomical changes via optical coherence tomography (OCT) in a cohort of patients with idiopathic intracranial hypertension (IIH) who met entry criteria for the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT),(1) with the exception of perimetric mean deviation (MD) score. Our hypothesis is that the IIHTT may not capture the full extent of vision loss associated with IIH on initial presentation to academic medical centers.

Methods:
A series of 299 patients diagnosed with IIH at an academic institution were retrospectively examined. Of these, 56 patients met stringent IIIHTT criteria except mild vision loss itself. Visual field data were compared by MD based on age. OCT measurements of retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) were correlated with visual function tests, including MD, visual field score (VFS), visual acuity score (VAS), and best corrected visual acuity (BCVA).

Results:
Younger patients fulfilling IIHTT criteria were more likely to have visual field loss than older patients, both according to MD (Kendall rank correlation 0.27, p-value < 0.01) and VFS (Kendall rank correlation 0.28, p-value = 0.02). Both the overall average RNFL (n=18) and GCL (n=14) thicknesses each positively correlated with three different vision metrics (VFS, VAS, and BCVA; $p<0.05$).

Conclusions:
Younger IIH patients fulfilling strict IIHTT criteria may have higher visual loss risk compared to older patients. The finding of thinner RNFL and GCL in IIHTT-eligible patients suggests that the IIHTT does not capture the extent of irreversible vision loss, given its inherent exclusion of patients outside the mild vision loss range.(2) Many patients meeting strict IIHTT criteria (over one-third based on MD and one-quarter based on VFS) were found to have worse vision than those enrolled in IIHTT, underscoring the severity of vision loss possibly found with IIH.

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Keywords: Pseudotumor Cerebri, Perimetry, Optic neuropathy, Visual fields, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 201
Intracranial Pressure, Intraocular Pressure, Translaminar Pressure Gradient, and Papilledema Severity

Jessica Chang[1], Anna Gruener[1], Clarissa Kum[1], Timothy McCulley[1]

[1]*Wilmer Eye Institute, Baltimore, Maryland, USA*

Introduction:
Recent studies have suggested that intracranial pressure (ICP) may play a role in glaucoma, hypothesizing that the gradient between intraocular pressure (IOP) and ICP transmitted via the subarachnoid space of the optic nerve determines optic nerve conformation and axonal damage. This study was designed to assess the correlation between ICP and papilledema severity in patients with idiopathic intracranial hypertension (IIH). We also assess the influence of IOP as a component of TPG on papilledema severity.

Methods:
In this university-based retrospective study, 261 consecutive patients with IIH between 2011 and 2015 were reviewed. Twenty-nine patients (4 males, 25 females, mean age 34 years, range 16-73) met inclusion criteria of having undergone lumbar puncture (LP), optical coherence tomography (OCT) of the peripapillary retinal nerve fiber layer (RNFL), and measurement of IOP, all within a three month period. Translaminar pressure gradient (TPG, the difference between ICP and IOP) and ICP were plotted against average RNFL thickness, and the Pearson correlation coefficient was calculated. Linear regression was used to evaluate IOP contribution to RNFL thickness. Further analysis evaluated whether asymmetric IOP correlates with asymmetric RNFL thickness.

Results:
Using single variable linear regression, there was a correlation between ICP and OCT RNFL average thickness ($R=0.4$, $p= 0.03$). TPG correlated less closely ($R=0.30$, $p=0.11$). On multivariate regression analysis, neither ICP nor TLG were found to significantly correlate with average OCT RNFL thickness. Among patients with asymmetry in IOP between right and left eyes, there was no trend to suggest a corresponding asymmetry in OCT RNFL thickness.

Conclusions:
Our data confirms a correlation between ICP and papilledema severity. This correlation was less than perfect ($R=0.4$), suggesting that disc edema is not a function of ICP alone. Our data suggests that IOP in the clinical setting has no significant influence on papilledema severity: TPG correlated less well than ICP alone.

References: None.

Keywords: Pseudotumor Cerebri, High intracranial pressure/headache, Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 202

Idiopathic Intracranial Hypertension: Update To A Retrospective Evaluation of Management and Outcomes at One Center

Bart Chwalisz[1], Joseph Rizzo III[1], Nicholas Koen[2], Judith Kempfle[3], Cinthi Pillai[4]

[1]Massachusetts Eye & Ear Infirmary Ophthalmology, Boston, Massachusetts, USA, [2]Brown University Medical School, Providence, Rhode Island, USA, [3]Masachusetts Eye and Ear Infirmary Otolaryngology, Boston, Massachusetts, USA, [4]NYU Longone Medical Center, New York, New York, USA

Introduction:

Idiopathic intracranial hypertension (IIH) is a potentially blinding disorder that typically affects young overweight women. The NORDIC IIH treatment trial established new standards regarding use and dosing of acetazolamide together with weight loss in the management of IIH. This study was designed to reflect upon our historical approach to the management IIH, in order to examine whether it should be modified in light of the NORDIC data.

Methods:

Retrospective acquisition of data from patients 14 years and older who were diagnosed with IIH at our center between 2004 and 2016. Data was entered into our customized database and analyzed over the first 10 clinic visits with respect to patient demographics, history, clinical and radiological signs, results of lumbar puncture, and whether surgery was performed.

Results:

Our preliminary data on 62 patients (9.7% M; 90.3% F) show headache as the major symptom in 82% and papilledema with concurrent vision changes in 82% of patients. The average mean deviation score among all patients in whom initial visual field testing was available (119 eyes in 62 patients) was -4.58 dB in the right and -4.35 dB in the left eye. With 87% of our patients prescribed 1500 mg of acetazolamide or less, the average mean deviation score after one year of treatment was -2.13 dB in the right and -3.71 dB in the left eye. Headache prevalence improved from 82% to 47% of patients after initiation of acetazolamide treatment (typical dose 1.0-1.5 g/d). Only 2 of these patients required surgery. The remainder of the analysis is in process.

Conclusions:

Our standard treatment approach employed acetazolamide at doses that were generally lower than what was used in the NORDIC trial, but nevertheless adequate to control symptoms and visual function in the great majority of patients. Surgery was only uncommonly required for management.

References: None.

Keywords: Pseudotumor Cerebri, High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 203
"Idiopathic Intracranial Hypertension at a Public Ophthalmologic Hospital; Our casuistry and comparison with the IIHTT"

Mariana de Virgiliis[1], Luciana Iacono[1], Pablo Perez Vega[1], Maria Laura Braccia Gancedo[1], Haydée Martinez[2], Dolores Ribero Ayerza[3], Lidia Sarotto[1], Luciana Lagos[1]

[1]Hospital Oftalmológico Dr. Pedro Lagleyze, Buenos Aires, Argentina, [2]Hospital de Clínicas Jose de San Martín, Buenos Aires, Argentina, [3]Hospital Británico, Buenos Aires, Argentina

Introduction:
IIH is a disorder affecting primarily young overweight women and typically presenting with signs and symptoms of raised ICP. The purpose of this study is to describe the characteristics of patients with IIH treated at a public hospital and its comparison with the IIHTT (The idiopathic intracranial hypertension treatment trial: clinical profile at baseline).

Methods:
Observational, retrospective and descriptive (case series) of medical records of patients with IIH treated at a Public Hospital between January 2011 and October 2016. We analised age of diagnosis, gender, initial symptom, visual acuity, body mass index (BMI), fundoscopic examination, visual field, optic coherence tomography (OCT), magnetic resonance with venography, CSF opening pressure, treatment and weight loss.

Results:
Total 26 patientsI. 23 met the modified Dandy Criteria for IIH: 22 females (95.62%) and 1 male (4.35%). Mean age of diagnosis was 33.39 years old. The most common presenting symptom was headache (73.91%). The BMI average was 37.57. The visual acuity remained well preserved in the 65.38% of the patients (20/20 to 20/70). Acute papilledema was present in 32 eyes (69.56%). The prototype visual field defect was an enlarged blind spot (47.82%). The thickness increased of the RNFL was the most common defect detected in the OCT (56.52%). The 86.95% of the patients had nonspecific signs of increased ICP in the neuroimaging studies. The average of CSF opening pressure was 35.2 cm H2o. 21 patients (91.3%) received oral medication. Mean weight loss was 62.2 kg of body weight.

Conclusions:
IIH was more frequent in young (mean 33.39 y.o) and obese (mean BMI 37.57) women (95.62%). In most cases the initial symptom was headache (73.91%), the visual acuity was well preserved and the visual field, neuroimaging and OCT were abnormal. These results are similar to the ones reported in the "The idiopathic intracranial hypertension treatment trial: clinical profile at baseline".

References: None.

Keywords: High intracranial pressure/headache, Pseudotumor Cerebri, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 204

Lumbar Puncture in Idiopathic Intracranial Hypertension (IIH) Diagnosis: Frequencies of Altered Diagnoses in Typical Patients

Adam DeBusk[1], Mark Moster[2], Robert Sergott[2], Molly Scannell Bryan[3]

[1]Wills Eye Hospital, Philadelphia, Pennsylvania, USA, [2]Neuro-Ophthalmology Department, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [3]Department of Public Health Sciences, University of Chicago, Chicago, Illinois, USA

Introduction:

For patients who present with symptoms of IIH, diagnostic criteria require lumbar puncture (LP) to confirm increased intracranial pressure and rule out other diagnoses,[1] such as infection or malignancy. However, LP is an invasive procedure, and can be associated with adverse events such as post-dural puncture headaches2. There has been little prior research to investigate the frequency with which the LP changes the initial suspicion of IIH in typical patients.

Methods:

Using retrospective chart reviews, we identified 60 women aged 55 and younger who presented symptoms consistent with elevated intracranial pressure and findings of papilledema, whose MRI and MRV scans indicated the absence of other diagnoses such as a mass lesion or dural venous sinus thrombosis. Each patient underwent an LP. Frequency of elevated white blood cell count (>5/µL) or protein (>55mg/dL), presence of infectious etiologies, and/or abnormal cytology were calculated, as well as the frequency of non-IIH final diagnoses.

Results:

Of the 60 participants, 45 had information on their body habitus (all of whom were overweight or pregnant). Two patients had mildly elevated protein, 3 had a mildly elevated WBC count and 1 had atypical lymphocytes on cytology (with only 2 WBC/µL). All patients were diagnosed with IIH and, in follow up, all followed a typical course for IIH and no alternative diagnoses were made.

Conclusions:

In these 60 patients with a typical clinical and imaging presentation of IIH, LP findings did not alter the diagnosis in any of them. If confirmed in larger population studies, it is possible that LP may not always be a necessary in the typical patient (overweight woman of child-bearing age with typical presentation and exam findings). These patients would require careful clinical follow up to be sure the course is consistent with IIH.

References: 1. Thurtell, M. J. & Wall, M. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Recognition, Treatment, and Ongoing Management. Curr. Treat. Options Neurol. 15, 1–12 (2013). 2. Basurto Ona, X., Osorio, D. & Bonfill Cosp, X. in Cochrane Database of Systematic Reviews (John Wiley & Sons, Ltd, 2015). 3. Williams, J., Lye, D. C. B. & Umapathi, T. Diagnostic lumbar puncture: minimizing complications. Intern. Med. J. 38, 587–591 (2008).

Keywords: Pseudotumor Cerebri, High intracranial pressure/headache, Neuroimaging, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 205

The Risk of Idiopathic Intracranial Hypertension and Papilledema among Patients Taking Cycline Antibiotics

Luai Eldweik[1], Collin McClelland[1], Joshua Stein[2], Michael Lee[1]

[1]Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, Minnesota, USA, [2]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan, USA

Introduction:
Reports have suggested an association between cycline antibiotics (CA) and idiopathic intracranial hypertension (IIH) and papilledema, yet no large-scale analysis has studied this association. We assessed whether exposure to CAs was associated with increased risk of papilledema or IIH.

Methods:
Beneficiaries aged 12-65, enrolled in a nationwide US managed-care network and diagnosed with acne, dry eyes syndrome (DES), or blepharitis with no pre-existing papilledema or IIH were studied. We quantified days of CA exposure for each enrollee as they were followed in the plan. Multivariable Cox regression modeling was used to assess the risk of developing papilledema or IIH from exposure to CAs, adjusting for confounding factors.

Results:
There were 728,811 enrollees with acne, DES/blepharitis (mean age 34.7 years, 72% female) who met the inclusion criteria, and 305,823 (42.0%) filled ≥1 CA prescription. Among all eligible enrollees, 291 (0.040%) received a papilledema or IIH diagnosis. Of the 305,823 CA users, 170 (0.056%) developed papilledema/IIH. By comparison, of the 422,988 non-CA users, 121 (0.029%) developed papilledema/IIH. In the unadjusted model, every additional year of CA use was associated with a 70% (doxycycline, p=0.06) or 91% (minocycline, p=0.02) increased hazard of papilledema/IIH. After adjustment for confounders, the findings lacked statistical significance (p=0.06,doxycycline and p=0.08, minocycline). Younger age (p<0.0001), female sex (p<0.0001), and systemic hypertension (p<0.0001) increased the hazard of papilledema/IIH. Assessing papilledema and IIH separately showed similar findings.

Conclusions:
The incidence of papilledema/IIH in patients taking CA for acne, DES/blepharitis is 6 in 10,000 and nearly double that of nonusers of CAs. However, after accounting for potential confounding factors, the apparent association between CA use and papilledema/IIH showed a trend toward, but was not statistically significant.

References: None.

Keywords: High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 206
Episcleral Venous Pressure And Intraocular Pressure As Biomarkers For Intracranial Pressure Changes

Deepta Ghate[1], Vikas Gulati[1], Shane Havens[1], Shan Fan[1], William Thorell[2], Junfei Tong[3], Carl Nelson[3], Linxia Gu[3], Sachin Kedar[4]

[1]Stanley F Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]Department of Neurosurgery, University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]Department of Engineering, University of Nebraska Lincoln, Lincoln, Nebraska, USA, [4]Department of Ophthalmology and Neurology, University of Nebraska Medical Center, Omaha, Nebraska, USA

Introduction:
There is need for non-invasive reliable intracranial pressure (ICP) monitoring. We hypothesize that ICP changes will affect ocular venous drainage and consequently affect the episcleral venous pressure (EVP), intraocular pressure (IOP) and retinal vein diameter (RVD) of the eye. EVP measurement is routine in aqueous humor dynamics glaucoma research. EVP has a predicted 1:1 correlation with IOP.

Methods:
A lumbar drain was used to vary ICP in 5 female domestic pigs in this established non-survival animal model. A parenchymal monitor (Integra Camino, USA) was inserted for accurate ICP monitoring. ICP was varied using normal saline infusion in 5 mm increments. The following parameters were measured at baseline and at all ICP increments after 10 minutes of ICP stability. 1) Right eye: IOP (pneumatonometry), EVP (venomanometry) 2) dilated left eye: OCT of optic nerve (Heidelberg Engineering, Germany). Retinal veins were identified on the OCT composite image and 2 independent graders measured RVD of 2 veins/ pig. The univariate correlation of EVP, IOP and RVD with ICP changes was evaluated using linear mixed models with random intercepts.

Results:
The baseline ICP was 4.5 mmHg (range 1.5-8 mmHg). Maximum stable ICP achieved ranged from 13-40 mm Hg. The EVP increased with increase in ICP (β=0.26, 95%, p = 0.01). IOP increased with increase in ICP (β=0.36, p=0.0002). There was a subjective increase in anterior segment congestion and venous congestion on examination and photography. There was an increase in retinal vein diameter thickness with ICP;this was correlated significantly with EVP (β=6.12, p=0.05).

Conclusions:
Acute ICP increase causes increased ocular venous congestion resulting in significant increase in EVP and IOP in a pig model. The increased EVP is correlated to RVD. This increased congestion could potentially be due to an increase in cavernous sinus pressure which drains the central retinal vein and episcleral veins.

References: None.

Keywords: High intracranial pressure/headache, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: Nebraska Research Initiative Research to Prevent Blindness

Poster 207
Effects of acute ICP changes on optic nerve head using OCT in humans and pig

Sachin Kedar[1], John Bader[2], Anna Adamson[2], Junfei Tong[3], Vikas Gulati[4], Shane Havens[4], Shan Fan[4], William Thorell[5], Kendra Schmid[6], Linxia Gu[7], Deepta Ghate[4]

[1]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]Department of Mechanical Engineering, University of Nebraska, Lincoln, Nebraska, USA, [4]Stanley Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Nebraska, USA, [5]Department of Neurosurgery, University of Nebraska Medical Center, Omaha, Nebraska, USA, [6]Department of Biostatistics, University of Nebraska Medical Center, Omaha, Nebraska, USA, [7]Department of Mechanical and Materials Engineering, University of Nebraska, Lincoln, Nebraska, USA

Introduction:
We assessed the effect on optic nerve head (ONH) morphology of acute intracranial pressure (ICP) decrease after lumbar puncture (LP) in humans and acute ICP increase in a pig model.

Methods:
LP study: ONH imaging (12 enhanced depth imaging (EDI) radial sections; Cirrus HD-OCT), intraocular pressure (IOP), CSF opening (OP) and closing (CP) pressures were obtained in 19 subjects before and after LP. Bruch's membrane opening diameter (BMOD) and anterior lamina cribrosa depth (ALCD) were measured by 2 graders for all 12 radial sections using Image J software. Repeated measures ANOVA evaluated differences in BMOD and ALCD before and after LP. Pig study: ICP was increased in 5mm Hg increments using lumbar drain in 3 anesthetized pigs, while ICP was monitored by a parenchymal monitor (Integra Camino). At each ICP level (stabilized to ±2mm Hg for 10 minutes), ONH imaging of right eye (12 EDI radial sections; Spectralis OCT), IOP of left eye (Pneumatonometery, Reichert Instruments) were obtained. ONH was graded as above. Change for each variable was calculated and modeled as a fixed effect for longitudinal data. Slopes were evaluated for statistical significance to determine if changes in ICP were associated with changes in BMOD and ALCD.

Results:
In the LP study, mean CSF-OP was 15.5mm Hg (range: 4- 31mm Hg) and mean ICP change was 8mm Hg (range: 2.6-17.7mm Hg). In the pig study, baseline ICP was 4.5 mm Hg (range 1.5-8 mm hg) and maximal stable ICP ranged from 18-32 mm Hg. In both LP study and pig model, there were no significant changes of BMOD and ALCD in all 12 radial sections following ICP changes.

Conclusions:
Acute ICP changes do not produce measurable changes of ONH morphology in humans and pig. The lamina cribrosa appears resistant to displacement despite large changes of ICP.

References: Hou R, Zhang Z, Yang D, Wang H, Chen W, et.al. Pressure balance and imbalance in the optic nerve chamber: The Beijing Intracranial and Intraocular Pressure (iCOP) Study. Sci China Life Sci. 59:495-503, 2016

Keywords: High intracranial pressure/headache, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: Department of Neurological Sciences Fremont Area Alzheimer's Committee Research to Prevent Blindness Nebraska Research Initiative

Poster 208

Differential diagnosis of papilledema vs. pseudopapilledema using customized optical coherence tomography parameters

Laura Pardon[1], Han Cheng[1], Rosa Tang[1], Roberto Saenz[1], Laura Frishman[1], Nimesh Patel[1]

[1]*University of Houston College of Optometry, Houston, Texas, USA*

Introduction:

Objective measures of the optic nerve head (ONH) and peripapillary tissue with optical coherence tomography (OCT) are useful for diagnosis of papilledema (PE) but limited to retinal nerve fiber layer (RNFL) thickness from a circular scan path centered on the ONH. The purpose of this study was to evaluate the use of additional OCT-derived measures in differentiating PE from pseudopapilledema (PPE).

Methods:

Cirrus HD-OCT ONH volume scans were acquired from 89 subjects: 21 PE, 27 PPE, and 42 controls. Scan data were exported, and total retinal thickness (TRT) within the ONH (TRTONH) plus RNFL thickness (RNFLT) and TRT at the following eccentricities were calculated using a MATLAB program: Bruch's membrane opening (BMO) to 250 µm (RNFL250 & TRT250), 250-500 µm (RNFL500 & TRT500), 500-1000 µm (RNFL1000 & TRT1000), and 1000-1500 µm (RNFL1500 and TRT1500). BMO height, measured from a reference plane connecting two points along Bruch's membrane at 2 mm eccentricity from the ONH center, and minimum rim width (MRW) were also calculated. Receiver operator characteristic (ROC) analysis compared the performance of these parameters with that of standard RNFLT (1.73 mm radius circular scan) in differentiating PE from PPE.

Results:

Standard RNFLT had an area under the ROC curve (AUC) of 0.87. While RNFL250, RNFL500, TRT250, TRT500, BMO height, and MRW demonstrated improved AUCs of 0.92, 0.90, 0.92, 0.90, 0.96, and 0.88, respectively, only BMO height was significantly different compared to standard RNFLT ($p = 0.039$). Positive BMO heights, above the reference plane, were observed in PE only.

Conclusions:

Using OCT volumetric data, additional parameters describing peripapillary tissue, ONH position, and ONH tissue thickness can be calculated and provide valuable measures for differentiating PE from PPE. Research investigating multimodal imaging will improve on these methods, establishing new metrics for the use of non-invasive clinical methods in accurate PE diagnosis.

References: None.

Keywords: Pseudotumor Cerebri, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

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Poster 209

The Relationship Between Optic Nerve Head Volume, Intracranial Pressure and Macular Ganglion Cell Complex Volume

Megh Patel[1], Kiran Malhotra[2], Zainab Shirazi[2], Heather Moss[3]

[1]University of Illinois at Chicago, Des Plaines, Illinois, USA, [2]University of Illinois at Chicago College of Medicine, Orland Park, Illinois, USA, [4]Stanford University, Department of Ophthalmology and Visual Sciences, Palo Alto, Illinois, USA

Introduction:

Enlargement of the optic nerve head(Papilledema) occurs in response to elevated intracranial pressure(ICP). Ganglion cell atrophy may decrease optic nerve head volume(ONHV) or limit its ability to enlarge. The objective of this study was to determine the interplay between these push/pull factors and optic nerve head volume in humans with and without elevated ICP.

Methods:

Six radial OCT B-scans spaced by 30° and centered over the optic nerve(Heidelberg Spectralis) were obtained in 19 subjects prior to undergoing lumbar puncture for clinical indications. ICP was estimated by the lumbar puncture opening pressure(range 10-55 cm H2O). Two raters independently segmented the internal limiting membrane and Bruch's membrane on each image. Customized software(MATLAB) calculated ONHV in a 3mm circle centered on the optic nerve and cup volume (CV, the negative space above Bruch's membrane opening) based on interpolation between segmented B-scans. Ganglion cell complex(GCC) volumes within a 3mm circle centered over the macula were extracted from automatically segmented, manually corrected volume scans of the macula(Heidelberg Eye Explorer). Generalized estimating equations(GEE) were used to model ONHV and CV as a function of ICP and GCC volume.

Results:

Neither univariate(u) nor multivariate(m) models demonstrated an association between CV and ICP (pu=0.45, pm=0.70) or GCC(pu=0.15, pm=0.36). Univariate models demonstrate an association between ONHV and both ICP(0.012 mm3/cm H2O[0.005-0.019]p<0.0005) and GCC(1.2mm3/mm3[0.66,1.87]p<0.0005). These associations persisted in a multivariate model of ONHV(ICP:0.01mm3/cm H2O[0.003-0.018, p=0.007; GCC:0.704 mm3/mm3 [0.17-1.24], p=0.01).

Conclusions:

Optic nerve head volume is associated with both ICP and ganglion cell atrophy in univariate and multivariate models. Optic nerve cup volume was neither associated with ICP nor ganglion cell atrophy in both univariate and multivariate models. These results support development of optic nerve head volume as a marker for chronic ICP and reinforce the importance of accounting for effects of ganglion cell atrophy.

References: Kaufhold, F. Optic nerve head quantification in idiopathic intracranial hypertension by spectral domain OCT. PLoS ONE 7(5): e36965, 2012 Wang, J. Automated Quantification of Volumetric Optic Disc Swelling in Papilledema Using Spectral-Domain Optical Coherence Tomography. Investigative Ophthalmology & Visual Science. 53: 4069-4075, 2012

Keywords: High intracranial pressure/headache, Neuroimaging

Financial Disclosures: The authors had no disclosures.

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Poster 210

Change in body mass index over time in non-overweight/obese children with Idiopathic Intracranial Hypertension (IHH)

Claire Sheldon[1], Edward Linton[2], Grace Paley[2], Shana McCormack[2], Grant Liu[3]

[1]University of British Columbia, Vancouver, British Columbia, Canada, [2]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [3]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Introduction:
Previous studies have characterized subgroups of pediatric IIH: 'a young' cohort, with normal weight, an 'early adolescent' cohort, who are typically overweight, and a 'late adolescent' cohort, who are typically obese. This study was designed to obtain follow-up anthropometrics and clinical data in pediatric IIH patients who were not overweight or obese at presentation.

Methods:
Charts of pediatric subjects with IIH diagnosed by a pediatric neuro-ophthalmologist were reviewed (7/1/1993-4/16/2013). Using recent diagnostic criteria for IIH, cases of definite, probable and 'unsure' IIH were identified. After limiting dates of diagnosis to 2011 or earlier, and BMI Z-scores of <=1.04 (i.e., not overweight or obese) at diagnosis, 27 cases remained. Follow-up anthropometrics and medical details for 17 cases were available via chart review(n=6) and included participant self-report in a telephone interview(n=11).

Results:
Median follow-up duration was 8.0years (IQI 6.14–9.28). Median age at follow-up was 15.2years (IQI 12.1–17.4). 60% were male(n=11/17). In subjects still 18years old average BMI was 22.10±1.34kg/m2 (range 21.2-23;n=2), indicating adult subjects were of normal weight. In telephone interviews (n=11), no subject developed diabetes, PCOS, or other endocrinopathies. One experienced a recurrence of IIH.

Conclusions:
This study illustrates that, in pediatric subjects with IIH who were not overweight/obese at presentation, the majority did not become overweight/obese. Children with lower than typical BMI Z-scores at diagnosis tended to gain weight, but remained within normal range. These data suggest that children with IIH may not exist on a clinical continuum. Rather, anthropometrics at presentation may define distinct sub-groups with respect to pathophysiology and clinical course.

References: None.

Keywords: Pediatric neuro-ophthalmology, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 211
Bruch's Membrane Opening in Papilledema and Pseudopapilledema

Atalie Thompson[1], M. Tariq Bhatti[2], Mays El-Dairi[1]

[1]Duke Eye Center and Duke University Medical Center, Department of Ophthalmology, Durham, North Carolina, USA, [2]Duke University Medical Center, Dep. Ophthalmology, Neurology and Neurosurgery, Durham, North Carolina, USA

Introduction:
To determine whether the horizontal diameter in Bruch's membrane opening (BMO) can distinguish papilledema from pseudopapilledema using optical coherence tomography (OCT).

Methods:
Retrospective chart review of 58 eyes/58 subjects with pseudopapilledema due to optic nerve head (ONH) drusen, 14 eyes/14 subjects with papilledema due to idiopathic intracranial hypertension (IIH), and 16 eyes/16 healthy control subjects. All subjects underwent OCT imaging (Spectralis, Heidelberg, Germany) of the ONH and average retinal nerve fiber layer (RNFL). Eyes with both papilledema and ONH drusen were excluded. The horizontal diameter of the BMO under the optic nerve in each eye was measured in micrometers at the time subjects with IIH had grade 1-2 papilledema by the Frisén scale, and when their papilledema had resolved. BMO was also measured on OCT in patients with ONH drusen and healthy controls. The three diagnostic groups' mean BMO and RNFL were compared using t-test. Receiver operating characteristics (ROC) were graphed to calculate the Area Under the Curve (AUC) for BMO and RNFL between subjects with papilledema and pseudopapilledema.

Results:
In eyes with papilledema, mean BMO and RNFL decreased as papilledema resolved (1909.5 vs. 1542.9, $p<0.001$; 181.9 vs. 107.9, $p=0.001$, respectively). Eyes with papilledema had greater mean BMO and RNFL than those with pseudopapilledema and controls (1909.5 vs. 1542.9 vs. 1570.7, $p<0.001$, $p=0.004$; 181.9 vs. 109.5 vs. 100.6, $p<0.001$, $p<0.001$, respectively). The AUC showed good diagnostic discrimination for BMO (AUC=0.83 (95% CI 0.72-0.94)) and RNFL (AUC=0.95 (95% CI 0.90-1.0). Using cut-offs of 1668 for BMO and 131 for RNFL, the combined sensitivity and specificity were 90% and 90.7%, respectively for distinguishing papilledema from pseudopapilledema.

Conclusions:
The size of BMO measured by OCT is enlarged in eyes with papilledema and reverses as papilledema resolves. BMO may be used to help distinguish papilledema from pseudopapilledema.

References: None.

Keywords: Pseudotumor Cerebri, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 212

The Relationship between Central Corneal Thickness (CCT) and Papilledema from Idiopathic Intracranial Hypertension (IIH)

Caroline Vasseneix[1], Michael Dattilo[2], Beau Bruce[3], Nancy Newman[4], Valerie Biousse[5], Jason Peragallo[6]

[1]Emory University, Atlanta, 30322, Georgia, USA, [2]Neuro-Ophthalmology unit, Department of Ophthalmology, Emory University, Atlanta, Georgia, USA, [3]Department of Ophthalmology, Neurology and Epidemiology, Emory University, Atlanta, Georgia, USA, [4]Department of Ophthalmology, Neurology and Neurological surgery, Emory University, Atlanta, Georgia, USA, [5]Department of Ophthalmology and Neurology, Emory University, Atlanta, Georgia, USA, [6]Department of Ophthalmology and Pediatric Ophthalmology, Emory University, Atlanta, Georgia, USA

Introduction:

Glaucoma studies have suggested that translaminar pressure gradients (TPG) may affect severity of optic nerve damage in glaucoma.(1) It has been demonstrated that CCT could possibly be a risk factor for developing ophthalmic disease from an altered TPG.(2) Alterations of TPG by decreasing intraocular pressure (IOP) have also been implicated in the development of papilledema.(3-4) Subgroups of patients with IIH and papilledema are at higher risk for severe vision loss, including black patients, men, and patients with fulminant presentations.(5) Our goal was to determine if CCT is related to severity of papilledema and vision loss in IIH.

Methods:

CCT was systematically recorded in IIH patients seen between 03/2015-10/2016. Demographic data, medications, BMI, IOP, CSF opening pressure, visual acuity, color vision, visual fields, and Frisén grade of papilledema on review of fundus photography were collected. We examined associations between CCT and other variables of interest controlling for age, race, and sex using linear, logistic, and ordinal generalized estimating equation models to account for intereye correlations.

Results:

Our 100 IIH patients included 95/100 women; 35 white, 56 black, 9 other race; with a median age 31 years (IQR 24.8-36.2), median BMI 35.7 (31.1-43), and median follow up 10.7 months (1.6-20.2). Median CCT was 551µ OD (525-578) and 553µ OS (529-577). Among 142/200(71%) eyes with papilledema at presentation, 39(20%) were Frisén scale grade 1 or 2, 40(20%) grade 3, 16(8%) grade 4, and 8(4%) grade 5. Median visual acuity was 0 logMAR and 36% had a visual field defect at first and final presentation. There was no association between CCT and IOP, CSF opening pressure, BMI, severity of papilledema and final visual outcome, controlling for age, race, and sex.

Conclusions:

IIH patients had a median CCT within the normal range. There was no association between CCT, IOP, or TPG and severity of papilledema or visual outcome.

References: 1) Guy AH, Wiggs JL, Turalba A, Pasquale LR. Translating the low translaminar cribrosa pressure gradient hypothesis into the clinical care of glaucoma. Semin Ophthalmol. 2016;31:131-9. 2) Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002 Jun;120(6):714-20 3) Greenfield DS, Wanichwecharungruang B, Liebmann JM, Ritch R. Pseudotumor cerebri appearing with unilateral papilledema after trabeculectomy. Arch Ophthalmol. 1997 Mar;115(3):423-6. 4) Kawasaki A, Purvin V. Unilateral optic disc edema following trabeculectomy. J Neuroophthalmol. 1998 Jun;18(2):121-3. 5) Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2012;83(5):488-494.

Keywords: Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

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Poster 213
Piloting A New Method For Estimating Visual Field Loss In A Panoramic Naturalistic Environment

Deepta Ghate[1], David Anderson[2], Vikas Gulati[1], Sachin Kedar[3], Matthew Rizzo[2]

[1]Stanley F Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]Department of Neurosciences, University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]Department of Neuroscienes and Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska, USA

Introduction:
Patients with field defects have increased motor vehicle accidents. Standard automated perimetry lacks external validity in naturalistic environments. To resolve this, Driving Simulator Visual Field(DSVF) was designed in a high-fidelity driving simulation system with 290° panoramic environment.

Methods:
DSVF tested 40 grid locations spanning 60° horizontal and 20° vertical visual angle at 2.5 m with grid similar to Humphrey visual field(HVF) 30-2 strategy(6 degrees between loci, straddling the horizontal and vertical meridian). Red supra-threshold stimuli (0.5° angle) on gray background were presented randomly with each location tested 4 times. Test duration was 4 minutes. Subjects, in driving simulator, maintained central fixation and responded to stimuli. Response rates(0 to -4) were used to generate grayscale and calculate a global visual field index(DS-VFI) using similar location weights as HVF- VFI. Subjects performed monocular and binocular DSVFs twice in randomized order. Grayscales and VFI for the DSVF and clinic HVF were compared. Subjects were experienced field takers.

Results:
3 glaucoma suspects with full HVFs (HVF-VFI range 99-100%) underwent DSVF. DS-VFI was 92±2% (mean ±SD) for binocular fields, 85±1% left eye (OS) and 83±4% right eye(OD). 1) DSVF were reproducible. VFI and grayscales of 2 trials performed per field were similar (absolute VFI difference between trials: 2 ±1%). 2) DVSF and HVF grayscales were similar. The blind spot mapped correctly (15° location) in 10/12 monocular fields. 3) A-pillar scotoma: A vertical scotoma caused decrease in DS-VFI compared to HVF-VFI and occurred in the same location (21-27 ° left of fixation) in all 18 trials. It corresponded to the vehicle's A-pillar which support the windshield.

Conclusions:
DSVF is a novel platform to estimate visual fields in a naturalistic setting reliably and reproducibly. We identified a new scotoma (A-pillar scotoma) in the DSVF attributable to in-cab geometry that may affect driving performance.

References: 1: Tanabe S, Yuki K, Ozeki N, Shiba D, Abe T, Kouyama K, Tsubota K. The association between primary open-angle glaucoma and motor vehicle collisions. Invest Ophthalmol Vis Sci. 2011 Jun 13;52(7):4177-8

Keywords: Visual fields, Higher visual functions

Financial Disclosures: The authors had no disclosures.

Grant Support: We thank the subjects for their participation and patience. This study was supported by a Pilot Grant award from the Department of Neurological Sciences at UNMC and by NIH R01 AG017177.

Poster 214
Utilizing the Visual System as a Proxy for Brain Function

Khizer Khaderi[1], Kimberly Gokoffski[2], Melita Moore[3], Jeffrey Pettey[1]

[1]University of Utah Moran Eye Center, Salt Lake City, Utah, USA, [2]University of Southern California Roski Eye Institute, Los Angeles, California, USA, [3]University of California Davis, Sacramento, California, USA

Introduction:
Over half of brain function is devoted to vision. As such, testing the visual system, including ocular motility, pupillary-light response, and visual acuity allows for real time assessment of global brain function. There is much interest in rapidly detecting patients who experience traumatically-induced transient disturbance of brain function, or mild traumatic brain injury (mTBI). Current guidelines for screening include rapid neurocognitive and balance exams (e.g. ImPACT and MACE). Unfortunately, these tests are limited due to effort-dependent performance, confounding variables and reliability. Here, we present our work on a method to screen for mTBI utilizing the visual system as a proxy for evaluation of brain function.

Methods:
We have integrated commercially available wearable sensor technologies to a proprietary TBI vision test platform. The TBI vision test evaluates a subject's eye movements during pro-saccade, anti-saccade, and smooth pursuit tasks; pupil reaction to standardized International Affective Picture System (IAPS) visual stimuli; and resting phase brainwave activity. Specific parameters measured in our study include alpha/theta brainwave activity; absolute change in pupil size, rate of change in pupil size; and speed, latency and accuracy of eye movements in response to the above mentioned tasks.

Results:
Our preliminary data of the mTBI visual testing system on normal controls shows measurements consistent with normative published data. Specifically, we were able to detect normal ranges for pro-saccadic, anti-saccadic, and smooth-pursuit eye movements, as well as predicted pupillary response.

Conclusions:
While we recognize additional studies are needed to confirm repeatability and reliability in detecting normative and pathologic values, our methodology is an important step towards demonstrating quantifiable measurements of the visual system as an indirect measurement of brain function. With continued evaluation, we hope that our technology will prove capable of detecting disrupted eye movements and altered EEGs that immediately follow mTBI.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Higher visual functions, Higher Visual Cortical functions, Ocular Motility, Pupils Retina

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Poster 215
Virtual Reality and Visual Ergonomics

Khizer Khaderi[1], Jeffrey Pettey[1], Behzad Mansouri[2], Jing Yuan[3]

[1]University of Utah Moran Eye Center, Salt Lake City, Utah, USA, [2]University of Winnipeg, Winnipeg, Canada, [3]Wuhan University, Wuhan, China

Introduction:
Although the origins of head-mounted visual displays (HMDs) trace back to the 1960s, widespread adoption of this technology in the form of virtual reality (VR) HMDs has only recently taken place. VR is a non-invasive simulation technology that provides an immersive, realistic, three-dimensional (3D) computer-simulated environment in which people perform tasks and experience activities as if they were in the real world. HMDs are goggles, helmets and glasses comprised of lens display systems. These display systems are monocular (one eye), binocular (both eyes, one screen) or dichoptic in nature (both eyes, different screens or image/eye), the latter allowing for stereopsis (depth cues). Recent advancements have been directed toward making HMDs more comfortable for longer duration of use, with HMD products including Google Glass, Epson Moverio, Vuzix Wrap, Oculus Rift, HTC Vive and Samsung Gear becoming commercially available. These technical advancements include higher resolution and refresh rates, lower persistence and lower latency from improved positional tracking. While advancements have made VR systems more commonplace, an inherent problem with these devices, visually induced motion sickness (VIMS) or simulation sickness, remains an obstacle to the widespread adoption and commercial development of technologies associated with VR based HMDs. In part, VIMS, which is related to visual-vestibular mismatch, has been attributed to significant systemic and perceptual problems with HMDs not commonly experienced with traditional displays; these include nausea, stomach discomfort, disorientation, postural instability and visual discomfort. The purpose of our review is to identify factors influencing visual ergonomics of virtual reality (VR) head-mounted display systems (HMDs).

Methods:
A comprehensive search query was performed on the Medline/PubMed, EMBASE, ProQuest Central, ACM Digital Library, and IEEE Xplore databases.

Results:
N/A

Conclusions:
Hardware, user and task characteristics contribute to visually induced motion sickness (VIMS). Industry awareness and optimization of these factors would improve the experience in virtual environments.

References: None.

Keywords: Vestibular, Ocular manifestations of vestibular disorders, Ocular Motility, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 216
What Do We Want? Results of the YONO 2016 Survey

Kevin Lai[1], John Pula[2], Prem Subramanian[3]

[1]Midwest Eye Institute, Indiana University, Richard L. Roudebush VA Medical Center, Indianapolis, Indiana, USA, [2]NorthShore University HealthSystem, Department of Neurology, Chicago, IL, Chicago, Illinois, USA, [3]University of Colorado School of Medicine, Aurora, CO, Aurora, Colorado, USA

Introduction:
The Young Neuro-Ophthalmologist (YONO) Committee of NANOS proposes to develop and provide useful resources for medical students, residents, fellows, and young neuro-ophthalmologists. To better understand their needs and interests, we created a survey to determine what topics interest young neuro-ophthalmologists.

Methods:
A 28-question survey was developed to assess a broad spectrum of topics the authors considered potentially relevant to the target members. The survey was distributed by e-mail through NANOS to junior members of NANOS and the YONO Forum 2016 attendees. The survey was available for approximately 1 month.

Results:
Of the 30 members contacted, 15 people (50%) responded. Seven (46.7%) respondents were practicing physicians, five (33.3%) were fellows, and three (20%) were residents. Of the seven practicing physicians, six (85.7%) had been in practice for less than 5 years. Only one respondent practiced 100% neuro-ophthalmology; seven of eight respondents practiced a mix of neuro-ophthalmology with general neurology or ophthalmology. Topics of greatest interest included practical neuro-ophthalmology, developing a time-efficient and financially viable neuro-ophthalmology practice, billing and coding, professional networking, and work/life balance. All respondents listed e-mail as their preferred method of contact. Eight of ten respondents expressed interest in contributing to the YONO website, specifically developing educational tools for young neuro-ophthalmologists (57.1%) and enhancing neuro-ophthalmology education in residency (42.9%).

Conclusions:
Despite a small sample size, the 2016 YONO survey suggests that resources focusing on everyday aspects of medical practice may benefit young neuro-ophthalmologists. Time efficiency and developing a financially viable practice are key concerns among young neuro-ophthalmologists. There is also a strong desire among the respondents to network with other neuro-ophthalmologists and to contribute to education. The YONO committee will use this information to refine its content and develop opportunities for young neuro-ophthalmologists to connect and contribute. We have created a new YONO e-mail listserv (NANOSYONO-DISC@LISTSERV.NANOSWEB.ORG).

References: None.

Keywords: Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 217
Alterations in photic drive responses and pupillographic responses in epilepsy patients

Christian Lueck[1], Eman Ali[2], Corinne Carle[2], Andrew James[2], Kate Martin[1], Angela Borbelj[1], Ted Maddess[2]

[1]Department of Neurology, The Canberra Hospital, Canberra, ACT, Australia, [2]John Curtin School of Medical Research, Australian National University, Canberra, Australia

Introduction:
The photic drive response (PDR) has been used to explore cortical hyperexcitability in neurological disorders. We explored changes in the PDR in epilepsy patients and looked for any interaction with pupillary responses obtained from multifocal objective pupillographic perimetry (mfPOP).

Methods:
15 patients who had a clear diagnosis of epilepsy (8 males; mean age ± SD 47.3 ± 4.6 years) and 15 controls (9 males; mean age 52.7 ± 4.6 years) underwent routine EEG with standard intermittent photic stimulation (IPS), as well as testing with mfPOP. EEG spectral amplitudes during IPS were obtained by Fourier transformation. 'Alpha-band gain' was calculated by comparing the effect of IPS in eyes-open and eyes–closed conditions, and this was examined at the fundamental and several harmonic frequencies. mfPOP responses were obtained from 44 regions/visual field; response time-to-peak and standardized amplitude were recorded for each test region.

Results:
Linear models showed that an epileptic attack within the previous 1 month increased the alpha-band gain by 1.33 dB ($p = 0.01$). Generalised epilepsy (i.e. not focal epilepsy) decreased the alpha-band gain by 1.03 dB ($p = 0.03$). Taking antiepileptic medication was associated with a reduction in the alpha band gain. For each decade increase in age the gain increased by 0.36 dB ($p = 0.007$). The pupil response was similarly increased in patients who had had an attack within the preceding 1 month ($p = 0.0001$) but there was an increase in pupil response in those with generalised epilepsy ($p = 0.0001$).

Conclusions:
Investigating alpha-band gain and mfPOP demonstrated changes in epilepsy patients, presumably due to alteration in cortical hyperexcitability. Both tools are worthy of further study as a non-invasive measure of cortical hyperexcitability.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Pupils Retina, Miscellaneous, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 218
LHON Genealogy Project – Identifying, Informing and Educating Maternal Relatives

Lissa Poincenot[1]

[1]LHON Project at UMDF, San Diego, California, USA

Introduction:
LHON patients often wish to know if any of their maternal ancestors had vision loss, and would like to inform living maternal relatives about LHON. However, they lack the knowledge of how to conduct a genealogical search, as well as how to communicate this sensitive genetic information. The patient advocacy group LHON Project at UMDF created the LHON Genealogy Project to fill that knowledge gap.

Methods:
A professional Genetic Genealogist worked with four LHON families to build their mitochondrial tree, first going back in time, then forward to identify and locate their living maternal relatives. Each family received a consultation with the genealogist and a LHON patient advocate, and was offered a consultation with an LHON-trained Genetic Counselor. Direct-to-Consumer DNA testing was used with one family to help build their mitochondrial tree, and to explore the issues surrounding this approach.

Results:
Results from the LHON Genealogy Project were presented at the 2016 LHON Conference, and the presentation was captured on video and posted online for ongoing education. Evidence of blindness was found in historical records. Many more childless women than expected were found, resulting in fewer living “mitochondrial cousins” than anticipated. Some genetic information found online is inaccurate.

Conclusions:
Patients need extensive support and guidance in developing their mitochondrial tree and contacting maternal relatives. Some patients are highly motivated to identify and contact their maternal relatives to educate them, especially about environmental factors to potentially reduce LHON carriers' risk of vision loss. Should vision loss occur, awareness will expedite diagnosis, increasing the opportunity to participate in a clinical trial or receive treatment if available especially while the therapeutic window remains open, and decreasing the incidence of depression, job loss, educational challenges, etc. which often occur with LHON vision loss by providing connection to resources via the LHON patient community.

References: None.

Keywords: Genetic Disease, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 219
Papilledema: Not A Good Surrogate For Elevated Intracranial Pressure In Cerebrospinal Fluid Shunt Diversion Failure

Alexander Port[1], Cristiano Oliveira[1], Marc Dinkin[1]

[1]*Weill Cornell Medicine, Ophthalmology, New York, New York, USA*

Introduction:
Cerebrospinal fluid (CSF) shunt procedures are performed to address elevated intracranial pressure (ICP). Ophthalmologists are often asked to evaluate for papilledema as a sign of shunt malfunction or failure. However, studies suggest that the presence or absence of papilledema is not a sensitive predictor of shunt dysfunction. This study aims to evaluate the utility of papilledema as a sign of shunt function.

Methods:
Retrospective chart review of inpatient and emergency department ophthalmology consults was performed. Consults from 2010-2016 where the primary clinical question involved evaluation for papilledema were included. Demographic data were recorded as were examination findings, the presence of papilledema, and intracranial pressure where noted. Subjects with clinical shunt failure were identified on the basis of imaging demonstrating an obstructed shunt or patients undergoing surgical revision for shunt malfunction.

Results:
There were 245 consultations to “rule-out papilledema;" 56 were specifically to evaluate for papilledema as a sign of shunt failure. Among these 56 consults, 13 patients (23%) had shunt failure and underwent surgical revision, the remaining 43 (77%) did not. Papilledema was present in 5/13 patients with confirmed shunt failure (38.5%), and one patient (2.3%) without the confirmed diagnosis (p= 0.0001). In our cohort, papilledema had a sensitivity of 38.5% (95%CI: 13.9%, 68.4%) but a specificity of 97.7% (95%CI: 87.7%, 99.9%). The positive predictive value of papilledema was 83.3% (95%CI: 35.9%, 99.6%) and negative predictive value was 84.0% (95%CI: 70.9%, 92.8%). 4/43 patients without shunt failure had ICP measurements, mean 13.6mmHg, compared to 8/13 with shunt failure, mean 26.4mmHg (p= 0.035).

Conclusions:
Papilledema is a specific, but not a sensitive, predictor of shunt failure. Clinicians who evaluate shunted patients should be aware that papilledema should not be considered the sole indicator of shunt function. Patients with clinical signs of shunt failure should be given further evaluation regardless of the presence of papilledema.

References: None.

Keywords: High intracranial pressure/headache, Miscellaneous, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

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Poster 220
Performance of a Portable Eye Tracker to Assess Eye Movements During the King-Devick Test

Jenelle Raynowska[1], John-Ross Rizzo[1], Janet Rucker[1], Weiwei Dai[2], Joel Birkemeier[1], Julian Hershowitz[1], Ivan Selesnick[2], Laura Balcer[1], Steven Galetta[1], Todd Hudson[1]

[1]New York University School of Medicine, New York, New York, USA, [2]New York University Tandon School of Engineering, New York, New York, USA

Introduction:
With increasing accessibility of portable, economical, video-based, infrared eye trackers, such as the EyeTribe, there is growing interest in eye movement recordings, including in the setting of sports-related concussion. However, prior to implementation, there is a primary need to establish the validity of these low-resolution (30-60 Hz) eye trackers via comparison with high-resolution (500-1000 Hz) devices such as the EyeLink.

Methods:
A convenience sample of 30 controls performed a digitized version of the King-Devick (K-D) test with EyeTribe and EyeLink eye movement recordings.

Results:
Signal loss and tracings inconsistent with eye movement physiology were common with EyeTribe. Saccade main sequence parameters (fit to decaying exponentials) were significantly different for the two devices (reported as best-fit parameter and 95% confidence interval). Peak velocity versus amplitude relationships revealed a main sequence asymptote of 1674°/s (CI: 1527, 1852°/s) for EyeTribe vs. 506°/s (CI: 499, 513°/s) for EyeLink and a time constant of 102.9° (CI: 93.5,115.7°) for EyeTribe vs. 6.1° (CI: 5.3, 6.3°) for EyeLink. Duration versus amplitude relationships also demonstrated significant differences, with an asymptote of 62.7ms (CI: 61.0, 64.3ms) for EyeTribe vs. 83.2ms (CI: 82.2, 84.4ms) for EyeLink and time constant of 4.9° (CI: 4.6, 5.3°) for EyeTribe vs. 13.8° (CI: 13.6, 14.1°) for EyeLink. Total number of saccades to complete the K-D was significantly lower with EyeTribe, with an average of 110.2 vs. 120.5 saccades recorded by EyeTribe and EyeLink respectively (paired t-test, p=0.001). There was no significant difference in the inter-saccadic interval, despite a discrepancy of 42ms between devices.

Conclusions:
The EyeTribe device was unable to capture valid saccade data during rapid number naming. Caution is advised regarding the implementation of eye trackers with low temporal resolution for objective saccade assessment or sideline concussion screening.

References: None.

Keywords: Ocular Motility

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Poster 221
Correlating Blindness with Patient Reported Outcomes, Demographics, and Performance in NMO

Meagan Seay[1], Hong Li[1], Mary Rensel[1]

[1]*Cleveland Clinic, Cleveland, Ohio, USA*

Introduction:
Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system. Variable clinical manifestations exist, leading to the development of NMO spectrum disorders. Relapsing NMO often leads to severe neurological deficits, including vision impairment. Patient reported outcomes (PRO) are increasingly used in clinics and clinical trials. These are subjective measures that provide insight into patients' quality of life and perceived functional status. The aim of this study was to correlate blindness in patients with NMO with PRO, demographics, and performance testing (PT).

Methods:
A NMO registry identified patients fulfilling the revised diagnostic criteria for NMO spectrum disorders. PRO, PT, and visual acuities (VA) were obtained from a clinical database and electronic medical record and compared between blind (VA ≤20/200 in ≥ 1 eye) and non-blind. Associations between blindness and PRO or PT were examined using Spearman correlation.

Results:
Fifty-one NMO patients (median age 43 years, median age of onset 29, 88.2% female, 39.2% blind) were included in the study. Blind patients were significantly younger (median 29.3 vs. 44.0 years) had an earlier age of disease onset (16.5 vs 36.0 years, p = <0.001) and a longer disease duration (13.5 vs 3.0 years, p = 0.02) compared to non-blind patients. More blind patients used gait assistant devices and had longer times on the 9-hole peg test. Blind patients rated their visual disability worse, yet depression rates were similar in blind and non-blind.

Conclusions:
Blindness in NMO is common and was seen in those with early age of onset, longer disease duration, and younger current age. Though blindness was associated with PT and visual PRO, it did not influence depression. Adult onset NMO ranked their quality of life worse as compared with pediatric onset NMO. Future studies with larger cohorts are needed to better assess PRO in NMO.

References: None.

Keywords: Demeylinating disease, Pediatric neuro-ophthalmology, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 222

Visual Field Deficits in Patients with Headache Disorders: A 2- year Prospective Cohort Study

Padmaja Sudhakar[1], Fred Odago[1], Jonathan Smith[1], Sachin Kedar[2]

[1]University of Kentucky, Lexington, Kentucky, USA, [2]University of Nebraska Medical Center, Omaha, Nebraska, USA

Introduction:

Primary and secondary headache disorder patients are often seen in ophthalmology clinics with visual symptoms. Their exam is usually normal but visual field abnormalities may be seen.

Methods:

We performed a single-center prospective evaluation of visual complaints in the setting of a headache disorder at our eye Clinic between June 2012 and May 2014. Subjective visual complaints included blurred vision, visual distortions, double vision, transient visual loss and visual field loss. All underwent a detailed neuro-ophthalmology exam including visual acuity, color vision, contrast sensitivity, Humphrey visual field 24-2 SITA fast, pupil exam, anterior segment and dilated posterior segment exam and intraocular pressure.

Results:

Our cohort included 56 individuals, 76.8% female with a median age of 46 (range: 11-76). Visual complaints prompting consultation included visual distortions (46.4%) blurred vision (17.9%), diplopia (16.1%), visual field loss (8.9%), transient visual loss (7.1%), eye pain (5.4%) and tunnel vision (1.8%). These were attributed to a headache disorder after a thorough neuroophthalmology exam that was normal. Per ICHD-II criteria, their pre-existing headache disorder included: Migraine with aura (n=20), migraine without aura(n=11), chronic migraines (n=13), retinal migraines (n=1), occipital neuralgia(n=1). 10 patients had no pre-existing headache disorder. Clinical diagnoses for presenting symptoms (ICHD-II criteria) included typical aura without headache (40%), migraine with aura (21%), chronic migraine (8.8%), migraine without aura (3.5%) and retinal migraine (1.8%). Visual fields were normal in 28 patients (49.1%), unreliable in 7 (12.2%), bilateral clover leaf pattern in 3 (5.3%), and nerve fiber bundle pattern in 19 (33.3% -8 cases with bilateral involvement).

Conclusions:

In our study of patients with visual symptoms attributable to a headache disorder, visual field abnormalities were not uncommon, and most often monocular.

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Keywords: Visual fields, Perimetry, High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 223

Radiographic Comparison of Carotid Anatomy in Patients Who Experienced Retinal versus Middle Cerebral Artery Emboli

Aubrey Gilbert[1], Mary Beth Cunnane[1], Thabele Leslie-Mazwi[2], Joseph Rizzo[1]

[1]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA, [2]Massachusetts General Hospital, Boston, Massachusetts, USA

Introduction:

Emboli that arise from or pass through the carotid arteries can cause transient or permanent monocular blindness or dysfunction secondary to middle cerebral artery occlusion. A substantial foundation of literature has revealed that there is a lowered risk of developing ipsilateral hemispheric strokes in patients who initially experienced transient or permanent ipsilateral blindness. This difference in risk plausibly is secondary to differences in vascular anatomy. This study was designed to assess potentially relevant anatomical features of the carotid siphon in patients who were clinically evaluated by our service for monocular blindness or middle cerebral artery infarctions.

Methods:

A retrospective, comparative case-control study of two cohorts of patients who had established or suspected embolic events: A) Adults with monocular blindness due to either visualized central or branch retinal artery occlusion or a history of transient monocular blindness; and B) Adults with middle cerebral artery infarction. The monocular blindness patients were identified by searching hospital billing records for appropriate ICD codes and then reviewing their records to confirm an embolic etiology. The cerebral infarction patients were identified from a database of patients who had undergone an endovascular neurointerventional procedure for treatment of their stroke. The location of ophthalmic artery take off from the carotid artery was assessed on computerized tomographic angiographic scans that were reviewed by a board-certified neuroradiologist who was blinded to clinical history.

Results:

Preliminary comparisons were undertaken to compare the anatomy of the ophthalmic artery take off on the ipsilateral versus contralateral side of individual patients and to compare the ipsilateral sides of monocular blindness versus hemispheric stroke patients.

Conclusions:

Neurovascular anatomy may factor into clinical presentation of embolic phenomena.

References: None.

Keywords: Neuroimaging, Vascular disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 224

"Sphenoid sinus mucosal thickening" plus the "pituitary ring sign" together are pathognomonic for pituitary apoplexy

Michael Vaphiades[1]

[1]*University of Alabama at Birmingham, Birmingham, Alabama, USA*

Introduction:

Pituitary apoplexy is due to acute infarction or hemorrhage of a pituitary gland. Two MRI signs of pituitary apoplexy are the "pituitary ring sign" and "sphenoid sinus mucosal thickening", the former unique only to ischemic type and the later in both types. Each sign alone may exist in patients without pituitary apoplexy. However, in the appropriate clinical context, each is a strong predictor of pituitary apoplexy. To the best of my knowledge, these 2 MRI signs have never been correlated with one another in the setting of pituitary apoplexy.

Methods:

A review of the literature searching the terms "pituitary ring sign" and "sphenoid sinus mucosal thickening" in the context of pituitary apoplexy was performed. To be included, each case had to have pituitary apoplexy and a contrasted MRI which clearly shows both "sphenoid sinus mucosal thickening" and a clear "pituitary ring sign". The addition of a recent hospital patient with both signs was added.

Results:

Ten cases of ischemic (not hemorrhagic) pituitary apoplexy were discovered, all with clear MRI images showing both the "pituitary ring sign" and "sphenoid sinus mucosal thickening". Six 6 of the 10 cases were evaluated by this author, 5 of which had MRI scans in prior publications highlighting the "pituitary ring sign" in pituitary apoplexy. Four of the cases were from the neurosurgery literature in papers highlighting "sphenoid sinus mucosal thickening" in pituitary apoplexy. Upon review of these published MRI scans, both signs were present in all cases.

Conclusions:

The "pituitary ring sign" and "sphenoid sinus mucosal thickening" may significantly aid in the diagnosis of ischemic pituitary apoplexy. Each sign alone, in the appropriate clinical context, is suggestive of pituitary apoplexy, however the presence of both signs together is virtually pathognomonic of the diagnosis. This is important because timely diagnosis treatment may be vision and lifesaving in this disorder.

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Keywords: Neuroimaging, Tumors, Skull Base, Optic neuropathy, Visual fields

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Poster 225
Optic neuritis in Behçet's Disease

Gulden Akdal[1], Gulden Akdal[1], Hülya Ertaşoğlu Toydemir[2], Murat Kürtüncü[3], Osman Saatçi[4], Uğur Uygunoğlu[5], Suzan Güven Yılmaz[6], Aylin Yaman[4], Meltem Söylev Bajin[7], Gülşen Akman Demir[8]

[1]Dokuz Eylül University Hospital Neurology Department, Izmır, Turkey, [2]Bakırköy Dr. Sadi Konuk Teaching Hospital, Department of Neurology, Istanbul, Turkey, [3]Istanbul University Istanbul Medical School Neurology Department, Istanbul, Turkey, [4]Dokuz Eylül University Hospital Opthalmology, Izmır, Turkey, [5]Istanbul University Cerrahpaşa Medical School Neurology Department, Istanbul, Turkey, [6]Ege University Medical School Opthalmology Department, Izmir, Turkey, [7]Dokuz Eylul University Hospital Opthalmology Department, Izmir, Turkey, [8]Bilim University Hospital Neurology Department, Istanbul, Turkey

Introduction:
Behçet's disease (BD) is an autoimmune multisystem inflammatory diseases small vessels of unknown etiology which is characterized by relapsing uveitis, oral aphtae and genital ulcerations. Uveitis is the most common ocular manifestation of whereas optic neuropathy (ON) is rare.

Methods:
BD optic neuritis patients seen in 5 different University Neurology/Neuroophthalmology departments from 1996-2016 were reviewed. The patients' data were first evaluated by a neurologist of each hospital and then re-evaluated in joint sessions by one senior neurologist in one center (GA).

Results:
Of the twenty-five patients (13M,12F) whose optic neuritis was related to BD, 14 had already been diagnosed as BD when ON developed whereas in 11 BD was diagnosed during evaluation of the etiology ON. Bilateral ON occurred in 8 patients. Disc swelling was seen in 15 patients. Neurological involvement other than optic neuritis occured in 6 patients. Final visual acuity varied between light perception to full vision. All patients except one received immunosuppressive medications such as azathioprine, cyclophosphamide and infliximab. In about 1/3 of the patients vision improved, in another 1/3 it deteriorated and in another 1/3 it remained the same.

Conclusions:
BD may be diagnosed earlier if it is considered and investigated during the assessment of ON. Simply asking about recurrent mouth or genital ulceration will reveal almost all cases. ON in BD should be considered as neuro-BD and treated accordingly.

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Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 226
Pseudotumor cerebri without thrombosis in Behçet's Disease

Gülden Akdal[1], Gülden Akdal[1], Suleyman Men[2], Aylin Yaman[3], Murat Kürtüncü[4], Hulya Ertaşoğlu Toydemir[5], Neşe Çelebisoy[6], Gülnar İbrahimova[7], Meltem Soylev Bajin[8], Gülşen Akman Demir[9]

[1]Dokuz Eylül University Hospital Neurology Department, Izmir, Turkey, [2]Dokuz Eylül University Hospital Radiology Departmnet, Izmir, Turkey, [3]Dokuz Eylül University Hospital Ophthalmology, Izmir, Turkey, [4]İstanbul Univesity Istanbul Medical School Hospital Neurology Department, İstanbul, Turkey, [5]Sadi Konuk Teaching Hospital, İstanbul, Turkey, [6]Ege University Hospital Neurology Department, Izmir, Turkey, [7]Istanbul University Istanbul Medical School Hospital Neurology Departmnet, Istanbul, Turkey, [8]Dokuz Eylul University Hospital Opthalmology Department, Izmir, Turkey, [9]Bilim University Hospital Neurology Department, Istanbul, Turkey

Introduction:
Behçet's disease (BD) is a chronic inflammatory disease affecting small and large, arteries and veins. The most common CNS presentation is brainstem meningoencephalitis involving particularly the diencephalon (parenchymal neuro-BD). Another manifestation of BD is pseudotumor cerebri (PTC) syndrome which is in most cases due to cerebral venous sinus thrombosis (CVST) ; in these cases it is presumed/accepted that venous hypetension impairs CSF absorption across the arachnoid villi and this results in CSF hypertension and PTC. However some BD patients with PTC appear not to have CVST. Here we focus on such cases – describe the clinical features and speculate on possible mechanism.

Methods:
BD-PTC seen in 4 different University Neurology/Neuroophthalmology departments from 1996-2016 were reviewed. All cases whose imaging did NOT show CVST are reported here. All patients had MRI/MRV scans which were reviewed by one neuroradiologist (SM). Patients were followed for 6-144 months.

Results:
There were 15 patients (8M/7F). The ages of patients were varied between 25-56 years. In five patients, PTC was the presenting syndrome of BD; the diagnosis of BD was made as a consequence of the PTC presentation; in 10 patients PTC occurred in the course of previously diagnosed BD. In one patient CNS parenchymal involvement developed a year after PTC diagnosis which is severe disabling type. One patient had the emergency optic nerve sheath fenestration (ONSF). All patients were treated with 1gram/day intravenous methylprednisolone for five days, then longterm immunosupression. All patients receive acetazolamide during the PTC diagnosis period..

Conclusions:
PTC can occur in BD with or without CVST. In cases without CVST we presume that the mechanism of the CSF hypertension is an immune mediated obstruction to CSF absorption across arachnoid villi. The good clinical response to immunosuppresive treatment could support this explanation. PTC BD patients have a better outcome than BD patients who have parenchymal involvement.

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Keywords: Pseudotumor Cerebri, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

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Poster 227

Retinal Layer Thinning May Reflect Gray Matter Atrophy in Relapsing Remitting Multiple Sclerosis: Ethnicity Role

Poonam Bansal[1], Samuel Lichtman-Mikol[1], Sheridan reed[1], Sara Razmjou[1], fen Bao[2], Kalyan Yarraguntla[2], Rishi Sood[2], Christina Caon[2], Carla martinez[2], evanthia bernitsas[2], Navid Seraji- Bozorgzad[2]

[1]Wayne State University, Detroit, Michigan, USA, [2]Wayne State University School of Medicine, Detroit, Michigan, USA

Introduction:

Optical Coherence Tomography (OCT) allows the visualization and quantification of thickness of retinal layers, which are known to thin over time in RRMS. Correlations between ganglion cell and inner plexiform layers (GCL + IPL) and whole brain gray matter volumes, (GMV) have been shown in longitudinal studies in a predominantly White population. The objective was to investigate the effect of ethnicity on such correlations in patients with relapsing-remitting multiple sclerosis (RRMS) through a retrospective cross-sectional study.

Methods:

39 African-American and 38 White patients with RRMS (52 women, 25 men, mean age 43.8: range 23-64y, EDSS range 1.5-6.5, disease duration range 1-26y) on various disease modifying therapies underwent Ocular coherence tomography and magnetic resonance imaging in this retrospective study. Patients with history of optic neuritis were excluded from the study. 3D-T1W MPRAGE images were used in SPM8 to calculate GMV. General estimating equations analysis with a logarithmic link function and exchangeable correlation was used to explore the effect of ethnicity on the relationship between GMV and retinal layers (STATA v13).

Results:

Thickness of GCL and IPL directly correlated with GMV in the White patients with RRMS (R2=0.282 p=0.009, p=0.020; respectively). In African-American patients with RRMS, however, GCL and IPL did not show a correlation to GMV (R2=0.132 p=0.889, p=0.741; respectively). Similar pattern was also seen in papillomacular bundle, inner nuclear layer and temporal retinal nerve fiber layer, whereby a direct correlation was observed with GMV in the White patients with MS, but not in the African American group.

Conclusions:

Our results confirm that different retinal layer thickness correlate directly with markers of brain atrophy in patients with RRMS, even without history of optic neuritis. Ethnic background, however, plays a significant role in this relationship, and needs to be further evaluated in longitudinal, prospective studies.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Demeylinating disease, Neuroimaging, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Poster 228

Optical Coherence Tomography Segmentation Analysis in Relapsing Remitting versus Progressive Multiple Sclerosis

Raed Behbehani[1], Abdullah Abu Al-Hassan[1], Ali Al-Salahat[1], Devarajan Sriraman[1], Raed Alroughani[1]

[1]Dasman Institute, Kuwait, Kuwait

Introduction:

Optical coherence tomography (OCT) is a valuable tool in assessing axonal loss and neuro-degeneration in multiple sclerosis (MS) by in-vivo imaging, nd quantification of retinal layers. The ultra-structural retinal changes in MS in different MS phenotypes can reflect differences in the pathophysiologic mechanisms. There is limited data on the pattern of deeper retinal layer involvement in progressive MS (PMS) versus relapsing remitting MS (RRMS). We have compared the OCT segmentation analysis in patients with relapsing-remitting MS and progressive MS.

Methods:

Cross-sectional study of 113 MS patients (29 PMS, 84 RRMS) and 38 healthy controls. Spectral domain OCT (SDOCT) using the macular cube acquisition protocol (Cirrus HDOCT 5000; Carl Zeiss Meditec) and segmentation of the retinal layers for quantifying the thicknesses of the retinal layers. Segmentation of the retinal layers was carried out utilizing Orion software (Voxeleron, USA) for quantifying the thicknesses of individual retinal layers.

Results:

The retinal nerve fiber layer (RNFL) ($p = 0.023$), the ganglion-cell/inner plexiform layer (GCIPL) ($p = 0.006$) and the outer plexiform layer (OPL) ($p= 0.033$) were significantly thinner in PMS compared to RRMS. There was significant negative correlation between the outer nuclear layer (ONL) and EDSS ($r= -0.554$, $p= 0.02$) in PMS patients. In RRMS patients with prior optic neuritis, the GCIPL correlated negatively ($r = -0.317$; $p = 0.046$), while the photoreceptor layer (PR) correlated positively with EDSS ($\beta = 0.478$; $p = 0.003$).

Conclusions:

Patients with PMS exhibit more atrophy of both the inner and outer retinal layers than RRMS. The ONL in PMS and the GCIPL and PR in RRMS can serve as potential surrogate of disease progression. The specific retinal layer predilection and its correlation with disability may reflect different pathophysiologic mechanisms in MS and various stages of progression in MS.

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Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

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Poster 229

Optic neuritis in patients with anti-MOG spectrum disorder: MRI and clinical features

Damien Biotti[1], Fabrice Bonneville[2], Xavier Ayrignac[3], Clarisse Carra Dallière[3], Laurence Mahier[4], Catherine Vignal[5], Olivier Gout[5], Pierre Labauge[3], David Brassat[6], Romain Deschamps[7]

[1]Hôpital Pierre Paul Riquet - CHU Purpan, Toulouse - CNS inflammatory disorders Unit, TOULOUSE, France, [2]CHU Purpan, Radiology Unit, Toulouse, France, [3]CHU Montpellier - Neurology Unit, Montpellier, France, [4]Hôpital PPR - CHU Purpan, Toulouse, France, [5]Fondation A. De Rothschild, Paris, France, [6]Hôpital PPR - CHU Purpan - Neurology Unit, Toulouse, France, [7]Fondation A. De Rothschild - Neurology Unit, Paris, France

Introduction:

In adults, the spectrum of MOG antibody-associated demyelinating diseases(MOG-SD) constitutes a recently described and challenging entity. It encompasses almost 25% of patients with neuro-myelitis optica spectrum disorder being negative for anti-aquaporine 4 antibodies(AQP4). The most frequently observed manifestation is optic neuritis(ON), more rarely myelitis. From the first publications, demographics and clinical presentation of these patients appeared different from those with AQP4-Abs.

Methods:

We present the results of a two-year(June 2014-June 2016), French, tricentric, prospective analysis of patients diagnosed with MOG-SD (and at least one ON event). We aimed to describe the clinical and radiological features related to ON events.

Results:

Out of thirty-nine patients included, 20 were female(51.3%, SR=1,05). The average ON-onset age was 36.4 years. Eighteen patients(46.2%) presented with bilateral optic neuritis. At the onset, ON events were painful(87.2%), severe(median additional [Right eye + left eye] visual score of 5) and associated with optic nerve head swelling in half cases. Cerebrospinal fluid examination did not show inflammation(<6 cells(71%), absence of intrathecal Immunoglobulin G synthesis(91.7%)). MRI findings were specific with an extensive optic nerve T2 hyperintensity(median of 3/6 segments), including almost systematically intra orbital segments(92.3%), and associated with Gadolinium enhancement(82%) and an edematous appearance(35.9%). Spontaneous or steroid-induced recovery was rapidly obtained and was, in most of the cases, dramatic(3-month median additional visual score of 0). Nevertheless, several patients had visual sequelae including significant visual field loss and/or severe atrophy on the RNFL OCT.

Conclusions:

Firstly, our cohort confirms the clinical and radiological features suggested by the first publications on anti-MOG ON patients. When observed, these features should justify testing anti-MOG Abs. Secondly, if ON events appeared clinically and radiologically severe at the onset, they generally have a good prognosis in terms of visual acuity. However, we stressed the possibility of visual sequelae and the need of discussing therapeutic approach to prevent relapses.

References: None.

Keywords: Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Neuroimaging, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 230

Neuro-ophthalmic complications of leukemia: prompt treatment can give good visual outcomes

Richard Blanch[1], Ruchika Batra[2], Mike Burdon[2], Andrew Jacks[2], Tim Matthews[2], Susan Mollan[2]

[1]University of Birmingham, Birmingham, United Kingdom, [2]University Hospital Birmingham NHS Foundation Trust, Birmingham, United Kingdom

Introduction:

Leukemia is typically treated using a combination of chemotherapy, radiotherapy and stem cell transplantation. Whilst it is rare for leukemia to present with ocular involvement, recurrence may present in the brain and optic nerve. Whole body irradiation before stem cell transplantation may be protective against optic nerve recurrence (1). Historically, the outcomes of optic nerve recurrence are variable and standard treatment indications and protocols are lacking (1).

Methods:

Retrospective case series including 24 patients seen between 2010 and 2016 presenting to the local neuro-ophthalmic service with complications of leukemia or its treatment. Notes were reviewed and treatment and outcome information extracted.

Results:

Four patients had optic neuropathy confirmed or presumed to be caused by leukemia recurrence. Two patients with acute myeloid leukemia and one with acute lymphocytic leukemia had the diagnosis confirmed by imaging and the presence of leukemic cells in the CSF. One patient with chronic lymphocytic leukemia died before investigations were completed. Two patients had had initial treatment with whole body irradiation. The three surviving patients were treated with a combination of intravenous methylprednisolone, intrathecal methotrexate and external beam radiotherapy, commenced within one week of diagnosis. After commencement of treatment, vision was maintained or improved in all patients, despite involvement of both optic nerves in two patients at presentation. Seven patients were treated for ocular graft-versus-host disease, three patients suffered ischemic optic neuropathy, two patients suffered retinoic acid-related intracranial hypertension, one patient developed parasellar and optic nerve meningiomas as a late complication of radiotherapy and one suffered posterior reversible encephalopathy syndrome.

Conclusions:

Optic nerve recurrence of leukemia is an uncommon but significant occurrence. In our experience, the diagnosis can be confirmed by imaging and lumbar puncture for cytology and prompt treatment with intravenous methylprednisolone and intrathecal methotrexate can preserve vision even in nerves already affected.

References: 1. Schwartz CL, Miller NR, Wharam MD, Leventhal BG. The optic nerve as the site of initial relapse in childhood acute lymphoblastic leukemia. Cancer. 1989 Apr 15;63(8):1616-20.

Keywords: Optic neuropathy, Chemotherapy and radiation injury, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Grant Support: None.

Poster 231
Ganglion Cell Layer in Optic Neuritis and Multiple Sclerosis - A Systematic Review and Meta-analysis

Josefine Britze[1], Jette Frederiksen[2], Gorm Pihl-Jensen[1]

[1]Rigshospitalet Glostrup, Copenhagen University teaching hospital, Glostrup, Denmark, [2]Rigshospitalet Glostrup, University Hospital, Glostrup, Denmark

Introduction:
The aim of this study was to summarize existing findings regarding optical coherence tomography (OCT) measurements of ganglion cell layer (GCL) alterations in optic neuritis (ON) and multiple sclerosis (MS).

Methods:
Peer-reviewed studies published prior to April 2016 were searched using PubMed, EMBASE, Web of Science and Scopus. Studies were included if they (a) included data on GCL measured using OCT (b) in patients with either ON, MS or clinically isolated syndrome and (c) were in English.

Results:
42/251 studies involving 4745 subjects were reviewed. Studies showed significant thinning of the GCL over the first weeks-12 months after acute ON (n=7). GCL thinning was measurable within the first 5 weeks (n=5), earlier than retinal nerve fiber layer (RNFL) thinning. GCL thinning at 1-2 months after acute ON predicted visual function at 6 months (n=3). The thickness of the GCL was significantly reduced in eyes of MS patients with and without previous ON compared to healthy controls. GCL thinning was associated with visual function in most studies (n=10), particularly low contrast letter acuity (LCVA) (n=6). Most of the studies found a significant inverse correlation between GCL thickness and expanded disability status scale (EDSS) scores (n=6).

Conclusions:
In acute ON, thinning of the GCL occurs early on and may be detectable prior to thinning of the RNFL. GCL thinning occurs in MS eyes with and without prior ON, and may be associated with visual function and EDSS score. This suggests that the GCL is a promising biomarker, which may be used to examine in vivo neurodegeneration in ON and MS, and predict short-term visual function in acute ON.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

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Poster 232

Ganglion Cell Atrophy and Optic Nerve Cupping in Patients with Postgeniculate Homonymous Visual Field Loss

Rebecca Chen[1], Cristiano Oliveira[2], Bryan Pham[2], Marc Dinkin[2]

[1]Weill Cornell Medical College, New York, New York, USA, [2]Weill Cornell Medicine, New York, New York, USA

Introduction:

There is increasing evidence for retrograde trans-synaptic degeneration (RTSD) in the retina following cortical injury, even in adults. Homonymous ganglion cell layer (GCL) thinning following postgeniculate injury, consistent with RTSD has recently been demonstrated,[1],[2],[3] but no funduscopic correlate has been demonstrated. Optic disc cupping has been attributed to RTSD following cortical ischemia in children with congenital periventricular leukomalacia[4]. We therefore hypothesized that cupping might accompany adult-onset RTSD.

Methods:

Charts of patients with the diagnosis homonymous hemianopsia (HH), from 2010-2016, were reviewed. Out of 395 patients with HH, 113 had undergone SD-OCT. After excluding subjects with eye and pregeniculate brain pathology, 68 were remained. Cup size (CS) and cup-to-disc ratio (CDR) were collected and compared with the data from 43 controls.

Results:

Homonymous GCL thinning ipsilateral to the post-geniculate lesion, consistent with RTSD, was found in 41 of the 68 patients, whereas a similar pattern of right/left asymmetry was found in only 6 of 43 controls. The magnitude of thinning was also much greater in subjects compared with controls. Average CDR in the RTSD group was 0.53 (OD) and 0.51 (OS) vs. 0.41 (P=0.005) and 0.40 (P=0.006) in the control group. Average CS was 0.18 (OD) and 0.16 (OS), vs. 0.09 (P=0.001) and 0.08 (P=0.006) in controls.

Conclusions:

Using SD-OCT, an increase in CDR and CS was found in patients with post-geniculate visual pathway pathology and RTSD, as compared to controls, providing evidence suggesting a structural correlate of optic disc morphology to the observed RNFL and GCL atrophy in these patients.

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Keywords: Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 233

Abnormalities of retinal vasculature in neurofibromatosis type I : Expansion of the ophthalmologic clinical spectrum

Bo Young Chun[1], Hee Young Choi[2], Hyun-Taek Lim[3], Soolienah Rhiu[4]

[1]Department of Ophthalmology, Kyungpook National University School of Medicine, Daegu, Korea, Republic of, [2]Department of ophthalmology, Pusan National University School of Medicine, Pusan, Korea, Republic of, [3]Department of Ophthalmology Asan Medical Center Hospital, Seoul, Korea, Republic of, [4]Hallym University Dontan Sacred Heart Hospital, Hwaseung, Korea, Republic of

Introduction:
To evaluate the ophthalmologic features of retinal vasculature in the patients with neurofibromatosis type 1 (NF-1)

Methods:
Comparative observational case series. Data was collected retrospectively on medical records of 36 patients (71 eyes) who were diagnosed as NF-1 by National Institutes of Health (NIH) criteria between January, 2009 and July 2016. Analysis of fundus photography and comparison with age-matched normal control group (35 patients, 70 eyes) were performed.

Results:
The NF-1 group was composed of 25 male and 11 female, with a mean age of 11 years (range, 2 to 29 years), and the control group was composed of 24 male and 11 female, with a mean age of 7 years (range, 3 to 14 years). The majority of NF-1 patients (34 patients, 94%) had abnormalities of retinal vasculature. Supernumerary optic disc vessels were found in 32 patients (64 eyes, 91%) and spokewheel-like vascular branching was observed in 28 patients (56 eyes, 79%).). In addition, there were findings of triple branching in 18 eyes, anomalous macular arteries in 5 eyes, increased vascular tortuosity in 3 eyes and prepapillary vascular loop in one eye. On the other hand, there were 1 eye of triple branching and 1 eye of anomalous course in retinal vessels in control group.

Conclusions:
Patients with NF-1 demonstrated a wide spectrum of abnormalities of retinal vasculature, most notably supernumerary optic disc vessels and spokewheel-like vascular branching. We propose to consider these findings to be included in the clinical spectrum of ocular features in NF-1.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Vascular disorders, Genetic Disease, Pupils Retina, Pediatric neuro-ophthalmology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 234
OCT in Clinical Practice: An International Survey from a Consortium of MS Providers

Julie DeBacker[1], Rachel Nolan[1], Steven Galetta[1], Friedemann Paul[2], Pablo Villoslada[3], Peter Calabresi[4], Laura Balcer[1]

[1]NYU School of Medicine, New York, New York, USA, [2]Charité – Universitätsmedizin Berlin, Berlin, Germany, [3]Institut Biomedical Research August Pi Sunyer (IDIBAPS), Hospital Clinic of Barcelona, Barcelona, Spain, [4]Johns Hopkins University, Baltimore, Maryland, USA

Introduction:
Eyes of patients with multiple sclerosis (MS) demonstrate thinning of the retinal nerve fiber layer (RNFL) and ganglion cell/ inner plexiform layer (GCL+IPL) that is evident by optical coherence tomography (OCT) even in the absence of acute optic neuritis (ON). OCT is also useful for the differential diagnosis of visual loss in MS, and is emerging as a potential tool to identify optic nerve involvement that could support an MS diagnosis or disease progression. We examined results of a survey of MS providers that was international in scope to determine current self-reported clinical uses of OCT for patients with MS.

Methods:
Surveys were conducted for administrative purposes to establish the clinical and research needs for an international consortium of MS providers, including those who self-identified interest in neuro-ophthalmology and vision research. Members were surveyed regarding their current use of OCT in clinical practice by a multi-choice question for which they could select all answers that applied from a list of nine possibilities.

Results:
Among the 23 providers surveyed, current uses of OCT were reported as follows: evaluate for non-ON causes of visual loss (n=17, 74%); monitor patients on fingolimod for macular edema (n=15, 65%); confirm an ON diagnosis (n=14, 61%); evaluate progressive visual loss (n=13, 57%); monitor disease progression/prognosis (n=11, 48%); and monitor efficacy of disease-modifying therapy (n=10, 44%). Nearly all of those surveyed in this consortium (n=20, 87%) use OCT as part of research protocols.

Conclusions:
A consortium of MS providers with self-identified interests in vision and vision research consider OCT to be a useful clinical tool. A large proportion of these investigators routinely use OCT for MS diagnosis and for monitoring disease progression and drug efficacy. Such groups will have critical roles in establishing guidelines for use of OCT in MS diagnosis, monitoring and therapy.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Demeylinating disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 235
A Treatment Algorithm for Susac Syndrome

Robert Egan[1]

[1]*Northwest Neuro-Ophthalmology, Portland, Oregon, USA*

Introduction:
Susac syndrome (SS) presents with a clinical triad of vision loss, hearing loss, and encephalopathy and an imaging triad of white matter involvement, grey matter involvement, and leptomeningeal enhancement. The best treatment regimen is not known. This author reviewed the medical literature for treatment regimens comparing them to his professional experience and offers a treatment paradigm.

Methods:
The medical search engine PubMed was queried from 2000 to present on October 13th 2016 using the key words of Susac Syndrome versus different medications or medication groups.

Results:
A total of 61 articles was discovered. There were six with prednisone, 19 with methylprednisolone, 22 with corticosteroids, 30 with immunoglobulin, six with methotrexate, 10 with azathioprine, five with mycophenolate, one with natalizumab, six with rituximab, one with tumour necrosis factor inhibitors, one with infliximab, and none with alemtuzumab, adalimumab, and ocrelizumab. Personal experience revealed that immunoglobulin is necessary in keeping patients with recurrent retinal artery occlusions from progression which corresponds with personal communications with other providers.

Conclusions:
Review of the literature and professional experience strongly suggest that all patients with active SS should immediately be started on corticosteroids either oral prednisone or intravenous methylprednisolone plus intravenous immunoglobulin at 2 g/kg followed by monthly doses at 0.4 mg/kg. Should a patient break through on this regimen, the patient should be immediately started on either mycophenolate or rituximab and practitioners are recommended to have a low threshold to start either of these latter therapies. Other therapies also work but may have more side effects. A number of severely affected patients have been treated effectively with cyclophosphamide but I recommend this therapy after others have failed. It remains to be seen whether T cell mediated drugs or tumour necrosis factor inhibitors affect the course of this illness favorably in this illness.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Vascular disorders, Miscellaneous

Financial Disclosures: I have received honoraria for participation on advisory boards from Biogen and Genentech

Grant Support: None.

Poster 236
Retinal Arterial Collaterals in Susac Syndrome

Robert Egan[1], Guy Jirawuthiworavong[2], Norah Lincoff[3], John Chen[4], Courtney Francis[5], Jacqueline Leavitt[6]

[1]Northwest Neuro-Ophthalmology, Portland, Oregon, USA, [2]SouthernCalifornia Permanente Medical Group, Los Angeles, California, USA, [3]Department of Neurology and Ophthalmology, Jacobs School of Medicine, SUNY Buffalo, Buffalo, New York, USA, [4]Department of Ophthalmology and Neurology, Mayo Clinic, Rochester, Minnesota, USA, [5]Department of Ophthalmology, University of Washington, Seattle, Washington, USA, [6]Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, USA

Introduction:
Susac syndrome (SS) classically presents with a clinical triad of vision loss, hearing loss, and encephalopathy and an imaging triad of white matter involvement, grey matter involvement, and leptomeningeal enhancement. Historically, idiopathic branch retinal artery occlusions (BRAOs) have been linked with the development of retinal arterial collaterals but review of the literature has not supported this claim. We present a series of subjects with SS all harboring retinal arterial collaterals.

Methods:
Charts, fundus photography, and fluorescein angiography (FA) of unselected subjects with SS were reviewed retrospectively. A literature review was undertaken using PubMed over an unrestricted time frame using the search terms retinal collaterals and BRAO.

Results:
A total of 11 subjects were identified. Five were male. Ages ranged from 20 to 50 years. All collaterals were arterio-arterial and none were arterio-venous. No collaterals were present at onset of illness and none were seen at six weeks. The shortest interval to development of collaterals was 10 months. There was only a single case report of SS with retinal arterial collaterals; a second article from 1967 documented a single case of a 31 year old man with recurrent BRAO.

Conclusions:
The literature reveals scant evidence for the association between retinal arterial collaterals and BRAO. Our findings indicate that retinal arterial collaterals in SS are arterio-arterial and not arterio-venous and may be quite common in this disorder. This coincides with the currently held pathophysiology that this is a primary arterial disease. Collaterals do not develop early in the disease and there may be a sex predilection towards development in males. The chronic inflammatory state may be the mechanism for their development and further research is required to determine if they occur in the primary self-limited encephalopathic form of SS.

References: None.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Pupils Retina, Vascular disorders, Miscellaneous

Financial Disclosures: I have received honoraria for consulting on advisory boards with Biogen and Genentech

Grant Support: None.

Poster 237
Description of a historical cohort of patients with acute optic neuritis in the Middle East

Alberto Galvez-Ruiz[1], Adolfo Jiménez[2]

[1]Cleveland Clinic Abu Dhabi, Majadahonda, Spain, [2]Hospital Ruber Internacional, Madrid, Spain

Introduction:
Epidemiological studies suggest that the Middle East exhibits a low frequency of multiple sclerosis (MS). However, our clinical practice in Saudi Arabia contradicts these studies because our practice frequently sees patients with MS. This study will describe 282 patients with optic neuritis (ON) from January 2010 to December 2012 as the first episode of MS seen at King Khaled Eye Specialist Hospital.

Methods:
The clinical evolution will be described through a second visit at one year of follow-up for nearly all patients. Different representative clinical variables were selected: age, gender, visual acuity, color perception, relative afferent pupillary defect, visual field test, aspect of the optic nerve in fundoscopy, optical coherence tomography (OCT) follow-up (in patients with available OCT images), and findings from brain MRI.

Results:
The only variables that were related in a statistically significant way with low residual visual acuity were the presence of recurrent optic neuritis and the presence of pallor in the contralateral optic nerve. The only variables that were related in a statistically significant way with the presence of immunomodulator treatment at the second visit were the presence of periventricular lesions in cranial magnetic resonance and low visual acuity in the first visit

Conclusions:
The profile of a patient with optic neuritis in the Middle East is similar to that presented in the Optic Neuritis Treatment Trial (ONTT) study. One could hypothesize that a higher aggressiveness in the clinical manifestation of MS is present in an Arab population (greater presence of demyelinating-type lesions at the time of recruitment and a high percentage of patients with immunomodulator treatment at one year of evaluation), but these data must be interpreted with caution due to the clear limitations of this study.

References: 1. Evans C, Beland SG, Kulaga S, Wolfson C, Kingwell E, Marriott J, Koch M, Makhani N, Morrow S, Fisk J, Dykeman J, Jetté N, Pringsheim T, Marrie RA. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology. 2013;40(3):195-210. 2. Guimond C, Dyment DA, Ramagopalan SV, Giovannoni G, Criscuoli M, Yee IM, Ebers GC, Sadovnick AD. Prevalence of MS in Iranian immigrants to British Columbia, Canada. J Neurol. 2010 Apr;257(4):667-8. 3. Poppe AY, Wolfson C, Zhu B. Prevalence of multiple sclerosis in Canada: a systematic review. Can J Neurol Sci. 2008 Nov;35(5):593-601. 4 Ebers GC. Optic neuritis and multiple sclerosis. Arch Neurol. 1985 Jul;42(7):702-4.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

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Poster 238
Reassessment Of Whether Herpes Zoster is Associated With Giant Cell Arteritis

Charles Grose[1], Nasreen Syed[1], Erin Buckingham[1], Matthew Thurtell[1], Randy Kardon[2]

[1]University of Iowa College of Medicine, Iowa City, Iowa, USA, [2]University of Iowa College of Medicine and Iowa City VA Medical Center, Iowa City, Iowa, USA

Introduction:
The inciting cause of the inflammatory process in giant cell arteritis (GCA) is unknown. Herpes zoster (shingles) is the reactivation of varicella-zoster virus (VZV) during late adulthood. One recent report by Gilden et al found herpes zoster antigen in 74% of 82 temporal artery biopsies obtained from GCA patients (Neurology 2015). A second 2016 study conducted by Pisapia and Lavi of 19 biopsies failed to confirm the findings of the first study. Because of the conflicting reports about herpes zoster antigen, the goal of this project was to evaluate temporal artery specimens diagnosed as GCA by our Ocular Pathology Laboratory, to see if they have evidence of zoster antigen, and then to correlate positive laboratory findings with clinical data.

Methods:
Each artery sample was first examined by an ophthalmic pathologist for histologic evidence of GCA. Slides adjacent to sections with convincing evidence of GCA were examined for the presence of zoster antigen by immunohistochemistry and/or immunofluorescence. Results were then reviewed by 2 virologists and 2 neuro-ophthalmologists.

Results:
To date, 16 GCA samples have been analyzed and categorized into likely positive for VZV, equivocally positive for VZV, and likely negative for VZV. After initial analyses, we found three strong VZV positives out of the 16 (~19%). In addition, we discovered that calcifications in the arteries led to false positive immunohistochemistry results, a finding not reported in the earlier papers. We also discovered that some commercial zoster reagents were less reliable than those available only in a VZV research laboratory.

Conclusions:
We conclude that the percentage of zoster positivity in temporal artery biopsies during GCA from our ophthalmology clinic was far less than the 70% reported previously. Of importance, however, we also conclude that evidence of herpes zoster antigen was detectable in a smaller percentage of GCA biopsy samples.

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Keywords: Neuro-ophth & infectious disease (eg, AIDS, prion), Vascular disorders

Financial Disclosures: The authors had no disclosures.

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Poster 239
Vision and Other Sideline Testing in a Multidisciplinary Outpatient Concussion Center

G Kyle Harrold[1], Lisena Hasanaj[1], Nicholas Moehringer[1], Isis Zhang[1], Rachel Nolan[1], Liliana Serrano[1], Jenelle Raynowska[1], Steven Flanagan[1], Dennis Cardone[1], Steven Galetta[1], Laura Balcer[1]

[1]*New York University School of Medicine, New York, New York, USA*

Introduction:
This study investigated the utility of sideline concussion tests, including components of the Sports Concussion Assessment Tool, 3rd Edition (SCAT3) and the King-Devick (K-D), a vision-based test of rapid number naming, in an outpatient, multidisciplinary concussion center treating patients with both sports-related and non-sports related concussions. The ability of these tests to predict clinical outcomes based on the scores at the initial visit was evaluated.

Methods:
Scores for components of the SCAT3 and the K-D were fit into regression models controlling for age, gender, and sport/nonsport etiology in order to predict clinical outcome measures including total number of visits to the concussion center, whether the patient reached a SCAT3 symptom severity score ≤7, and the total types of referrals each patient received over their course. Patient characteristics, differences between those with sport and nonsport etiologies, and correlations between the tests were also analyzed.

Results:
SCAT3 total symptom score and symptom severity score at the initial visit predicted each of the clinical outcome variables. K-D score at the initial visit predicted the total number of visits and the total number of referrals. Those with sports-related concussions were younger, had less severe test scores, and fewer visits and types of referrals, were more likely to have clinical resolution of their concussion, and were more likely to reach a symptom severity score ≤7.

Conclusions:
This study supports the use of sideline concussion tests as part of outpatient concussion treatment, especially the total symptom and symptom severity score portions of the SCAT3 and the K-D. It also suggests that nonsports-related concussions tend to be more long lasting than sports-related concussions and that these two groups should perhaps be regarded separately.

References: None.

Keywords: Ocular manifestations of vestibular disorders, Vestibular, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 240

Vascular Autoregulatory Response In Neural Tissue: A Prospective Cohort Study Of The Eye In Pregnancy

Robert Herman[1], T. Lee-Ann Hawkins[2], R. Geoff Williams[3], Kara Nerenberg[4], Kelly Zarnke[1], Fiona Costello[5]

[1]Division of General Internal Medicine, Department of Medicine, University of Calgary, Calgary, Canada, [2]Obstetric Internal Medicine, Department of Medicine, University of Calgary, Calgary, Canada, [3]Section of Ophthalmology, Department of Surgery, University of Calgary, Calgary, Canada, [4]Obstetric Internal Medicine, Department of Medicine, University of Calgary, Calgary, Canada, [5]Section of Neuro Ophthalmology, Department of Neurosciences, University of Calgary, Calgary, Canada

Introduction:

Eye is brain and the superficial retinal circulation is homologous in structure and function to that of brain, including its ability to autoregulate (AR). Earlier studies of the human eye suggest hemodynamic changes that accompany normal pregnancy invoke and test the integrity of neural-type AR and this can be measured using Spectral Domain Optical Coherence Tomography (SD-OCT). Specifically, the macula thins by 3-5% of its thickness in early normal pregnancy. We propose this is due to a leftward shift in AR caused by increased capillary permeability. If correct, it should be possible to interrogate the limits of AR against systemic BP.

Methods:

Repeated measurements of mean arterial pressure (MAP) and SD-OCT were prospectively collected in 105 normal pregnant and pregnant patients with high-risk for hypertensive disorders of pregnancy (HDP) at gestational dates < 20wks, 20-40wks, at delivery and post partum/non-pregnant. Macular thickness was measured from the internal limiting membrane to the retinal pigment epithelium over the ETDRS grid. Clinically meaningful change was defined as ≥ ±4μ (Coefficient of Repeatability) in ≥3 contiguous segments.

Results:

We report early findings in a subgroup of 11 normal pregnant (NP) patients and 26 patients with HDP. After initial thinning, the retina was stable in all NP patients with no capillary leak up to and including delivery. In 15 HDP patients, the retina leaked following initial thinning. MAP at the time of leak in those with no prior history of hypertension (no pHTN) was significantly lower (90 mmHg; 95%CI 84-95; n=8) than those without leak (109 mmHg; 95%CI 104-113; n=10), of which, all had pHTN. In those with pHTN and leak, MAP at leak was higher (124 mmHg; 95%CI 108-139; n=6) than both other groups.

Conclusions:

Patients with HDP leak at much lower MAP than normal individuals (147 mmHg; 95%CI 143-150, n=149). Prior HTN right-shifts the AR curve.

References: None.

Keywords: Vascular disorders, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 241
Clinical Assessment of Biopsy-Proven Temporal Arteritis in an Australian Tertiary Referral Hospital

Neeranjali Jain[1], Shahriah Amjadi[1], Farshad Abedi[1], Ying Liu[1], Ian Francis[1]

[1]*Department of Ophthalmology, Prince of Wales Hospital, Sydney, Australia*

Introduction:
Patients with temporal arteritis may present initially not only to ophthalmologists and neurologists, but also to emergency departments and other physicians. All groups must be confident in assessing patients presenting with possible temporal arteritis, as delays in treatment may have devastating consequences. This study aimed to review and to compare the initial assessments of patients with biopsy-confirmed temporal arteritis by doctors at the eye clinic and the emergency department of a major Australian teaching hospital.

Methods:
The case records of patients with positive temporal artery biopsies between 2000 and 2012 at an Australian tertiary referral teaching hospital were examined. Data regarding patient demographics, medical and ophthalmological history, signs and laboratory findings were recorded.

Results:
412 patients underwent temporal artery biopsies of which 61 (15%, average age 77±9) were positive for temporal arteritis. 50% of patients were seen at the eye clinic and 34% at the ED. Compared with patients presenting at the ED, patients assessed at the eye clinic were asked more frequently about symptoms of jaw claudication (71% vs. 27%), visual changes (57% vs. 33%) and proximal pain or stiffness (38% vs. 20%). Reduction in visual acuity and the presence of a relative afferent pupillary defect were also sought more frequently in the eye clinic compared to the ED (91% vs. 41% and 76% vs. 33% respectively). Systemic features of temporal arteritis including weight loss, malaise and fever were asked about in less than a third of cases in both settings.

Conclusions:
The assessment of patients with suspected temporal arteritis varied between doctors at the ED and the eye clinic. A proforma with the important symptoms and signs of temporal arteritis might facilitate a more similar comprehensive assessment in all settings in which patients with potential temporal arteritis are assessed.

References: None.

Keywords: Optic neuropathy, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 242

Video-oculographic recording of the electronic Mobile Universal Lexicon Evaluation System (eMULES) rapid picture naming task

Todd Hudson[1], John-Ross Rizzo[1], Wei-Wei Dai[2], Lisena Hasanaj[1], Janet Rucker[1], Steven Galetta[1], Laura Balcer[1]

[1]NYU Langone Medical Center, New York, New York, USA, [2]NYU Tandon School of Engineering, New York, New York, USA

Introduction:

The Mobile Universal Lexicon Evaluation System (MULES) is a new test of rapid picture naming under investigation as a concussion screen(1). The MULES includes 54 color photographs of fruits, objects and animals. It has demonstrated excellent feasibility for administration among adult volunteers and in cohorts of athletes of all ages. MULES likely captures a more extensive neural network compared to rapid number naming (e.g., the King-Devick test), integrating saccades, color perception, figure-ground separation, and object identification. The present study examines the ocular motor underpinnings of performance in this vision-based measure.

Methods:

Participants underwent testing with an electronic (computer-screen-based) version (eMULES) designed for simultaneous testing with infrared-based video-oculography (Eye Link 1000+). Saccade data were extracted from raw gaze position traces, and saccade metrics including velocities, durations and inter-saccadic intervals were measured.

Results:

Among adult volunteers (n=23, aged 19-45) and patients with recent concussion (n=6, aged 17-43), those generating the greatest number of saccades had the longest eMULES completion times (r_s=.48, p=.008). In this cohort, prolonged ISI was not associated with greater eMULES testing times (r_s=.06, p=.76).

Conclusions:

Video-oculographic studies of the King-Devick (K-D) test of rapid number naming demonstrate prolonged inter-saccadic intervals (ISI) and an increased number of saccades among individuals with prolonged testing times(2). Here we demonstrate a correlation between the number of saccades generated to name pictures and total test time, but not between the median ISI duration and test time, possibly reflecting different degrees of visual and cognitive processing for picture compared to number naming. difference in correlations between eye movement metrics and completion times in the K-D and eMULES tests suggest slightly different underlying dynamics responsible for the overall completion times. This pattern Underlying dynamics for eye movements are likely to differ between picture- and number-naming, supporting complementary roles for each in concussion assessment.

References: (1) Cobbs, Hasanaj, Amorapanth, Rizzo, Nolan, et. al., Mobile Universal Lexicon Evaluation System (MULES) test: A new measure of rapid picture naming for concussion, Journal of the Neurological Sciences, http://dx.doi.org/10.1016/j.jns.2016.10.0442, 2016. (2) Rizzo, Hudson, Dai, Birkemeier, Pasculli, et. al., Rapid number naming in chronic concussion: eye movements in the King–Devick test. Annals of Clinical and Translational Neurology, 3(10): 801–811, 2016.

Keywords: Stroke Trauma, Higher Visual Cortical functions

Financial Disclosures: The authors had no disclosures.

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Poster 243

Characterization of Serological Markers (ESR, CRP, Platelets) of Healed/Healing Arterial Injury and Biopsy Positive GCA

Vinay Kansal[1], Sangsu Han[1], James Farmer[1], Danah Albreiki[1]

[1]*University of Ottawa, Ottawa, Canada*

Introduction:

Temporal artery biopsy (TAB) confirms the diagnosis of giant cell arteritis (GCA). However, the histopatholgic diagnosis of healed/healing arterial injury is not well understood. The purpose of this study was to further elucidate the clinical significance of this finding on TAB, by determining its association with seromarkers typically predictive of GCA.

Methods:

Single-centre, retrospective, cohort study. 385 consecutive TABs for clinically suspected GCA between January 2009 and January 2016 were reviewed. Elevations of inflammatory seromarkers, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelets were compared between patients with negative, GCA positive, and healed/healing (HH) arterial injury TAB using statistical trend testing (Mantel-Haenszel and Jonckheere-Terpstra tests). Odds ratios of seromarker elevations for healed/healing arterial injury versus GCA were calculated.

Results:

76 GCA positive, 69 HH, and 240 negative TABs. Trend tests indicated that platelets>400,000/µL (p400,000/µL. Neither ESR nor CRP were predictive of HH TAB. The odds ratio of positive TAB was 7.1 (3.3-15.6) with platelets>400,000/µL, 2.2 (1.2-3.8) with ESR≥50mm/hr, and 3.2 (1.8-5.8) with CRP≥24.5mg/L. Combined elevated platelets, ESR and CRP had odds ratio of predicting HH TAB of 3.9 (1.2-16.1). Elevated platelets combined with ESR had odds ratio of 4.0 (1.1-14.4). Elevated platelets combined with CRP has odds ratio of 4.8 (CI95% 1.5-15.1). Combining elevated ESR and CRP was not predictive of healed/healing TAB.

Conclusions:

In the proper clinical setting, HH TAB should be treated as GCA to prevent potential adverse outcomes. This study shows that thrombocytosis is an independent predictor of HH TAB. Thrombocytosis might be considered when deciding to treat this entity. Further studies are required to better understand this entity.

References: None.

Keywords: Vascular disorders, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 244

Analysis of Standard Visual Function Measures Among Children with Cortical Visual Impairment

Richard Legge[1], James Legge[2]

[1]Truhlsen Eye Institute - University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]George Mason University, Fairfax, Virginia, USA

Introduction:

Pediatric cortical visual impairment (PCVI) is the most common cause of visual impairment in children in industrialized countries (1,2,3). Such children are frequently unable to perform standard tests of visual function. The purpose of this study is to analyze the prevalence of the ability to do age appropriate standard visual function measurements in a clinic population of PCVI patients, and correlate these findings with neurologic and ophthalmologic disease states.

Methods:

65 consecutive cases were retrospectively studied. The ability to perform standard visual function measures, neurologic and ophthalmologic diagnoses were tabulated. Prevalence of these measures, and correlations with diagnoses were calculated. The cases were divided into age cohorts: 0.5-2, 3-4 and 5-18 years of age.

Results:

45/65 (69%) of patients were unable to do standard tests of visual function. In the 5-18 year old cohort, 31/42 (74%) were unable to perform visual acuity testing, The 3-4 year old cohort had the highest rate of inability to do testing at 82%. Of the 5-18 year olds with measurable visual acuity, 82% had better than 20/200 visual acuity. The presence of seizure disorder and optic nerve head pallor in the same patient highly correlated with an inability to do standard visual acuity measurements, 12/13 (92%, $p<.001$).

Conclusions:

A large proportion (69%) of PCVI patients were unable to be assessed with standard measures of visual function. Therefore, alternative methods should be developed by which to measure visual function in PCVI patients. However, the prevalence of measurable visual acuity in the 5-18 year olds was not insignificant (26%) and therefore, standard measures of visual function testing should be attempted in this cohort. Of the children with measurable visual acuity, most were better than 20/200. The presence of both seizure disorder and optic atrophy correlated highly with the inability to do standard visual function testing.

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Keywords: Pediatric neuro-ophthalmology, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 245
Matched eyes from a natural history study as an external control group in LHON

Marc Levin[1], Diana Petraki[2]

[1]Palo Alto Medical Foundation, Palo Alto, California, USA, [2]Santhera Pharmaceuticals (Canada), Montreal, Canada

Introduction:
Leber's Hereditary Optic Neuropathy (LHON) is an orphan mitochondrial disease resulting in loss of vision due to optic nerve atrophy. The efficacy of idebenone, a synthetic analogue of coenzyme Q10, in LHON has been demonstrated in a randomized controlled trial (Klopstock et al., 2011) and in a case series comparing treated and untreated patients (Carelli et al., 2011); further placebo-controlled trials in LHON are therefore considered unethical. However, inability to control bias due to the lack of randomization, blinding and comparability of the control group is the major and well-recognized limitation of externally controlled open-label studies (OLS). More persuasive and potentially less biased approaches include selection of patient data from a control group, as similar as possible to the OLS population and in which observations use timing and methodology similar to those used in the OLS, prior to performing comparative analyses.

Methods:
Here we report the baseline data for an OLS (Expanded Access Program (EAP)) in LHON and compare these data to the baseline data from a previously conducted natural history case record survey (CRS).

Results:
120 eyes from the EAP had a mean (SD) time to treatment of 6 (3) months and a baseline visual acuity of 1.41 (0.61) logMAR. These compared favorably with characteristic from 102 matched eyes in the CRS [5 (4) months, 1.33 (0.65) logMAR] that were selected from a total of 212 eyes [4 (4) months; 1.03 (0.64) logMAR] in the CRS.

Conclusions:
Matching treated and untreated eyes or patients can improve comparability and reduce selection bias in natural history control datasets. A prospectively planned matching scheme will therefore be used to select control group data from an expanded CRS. The visual acuity outcomes from this control group will be compared to the outcomes of the on-going LEROS OLS of idebenone in LHON.

References: Carelli V, La Morgia C, Valentino ML, Rizzo G, Carbonelli M, De Negri AM, Sadun F, Carta A, Guerriero S, Simonelli F, Sadun AA, Aggarwal D, Liguori R, Avoni P, Baruzzi A, Zeviani M, Montagna P, Barboni P. Idebenone treatment in Leber's hereditary optic neuropathy. Brain. 2011 Sep;134(Pt 9):e188. Epub 2011 Aug 2. Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain. 2011; 134:2677-2686.

Keywords: Optic neuropathy, Genetic Disease

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Poster 246

Identifying Incidence and Risk Factors of Post Lumbar Puncture Low-Pressure Syndrome in Pseudotumor Cerebri Patients

Patricia Lu[1], Manu Goyal[1], Gregory Van Stavern[1]

[1]*Washington University School of Medicine, Saint Louis, Missouri, USA*

Introduction:

Pseudotumor cerebri (PTC) is a condition where intracranial pressure is elevated idiopathically, resulting in disabling headaches and the risk of permanent vision loss. It is diagnosed with fluoroscopy-guided lumbar puncture, which often improves symptoms but can also inadvertently lead to low-pressure syndrome. Severe low-pressure syndrome requires a blood patch to plug the leak of cerebrospinal fluid, an effective way to resolve symptoms. The incidence of post-lumbar puncture low-pressure syndrome in PTC is unknown but traditionally thought to be low. Therefore, the purpose of this study is to examine the rates of low-pressure syndrome in PTC patients and identify correlations between lumbar puncture techniques and subsequent low-pressure syndrome.

Methods:

We retrospectively reviewed patient records from the Neuro-Ophthalmology and Neuroradiology database at our institution. Demographics, diagnostic lumbar puncture parameters, and blood patch status were collected for PTC patients and a control group of multiple sclerosis patients who also received diagnostic lumbar punctures.

Results:

106 PTC patients and 149 controls were analyzed. There was no significant difference in blood patch rate between the groups, although PTC trended to be higher ($p=.08$). PTC patients had a significantly higher BMI ($p<.001$) and opening pressure ($p<.001$) than the controls, as expected. Within the PTC group, a lower BMI and a larger difference between opening and closing pressure after the LP were linked to a higher rate of blood patches, although the differences did not reach statistical significance ($p=.08$ for both).

Conclusions:

PTC patients have a similar incidence of low-pressure syndrome compared to controls, suggesting that elevated intracranial pressure may not be protective. Within PTC patients, a lower BMI and a greater pressure difference may increase the chances of needing a blood patch. An understanding of these risks and associations of low-pressure syndrome is important when making decisions on diagnostic procedures and follow-up in PTC patients.

References: Monserrate, Ryman, Ma, Xiong, Noble, Factors Associated with the Onset and Persistence of Post-Lumbar Puncture Headache, JAMA Neurology, 72, 325-332, 2015 Ahmed, Jayawarna, Jude, Post Lumbar Puncture Headache: Diagnosis and Management, Postgraduate Medical Journal, 82, 713-716, 2006

Keywords: Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 247

Evaluating Multiple Sclerosis and Traumatic Brain Injury Using OCT-Based Quantification of Visual Fixation

Robert Mallery[1], Pieter Poolman[2], Matthew Thurtell[3], Jan Full[2], Gavin Thorsrud[4], Alicia Kielbasa[5], Teresa Frohman[6], Casey Gilmore[7], Kelvin Lim[7], Elliot Frohman[8], Randy Kardon[9]

[1]Neurology, Brigham and Women's Hospital; Ophthalmology, Mass Eye and Ear, Boston, Massachusetts, USA, [2]Ophthalmology & Visual Sciences, University of Iowa; Iowa City VA Healthcare System, Iowa City, Iowa, USA, [3]Ophthalmology & Visual Sciences, University of Iowa, Iowa City, Iowa, USA, [4]Minneapolis VA Healthcare System, Minneapolis, Minnesota, USA, [5]Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota, USA, [6]Neurology & Neurotherapeutics, UT Southwestern School of Medicine, Dallas, Texas, USA, [7]Defense and Veterans Brain Injury Center, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA, [8]Neurology & Neurotherapeutics and Ophthalmology, UT Southwestern School of Medicine, Dallas, Texas, USA, [9]Ophthalmology & Visual Sciences, University of Iowa; Iowa City VA Health Care System, Iowa City, Iowa, USA

Introduction:

This study assessed visual fixation as a novel indicator of neurologic dysfunction in multiple sclerosis (MS) and traumatic brain injury (TBI). Fixation, which relies on interactions between widely distributed visual sensory, motor, and attention centers, may become disturbed in MS or TBI. Optical coherence tomography (OCT) devices that utilize scanning laser ophthalmoscope (SLO)-based eye tracking offer an accessible means for obtaining highly accurate visual fixation data.

Methods:

Twenty-seven normal subjects, 17 patients with relapsing-remitting MS, and 44 patients with mild TBI without optic neuropathy underwent macular OCT with 30 seconds of SLO-based eye tracking during fixation. Six of the MS patients had a history of unilateral optic neuritis. Kernel density estimation quantified fixation instability (measured in degrees-squared) from the distribution of fixation points on the retina. For a subset of control, MS, and TBI patients, microsaccade data from 30 second epochs of fixation were derived from SLO movie using a novel B-spline-based non-rigid image registration method.

Results:

Fixation instability was increased in MS eyes without prior optic neuritis (n=25, median 0.061 deg-squared, IQR 0.043-0.090 deg-squared) compared to normal eyes (n=87, median 0.030 deg-squared, IQR 0.020-0.076 deg-squared; p=0.013, Mann-Whitney U test). A further increase in fixation instability was seen for MS eyes with prior optic neuritis (n=6, median 0.12, IQR 0.077-0.21; p=0.04) compared with MS eyes without prior optic neuritis. There was no significant difference in fixation instability comparing TBI eyes (n=87, median 0.038 deg2, IQR 0.026-0.058, p=0.98) with normal eyes.

Conclusions:

Fixation instability was increased in patients with relapsing-remitting MS, independent of the history of optic neuritis, suggesting that fixation instability may be a useful marker of neurologic dysfunction in MS. Fixation instability was not apparent in patients with mild TBI. Further study is underway to assess for microsaccade abnormalities in MS and TBI patients.

References: Mallery, Poolman, Thurtell, Wang, Garvin, Ledolter, Kardon, The Pattern of Visual Fixation Eccentricity and Instability in Optic Neuropathy and Its Spatial Relationship to Retinal Ganglion Cell Layer Thickness, Invest Ophthalmol Vis Sci, 57(9), OCT429-37, 2016.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Ocular Motility, Demeylinating disease

Financial Disclosures: The authors had no disclosures.

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Poster 248
Causes of Reduced Visual Quality of Life in Patients with Migraine

Anastasia Neufeld[1], Seniha Ozudogru[1], Susan Baggaley[1], Melissa Cortez[1], Christina Bokat[1], Karly Pippitt[1], Judith Warner[1], Alison Crum[1], Bradley Katz[1], Yue Zhang[1], Yingying Zhang[1], Kathleen Digre[1]

[1]*University of Utah, Salt Lake City, Utah, USA*

Introduction:
The purpose of the study is to determine the causes of reduced vision-specific quality of life (QOL) in patients with migraine. Our group previously showed that visual QOL scores of patients with migraine are significantly reduced, and are similar to those with other neuro-ophthalmic disorders, such as multiple sclerosis and optic neuritis (1). Possible causes of reduced visual QOL are photophobia, visual aura, and dry eye syndrome.

Methods:
Patients with chronic and episodic migraine were recruited from the Headache Clinic at the University of Utah. We administered validated Visual Function Questionnaire-25 (NEI-VFQ-25), 10-item NEI-VFQ-25 Neuro-Ophthalmic (NO) Supplement, the Headache Impact Test (HIT-6), aura questionnaire, photophobia questionnaire, and ocular surface disease index (OSDI) questionnaire (2-6). We plan to enroll 150 participants. We used Pearson's correlation coefficients to perform statistical analysis.

Results:
We report initial findings on patients with chronic and episodic migraine with (n =11) and without aura (n=12). Mean age was 45 years, with a female to male ratio of 3:1 in both groups. In the migraine with aura group, a statistically significant relationship, using Pearson's correlation coefficient, was seen between VFQ25 and aura scores (R=-0.64, p=0.032), and HIT-6 and OSDI scores (R=0.62, p=0.044). In the migraine without aura group, a significant correlation was found between the VFQ25 and OSDI scores (R=-0.65, p=0.021), and HIT-6 and photophobia scores (R=0.61, p=0.037).

Conclusions:
Migraine with aura patients' reduced visual QOL correlated most closely with aura symptoms. Migraine without aura patients' reduced visual QOL correlated most closely with dry eye symptoms, and their HIT-6 scores correlated most closely with photophobia scores. These early findings support targeted treatment of dry eye, photophobia and aura symptoms to improve visual QOL in migraine patients. Further data will allow us to address differences between episodic and chronic migraine patients.

References: 1. Hanson, Ahmed, Katz, Warner, Crum et al. Visual Quality of Life in Migraine. Abstracts from the 58th Annual Scientific Meeting American Headache Society, 9 June 2016. 2. Mangione, Lee, Gutierrez, Spritzer, Berry et al. Development of the 25-item National Eye Institute Visual Function Questionnaire, Arch Ophthalmol, Jul: 119 (7), 2001. 3. Yang, Rendas-Baum, Varon, Kosinski. Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. Cephalalgia, 31(3): 357-67, 2011. 4. Schiffman, Christianson, Jacobsen, Hirsch, Reis. Reliability and validity of the Ocular Surface Disease Index, Arch Ophthalmol, May: 118 (5), 2000. 5. Eriksen, Thomsen, Olesen. The Visual Aura Rating Scale (VARS) for migraine aura diagnosis, Cephalalgia, Oct: 25(10), 2005. 6. Uddin, Katz, Digre. Visual Quality Of Life And Photophobia Thresholds In Migraine Patients. Manuscript in preparation.

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 249
Inter-Eye Difference Threshold in Retinal Nerve Fiber Layer Thickness that Predicts an Optic Nerve Lesion

Rachel Nolan[1], Steven Galetta[1], Laura Balcer[1]

[1]NYU School of Medicine, New York, New York, USA

Introduction:
The optic nerve and anterior visual pathway are frequent sites for involvement in multiple sclerosis (MS). OCT can be used to detect thinning of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL+IPL) in eyes of patients with MS or in the case of clinically- or radiologically-isolated syndromes. We sought to determine a threshold of inter-eye difference in RNFL thickness predictive of an optic nerve lesion.

Methods:
Participants in an ongoing study of MS and disease-free controls at a single study site underwent spectral-domain (SD-) OCT measurement of RNFL thickness as well as high- and low-contrast letter acuity testing.

Results:
Among 137 patients with MS (age 43±12 years) and 30 disease-free controls (age 30±9 years), RNFL thickness was similar between right and left eyes (86.7±17.6 microns right vs. 85.7±19.0 microns left for MS and 93.4±10.8 right vs. 93.5±10.9 microns left for controls). The average value of the inter-eye difference (7.7±9.5 microns for MS and 2.4±1.9 microns for controls) was a predictor of disease vs. control status (p=0.01, linear regression accounting for age). Within the MS cohort, an inter-eye difference equivalent to the 95th percentile or greater for controls was 6 microns or greater and was predictive for worse scores binocular low-contrast letter acuity at the 2.5% (p=0.01) and 1.25% levels (p=0.002, linear regression accounting for age).

Conclusions:
A 6-micron difference between MS eyes is an appropriate threshold at which to begin to validate the presence vs. absence of an optic nerve lesion for purposes of diagnosis and monitoring disease progression in patients with MS. Inter-eye differences in RNFL thickness at the 95th percentile or above predict MS eyes with impaired visual function.

References: None.

Keywords: Demeylinating disease, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 250
Are patients with thyroid orbitopathy deficient in selenium and/or vitamin D?

Ama Sadaka[1], Shauna Berry[1]

[1]*Houston Methodist Hospital, Houston, Texas, USA*

Introduction:
Selenium is a potent nutritional antioxidant that regulates reactive oxygen species and redox status in all tissues influencing inflammation and immune responses. A European study on mild Graves' orbitopathy showed that supplementation with selenium improved quality of life, reduced ocular involvement, and slowed progression of the disease. Vitamin D has been hypothesized to promote the maintenance of immune homeostasis and supplementation is thought to benefit patients with multiple sclerosis for example. The aim of the study is to determine whether serum selenium and vitamin D levels are low in patients with thyroid orbitopathy.

Methods:
This is a retrospective chart review of all patients with known history of autoimmune thyroid eye disease with signs or symptoms of thyroid orbitopathy who had their selenium levels and vitamin D levels measured. Data analysis was performed. Patient with any deficiency were given supplements.

Results:
Data analysis is in progress and will be complete prior to the poster presentation.

Conclusions:
Conclusion is in progress and dependent on the results section.

References: None.

Keywords: Graves (systemic disease)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 251
Central retinal vascular bifurcation in Superior Segmental hypoplasia

Tarek Shazly[1]

[1]*University of Pittsburgh, Department of Ophthalmology, Pittsburgh, Pennsylvania, USA*

Introduction:
To characterize the central retinal artery bifurcation in relation to the vertical center of the optic nerve head (ONH) in nerves with superior segmental optic hypoplasia (SSOH) using fundus photography.

Methods:
Medline search revealed 35 publications about SSOH, 18 of which provided 51 fundus photos of nerves with confirmed SSOH. The photos were analyzed using image J to characterize the relationship between the point of CRA bifurcation and the vertical midpoint of the ONH.

Results:
The ratio of inferior nerve pole - bifurcation distance to the superior nerve pole - bifurcation distance was 1.4-3.3 (mean 1.9 +/- 0.37). The distance of the bifurcation to the vertical mid point of the ONH was 1-3.2 central vein diameter (mean 1.9 +/- 0.47).

Conclusions:
The publication provides a simple visual clue to the diagnosis of SSOH, especially in patients with confounding optic nerve pathologies such as glaucoma.

References: 1- Petersen RA, Walton DS. Optic nerve hypoplasia with good visual acuity and visual field defects. Arch Ophthalmol. 1977;95:254–8. 2- Bjork A, Laurell CG, Laurell U. Bilateral optic nerve hypoplasia with normal visual acuity. Am J Ophthalmol. 1978;86:524–9. 3- Nelson M, Lessell S, Sadun AA. Optic nerve hypoplasia and maternal diabetes mellitus. Arch Neurol. 1986;43:20–5. 4- Kim RY, Hoyt WF, Lessel S, et al. Superior segmental optic hypoplasia. A sign of maternal diabetes mellitus. Am J Ophthalmol. 1989;107:1312–15. 5- Brodsky MC, Schroeder GT, Ford R. Superior segmental optic hypoplasia in identical twins. J Clin Neuro-Ophthalmol. 1993;13:152–4.

Keywords: Genetic Disease, Visual fields, Orbit/ocular pathology

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 252

Retinal Nerve Fiber Layer may be Better Preserved in MOG versus AQP4-Positive Optic Neuritis

Hadas Stiebel-Kalish[1], Itay Lotan[2], Judith Brody[3], Gabriel Chodick[4], Omer Bialer[5], Romain Marignier[6], Michael Bach[7], Mark Hellmann[2]

[1]Sackler School of Medicine, Tel Aviv University & Rabin Medical Center, Petah Tikva, Israel, [2]Sackler School of Medicine & Neuro-Immunology Service, Rabin Medical Center, Petah Tikva, Israel, [3]Sackler School of Medicine & Ophthalmology Dept., Rabin Medical Center, Petah Tikva, Israel, [4]Department of Epidemiology and Preventive Medicine, Tel Aviv University, Tel Aviv, Israel, [5]Sackler School of Medicine & Neuro-Ophthalmology Unit, Petah Tikva, Israel, [6]Service de Neurologie A, Hôpital Neurologique Pierre Wertheimer, Lyon, France, [7]Eye Center, Medical Center, University of Freiburg, Freiburg, Germany

Introduction:
Optic neuritis (ON) in patients with anti-myelin oligodendrocyte glycoprotein (MOG)-IgG antibodies has been associated with a better clinical outcome than anti-aquaporin 4 (AQP4)- IgG ON. Average retinal nerve fiber layer thickness (RNFL) correlates with visual outcome after ON. The aim of this study was to examine whether anti-MOG-IgG ON is associated with better average RNFL compared to anti-AQP4-IgG ON, and whether this corresponds with a better visual outcome.

Methods:
A retrospective study was performed in a consecutive cohort of patients following anti-AQP4-IgG and anti-MOG-IgG ON. A generalized estimating equation (GEE) models analysis was used to compare average RNFL outcomes in ON eyes of patients with MOG-IgG to AQP4-IgG-positive patients, after adjusting for the number of ON events. The final mean visual field defect, visual acuity, and latency of the visual evoked potential were compared between ON eyes of MOG-IgG and AQP4-IgG-positive patients. A correlation between average RNFL and visual function was performed in all study eyes.

Results:
Sixteen patients were analyzed; ten AQP4-IgG-positive and six MOG-IgG-positive. The six patients with MOG-IgG had ten ON events with disc edema, five of which were bilateral. In the AQP4-IgG-positive ON events, 1/10 patients had disc edema. Final average RNFL was significantly better in eyes following MOG-IgG-ON (75.33µm), compared to 63.63µm in AQP4-IgG-ON, after adjusting for the number of ON attacks (GEE, p=0.023). Mean visual field defects were significantly smaller (GEE, p=0.046) among MOG-IgG positive ON eyes compared to AQP-IgG positive ON eyes, but last visual acuity did not differ between the groups (GEE, p=0.153). Among all eyes, average RNFL positively correlated with mean visual field defect (GEE, p=0.00015) and negatively correlated with final visual acuity (GEE, p=0.00005).

Conclusions:
Following ON, RNFL is better preserved in eyes of patients with MOG-IgG antibodies compared to those with AQP4-IgG antibodies, correlating with better visual outcomes.

References: Wingerchuk, Banwell, Bennett, Cabre, Carroll, et al. , International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology, 85,:177-189, 2015. Kaneko, Sato, Nakashima, Nishiyama, Tanaka, et al. , Myelin injury without astrocytopathy in neuroinflammatory disorders with MOG antibodies, J.Neurol.Neurosurg.Psychiatry., 2016. Kleiter, Gahlen, Borisow, Fischer, Wernecke, et al. , Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses, Ann.Neurol., 79,:206-216, 2016. Petzold, de Boer, Schippling, Vermersch, Kardon, et al. , Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis, Lancet Neurol., 9,:921-932, 2010. Cruz-Herranz, Balk, Oberwahrenbrock, Saidha, Martinez-Lapiscina, et al. , The APOSTEL recommendations for reporting quantitative optical coherence tomography studies, Neurology, 86,:2303-2309, 2016. Marignier, Ruiz, Cavagna, Nicole, Watrin, et al. , Neuromyelitis optica study model based on chronic infusion of autoantibodies in rat cerebrospinal fluid, J.Neuroinflammation, 13,:111-016-0577-8, 2016.

Keywords: Demeylinating disease, Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 253
Pathologic markers for determining prognosis in patients with Giant Cell Arteritis

Harris Sultan[1], Patricia Chévez-Barrios[2]

[1]University of Texas Medical Branch, Galveston, Texas, USA, [2]Houston Methodist Hospital, Houston, Texas, USA

Introduction:
Recent advances in the understanding of the immunology of giant cell arteritis have suggested that chemokines expressed by vascular endothelium attract CD68+ macrophages to infiltrate the vascular endothelium and contribute in the vaso-occlusive disease of giant-cell arteritis. We hypothesize that the presence of these cells along the internal elastic lamina (IEL) of temporal artery biopsies (TAB) predict the prognosis for these patients.

Methods:
This is a retrospective study correlating clinical data with pathology specimens. The patients have been seen at a single neuro-ophthalmology clinic in a major U.S. city. The primary outcome measure was to define the number of CD68+ macrophages at the level of the IEL per histologic section with relation to clinical outcomes (referral to rheumatology, need for further immunomodulators, and recurrence of disease).

Results:
A total of 42 patients were reviewed, 15 male and 27 female. Average age of diagnosis was 72 with mean follow up of 57 weeks. Seventeen patients had recurrence of disease during their steroid taper, 25 requiring rheumatology referral, and 11 being placed on immunomodulators including methotrexate, azathioprine, and tocilizumab among others. When controlling for number of days on steroids prior to TAB, the number of disease recurrences were directly correlated to the number of CD68+ cells per histologic section ($p=0.037$, One-way ANOVA). Sections with greater than 2-CD68+ cells per slice were correlated with a greater chance of being placed on immunomodulators ($p=0.038$), however referral to rheumatology was not ($p=0.713$, Chi-square).

Conclusions:
The CD68+ macrophage marker and the location of these cells on the IEL can be a useful way to prognosticate clinical course in patients with presumed giant cell arteritis. Although referral to rheumatology was not found to be significant likely due to provider preferences, identifying an average of 2 or more CD68+ cells per section may predict likelihood of being placed on immunomodulator treatment.

References: None.

Keywords: Vascular disorders, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 254
Brain 3D DIR and Optic nerve functional analysis in Multiple Sclerosis

jean-philippe woillez[1], JULIEN BOULEAU[1], Christine Delmaire[1]

[1]CHRU LILLE, LILLE, France

Introduction:
To compare the results of optic nerve evaluation during Multiple Sclerosis (MS) Optical Neuritis (ON) with MRI 3D DIR imaging (Three-Dimensional Double Inversion Recovery) and Optic Nerve functional analyses.

Methods:
10 patients with Multiple Sclerosis (MS). Each patient was explored with brain MRI imaging: T2, Flair, 3D DIR. Results were performed by the same referring physician. Complementary ophthalmological investigations were performed: Visual Acuity (VA), VEP, Color Vision (CV), Central Visual Field (CFV), Contrast Vision (CV), OCT RNFL, OCT GCL.

Results:
Acute optical neuropathy is frequently an inaugural clinical manifestation of MS. Brain MRI is necessary to confirm diagnosis. Reference MRI imaging is T2. A recent additional imaging, 3D DIR, is performed. Optic nerve disturbances are frequently seen. We found dissociated results between 3D DIR Brain MRI imaging and Optic Nerve functional analyses performed in the same patient

Conclusions:
The 3D DIR Brain MRI imaging is frequently positive and appears to be more sensitive to detect optic nerve disturbances than reference brain MRI imaging. Optic Nerve functional analyses provide discriminant elements in the diagnosis.

References: MRI characteristics of neuromyelitis optica spectrum disorder: An international Update .Ho J. K., Friedemann P., M. A. Lana-Peixoto, et al. Neurology 2015;84;1165-1173 Comparison of 3D double inversion recovery and 2D STIR FLAIR MR sequences for the imaging of optic neuritis: pilot study.Hodel J, Outteryck O, Bocher AL, Zéphir H, Lambert O.Eur Radiol. 2014 Dec;24(12):3069-75.129:71–84

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuroimaging

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Grant Support: None.

Poster 255

Does the Combination of Acute Hearing Loss and Vertigo Increase Stroke Risk?

Tzu-Pu Chang[1], Zheyu Wang[2], Ariel Winnick[1], Hsun-Yang Chuang[3], Victor Urrutia[1], John Carey[4], David Newman-Toker[1]

[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [2]Department of Biostatistics, Johns Hopkins University School of Public Health, Baltimore, Maryland, USA, [3]Department of research, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan, [4]Department of Otolaryngology-HNS, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Introduction:

Hearing loss is often thought of as an inner ear ("peripheral") symptom, but SHL can be an initial manifestation of posterior circulation stroke ("central"), especially when co-occurring with vertigo. To date, no large-scale study has compared stroke risk across the following populations: (1) "sudden hearing loss (SHL) alone;" (2) "vertigo alone;" and (3) "SHL with vertigo." Here we compare long-term stroke risk among these patients using a large national healthcare database.

Methods:

Patients with first incident SHL (ICD-9-CM 388.2) or vertigo (ICD-9-CM 386.x, 780.4) identified from the National Health Insurance Research Database in Taiwan (2002-2009). We defined "SHL with vertigo" as patients with a vertigo-related diagnosis +/-30 days from the index SHL event. Those without a vertigo-related diagnosis (or temporally remote to the SHL) were considered "SHL alone." The "vertigo alone" group had no diagnosis of SHL. All of the patients were followed until stroke, death, withdrawal from database, or current end of database (December 31, 2012) for a minimum follow-up period of 3 years. Risks of stroke were compared across groups using hazard ratios (HR) and 95% confidence intervals (CI).

Results:

We studied 218,656 patients (1,998 SHL alone; 215,980 vertigo alone; 678 SHL with vertigo). Long-term stroke rates during follow-up were 3.0% (SHL alone), 3.9% (vertigo alone), and 5.5% (SHL with vertigo). The unadjusted hazard for stroke was higher in SHL with vertigo than SHL alone (p=0.001; HR=2.00, 95% CI=1.32-3.02) and vertigo alone (p=0.003; HR=1.63, 95% CI=1.18-2.25). After adjusting for age, gender, urban status, region, and cardiovascular risk, SHL with vertigo remained a stroke hazard relative to SHL alone (adjusted HR=1.75, 95% CI=1.15-2.65) but not vertigo alone (adjusted HR=1.22, 95% CI=0.89-1.69).

Conclusions:

The combination of SHL with vertigo appears to increase stroke risk over SHL alone. SHL in patients with vertigo is not necessarily a benign "peripheral" sign.

References: None.

Keywords: Vestibular, Stroke Trauma, Vascular disorders

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 256

Mobile Universal Lexicon Evaluation System (MULES): A New Rapid Sideline Picture Naming Test for Concussion

Lucy Cobbs[1], Lisena Hasanaj[1], Prin Amorapanth[1], John-Ross Rizzo[1], Rachel Nolan[1], Liliana Serrano[1], Jenelle Raynowska[1], Janet Rucker[1], Barry Jordan[2], Steven Galetta[1], Laura Balcer[1]

[1]NYU School of Medicine, New York, New York, USA, [2]Burke Rehabilitation Hospital, White Plains, New York, USA

Introduction:

Vision-based measures of rapid number naming (King-Devick [K-D]) have improved the sensitivity of sports-related concussion screening. K-D requires saccades and vergence, measuring aspects of frontal, parietal and brainstem centers. We developed the Mobile Universal Lexicon Evaluation System (MULES) to capture a more extensive vision network, integrating saccades, color perception, and object identification. This study introduces the MULES, a new vision-based test of rapid picture naming, in a cohort of youth and collegiate athletes at pre-season concussion testing.

Methods:

We administered MULES and K-D to youth and collegiate athletes during pre-season baseline testing. Sports for 2016-17 included ice hockey, football, soccer, volleyball and wrestling. Test administration order was randomized.

Results:

Among 165 athletes (age 14±5 years, range 6-24, 25% female), average K-D times (59.9±29.7 seconds) were similar to MULES (57.9±20.4 seconds). Higher K-D times predicted greater MULES times, accounting for age ($p<0.001$, linear regression). Age was itself a predictor of K-D and MULES time scores, with longer times noted for younger participants ($p<0.001$). Faster times with increasing age were noted primarily among athletes <16 years for K-D and <15 years for MULES. MULES showed greater degrees of improvement between two baseline trials (57.9 vs. 51.2 seconds, $p<0.0001$, paired t-test), vs. K-D (59.9 vs. 58.3 seconds, $p=0.01$).

Conclusions:

A complex task, the MULES test of rapid picture naming involves a more extensive visual network that captures not only rapid saccades but color perception and the characterization of objects. Color recognition is early in object processing and requires area V4 and the inferior temporal projections. In contrast, rapid number naming appears to engage a specific area of the inferior temporal cortex. Both tests use the centers responsible for initiating and sequencing saccadic eye movements, and will be further examined in our youth and collegiate cohorts during this athletic season for their ability to detect concussion.

References: None.

Keywords: Higher visual functions, Ocular Motility, Stroke Trauma

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Grant Support: None.

Poster 257
Hess screen testing shows an exodeviation shift compared to the Harms screen test

Muriel Dysli[1], Daniel Rappoport[2], Tanja Schmückle Meier[2], Christopher Bockisch[3], Klara Landau[2], Konrad Weber[1]

[1]Departments of Ophthalmology and Neurology University Hospital Zurich, Zurich, Switzerland, [2]Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland, [3]Depts of Ophthalmology, Neurology, Otorhinolaryngology, University Hospital Zurich, Zurich, Switzerland

Introduction:
Manifest ocular deviation (tropia) is present in strabismus patients while latent ocular deviation (phoria) is common in normal subjects. Besides the prism cover test for near and far, Hess and/or Harms screen testing are often performed to objectively assess the amount of ocular misalignment. This study investigates the differences of the results from Harms and Hess screen test, and the prism cover test.

Methods:
Ocular deviation measurements of 18 normal subjects and 41 patients with congenital or acquired paralytic or concomitant strabismus were assessed with a complete orthoptic examination including prism cover test for near (50cm) and far (3m) and compared to objective measurement methods using the Hess screen (50cm) and the Harms screen test (3m).

Results:
On average, subjects showed an exodeviation shift of 6.3° in the Hess screen when compared to the Harms screen test (3.6° for normals, 7.5° for patients). Subjects who were orthophoric in the prism cover test for near mainly showed an exodeviation in the Hess screen test, whereas in the Harms screen test no horizontal deviation was found. Likewise, subjects with a small esophoria in the cover test for near showed no deviation in the Hess screen test.

Conclusions:
Hess screen testing for near records a relative exodeviation compared to the Harms screen test for far and to the prism cover test for near. This shift most probably is due to the differences in measurement distance and convergence effort during the various tests. This study emphasizes the importance to consider the convergence angle when comparing the Hess screen test with other methods, and to test ocular deviations for near and far distances separately to get a representative assessment of the ocular deviations.

References: None.

Keywords: Ocular Motility, Adult strabismus with a focus on diplopia

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 258
Characteristics and Long Term Follow-Up of Isolated Vertical Nystagmus in Infancy

Imran Jivraj[1], Shannon Beres[2], Grant Liu[1]

[1]University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]Stanford University, Palo Alto, California, USA

Introduction:
Benign intermittent upbeat nystagmus has been described in otherwise healthy infants without a known cause (1, 2) but long term outcomes are not known. The clinical characteristics and long-term outcomes of infants who presented with vertical nystagmus and had normal neurological evaluation and neuroimaging were determined.

Methods:
IRB approval was granted. Medical records of 114 infants who were diagnosed with nystagmus from 1996-2016 were screened and patients with vertical nystagmus who were otherwise normal at presentation and had an unremarkable brain MRI were included. Parents of patients in the final study cohort were contacted by telephone to obtain long-term follow-up information.

Results:
Nine patients comprised the final cohort. Vertical nystagmus was first observed at a mean age of 2.0 (SD: 1.0) months and resolved in 88.9% of patients at an average age of 8.0 (SD: 9.4) months. One had persistent nystagmus. Vertical nystagmus was upbeat in 55.6%, pendular in 33.3%, downbeat in 11.1%; one patient with upbeat nystagmus later developed a horizontal waveform. 22.2% of patients underwent an EEG which was normal. 40% of patient guardians could be reached and completed the telephone questionnaire. The mean age of patients at follow-up was 3.3 (SD: 2.5) years. No patients had received an alternate diagnosis for the nystagmus. Iris transillumination was later discovered in one patient. 50% of children had speech delay. No other developmental delay or general medical conditions were identified. None of the patients had a known family history of nystagmus.

Conclusions:
We describe a large group of infants with isolated vertical nystagmus who were neurologically normal and had an unremarkable brain MRI. Nystagmus resolved in 88.9% of patients within the first three years. Follow-up questionnaire revealed that speech delay was present in half and iris transillumination was identified in one, but no other neurologic or ophthalmic conditions were identified.

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Keywords: Nystagmus, Pediatric neuro-ophthalmology, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 259
Wide Clinical Manifestations in Anti-GQ1b Antibody Syndrome with Ophthalmoplegia

Hyung-Keun Kim[1], Eun Hye Oh[1], Jae-Ho Jung[2], Kwang-Dong Choi[3], Jae-Hwan Choi[1]

[1]Department of Neurology, Pusan National University Yangsan Hospital, Yangsan, Korea, Republic of, [2]Department of Ophthalmology, Pusan National University Yangsan Hospital, Yangsan, Korea, Republic of, [3]Department of Neurology, Pusan National University Hospital, Busan, Korea, Republic of

Introduction:
Anti-GQ1b antibody is associated with acute paresis of extraocular muscles. It was mainly detected in Miller-Fisher syndrome (MFS) or acute ophthalmoplegia without ataxia (AO). The classic manifestations of MFS and AO are acute ophthalmoplegia and areflexia with or without ataxia. However, unusual presentations beyond a classic triad may also occur in MFS and AO. The aim of this study was to determine the frequency of clinical presentations other than a classic triad in anti-GQ1b antibody-associated MFS and AO.

Methods:
We retrospectively collected 25 patients who presented with acute diplopia due to anti-GQ1b antibody syndrome. The patients were classified into MFS (n=15) and AO (n=10). We analyzed clinical features beyond a classic triad (ophthalmoplegia, ataxia, and areflexia).

Results:
Of the 25 patients, 20 (80%) showed various neurological symptoms other than a classic triad. The most common symptoms were dysarthria (n=11, 44%) and limb paresthesia (n=6, 24%). Five (20%) had headache or ocular pain with moderate severity (mean Wong-Baker FACES Pain Rating Scale: 5.4 ± 1.1). Four (16%) had limb weakness with 4 or more on the Medical Research Council scale. Three showed horizontal diplopia and comitant esotropia that was larger at distance than at near without external ophthalmoplegia. Other manifestations included dysphagia (n=4), taste impairment (n=2), optic neuropathy (n=1), Bell's palsy (n=1) and facial dystonia (n=1).

Conclusions:
Our study demonstrated that MFS and AO associated with anti-GQ1b antibody can represent wide clinical manifestations beyond a classic triad. This suggests that the GQ1b gangliosides are widely expressed in central and peripheral nerve systems.

References: None.

Keywords: Ocular Motility, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 261
Thyroid autoantibodies in adults with acquired binocular diplopia

Haeng Jin Lee[1], Seong-Joon Kim[1]

[1]Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea, Republic of

Introduction:
To evaluate the presence of thyroid autoantibodies and relationship with the clinical features in adults with acquired binocular diplopia.

Methods:
The patients more than 17 years old with acquired binocular diplopia from January 2008 to July 2016 were retrospectively reviewed. Thyroid autoantibodies tests were performed for all the patients unless other causes of diplopia were clarified. Factors including age, sex, duration of diplopia, and angle of deviation were investigated. Patients were divided into two groups according to the results of thyroid autoantibodies: positive (TAb+) and negative (TAb-) group.

Results:
Among the total 136 patients, 81 patients (59.6%) showed TAb+. There were no differences in factors such as age, sex, and duration of diplopia between the two groups. In TAb+ group, there were 32 patients with microsomal Ab, 27 patients with TSH receptor Ab, 14 patients with thyroglobulin Ab, and 8 patients with thyroid stimulating Ab. The angle of horizontal deviation was 11.9 ± 11.1 prism diopters (PD) in TAb- group and 12.5 ± 14.8 PD in TAb+ group, and the angle of vertical deviation was 4.1 ± 7.0 PD in TAb- group and 9.2 ± 11.5 PD in TAb+ group (p=0.788, 0.005, respectively). The degree of duction limitation was -0.1 ± 0.3 in TAb- group and -0.6 ± 0.5 in TAb+ group (p<0.001). The ocular torsion was 16.4% in TAb- group and 39.1% in TAb+ group (p=0.009). In the TAb+ group, thyroid dysfunction was more common than TAb- group, but thyroid hormone levels did not associate with the clinical characteristics among them.

Conclusions:
In the patients with acquired binocular diplopia, the angle of vertical deviation and degree of duction limitation were larger, and ocular torsion and thyroid dysfunction were more common in the TAb+ group. Thyroid autoantibodies might be helpful in diagnosis of thyroid associated ophthalmopathy of euthyroid patients.

References: None.

Keywords: Adult strabismus with a focus on diplopia, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Ocular Motility, Graves (systemic disease)

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 262
Clinical Utility Of Assessing Acute/Subacute Vertical Strabismus In Different Head Positions

Joao Lemos[1], Mario Sousa[1], Jose Coelho[1], Luis Cunha[1], Adnan Subei[2], Christopher Glisson[2], Eric Eggenberger[2]

[1]Coimbra University Hospital Center, Coimbra, Portugal, [2]Michigan State University, Lansing, Michigan, USA

Introduction:
Skew deviation is a common cause of vertical strabismus. Occasionally, it may be difficult to distinguish skew from other causes (e.g., acquired 4th nerve palsy [4NP]). The upright-supine test showed excellent diagnostic accuracy for differentiating between longstanding skew and 4NP; however, there is no data concerning its diagnostic utility during acute/subacute presentation of vertical strabismus.

Methods:
We prospectively assessed patients with skew and 4NP within 2 months of initial presentation. The diagnosis was supported by brain MRI. Vertical strabismus was measured using alternate cover test with prisms in the upright and supine positions, both with the head straight and head tilt. Subjective cyclotorsion was evaluated with double Maddox rods in the upright and supine positions. The upright-supine test was considered positive if there was >50% improvement of vertical strabismus between upright and supine positions.

Results:
Twenty-one skew patients and 14 4NP patients were included, with a mean age of 58.9+/-16.8 and 59.3+/-13.4 years (p=0.91), male/female ratio of 13/8 and 10/4 (p=0.72), and mean duration of symptoms of 10+/-10 and 20+/-20 days (p=0.21), respectively. The head straight upright-supine test was positive in 1 patient with skew and in no 4NP patient (sensitivity, 5% specificity, 100% for skew). The upright-supine test with head tilt to the hyperdeviated eye side showed similar results; the upright-supine test with head tilt to the hypodeviated eye side was negative in all skew patients, but showed >50% worsening in supine position in 10 4NP patients (sensitivity, 71% specificity, 100% for 4NP). Ocular torsion changes between positions were either nonsignificant or without consistent direction both in skew and 4NP group.

Conclusions:
In the acute/subacute phase, skew deviation does not seem to be significantly modulated by head positions. In contrast, the hypertropia in contralateral head tilt in 4NP patients often increases in supine compared to upright position.

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Keywords: Adult strabismus with a focus on diplopia, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 263
Stroke And Transient Ischemic Attack Incidence After Acute Microvascular Ocular Motor Palsies

Ines Martins[1], Ricardo Varela[1], Mario Carvalho[2], Cristina Duque[1], Miguel Patrício[3], Joao Sargento-Freitas[1], Antonio Goncalves[1], Luis Cunha[1], Joao Lemos[1]

[1]Coimbra University Hospital Center, Coimbra, Portugal, [2]Coimbra University, Coimbra, Portugal, [3]Laboratory of Biostatistics and Medical Informatics, Health/Institute for Biomedical Imaging and Life Sciences, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Introduction:
Microvascular ocular motor palsies (OMP) have been regarded as a benign vascular condition with excellent prognosis. Contrasting with other types of stroke (e.g., lacunar), stroke recurrence after an episode of microvascular OMPs is largely unknown. We sought to determine the incidence of subsequent stroke or transient ischemic attack (TIA) in acute isolated microvascular third, fourth and sixth cranial nerve palsies.

Methods:
We reviewed the medical records of consecutive patients presenting either with OMP or lacunar stroke (LS) (controls) in the Emergency Department between January 2007 and October 2012. Outcome was defined as stroke or TIA during 36-months follow-up. Propensity score matching of OMP and LS patients was used to ensure balance between the two groups.

Results:
Fifty-seven OMP patients and 53 LS patients were included with a mean age of 66,6±13,4 and 65,3±12,4, respectively (p>0,05); 35,0% (OMP) 35,8% (LS) were male (p>0,05). There were no differences between groups (p>0,05) regarding previous history of diabetes, high blood pressure, dyslipidemia, ischemic heart disease, previous stroke or antiplatelet drug medication. Six out of 57 OMP patients (10,5%) had subsequent stroke or TIA, 4 during the 1st year, 1 during the 2nd year and 1 patient after this period. Three out of 53 LS patients (5,6%) had subsequent stroke, 2 during the 1st year and 1 during the 2nd year. No significant differences were found between groups concerning global/annual stroke rate, or its cumulative incidence (p=0,352 and 0.081, respectively). Neither risk factors, nor antiplatelet drug medication status, nor group status (OMP vs. LS) showed a significant impact on stroke recurrence in logistic-regression analysis.

Conclusions:
A significant proportion of patients with presumed microvascular ocular motor palsies developed subsequent stroke, matching the stroke recurrence rate of lacunar stroke patients. This finding stresses the importance of secondary prevention strategies in patients with microvascular ocular motor palsies.

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Keywords: Adult strabismus with a focus on diplopia, Vascular disorders, Ocular Motility, Stroke Trauma

Financial Disclosures: The authors had no disclosures.

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Poster 264
FRMD7 Variants Associated with Congenital Nystagmus in Korean Population

Eun Hye Oh[1], Hyung-Keun Kim[1], Jae-Ho Jung[2], Kwang-Dong Choi[1], Seung-Han Lee[3], Jae-Hwan Choi[1]

[1]Department of Neurology, Pusan National University Yangsan Hospital, Yangsan, Korea, Republic of, [2]Department of Ophthalmology, Pusan National University Yangsan Hospital, Yangsan, Korea, Republic of, [3]Department of Neurology, Chonnam National University Medical School, Gwangju, Korea, Republic of

Introduction:
Congenital nystagmus (CN) is the involuntary oscillation of the eyes with onset in the first few months of life. CN can be an idiopathic disease (idiopathic infantile nystagmus, IIN) or can be a feature of other ocular diseases. The inheritance of CN are heterogenous, but the most common form is X-linked-IIN. FRMD7 resides at Xq26-27 and approximately 50% of X-linked IIN families map to this region. Currently, over 70 different mutations within FRMD7 have been reported. The aim of this study is to determine the role of FRMD7 in a Korean CN cohort.

Methods:
We recruited 33 unrelated Korean patients (11 familial cases and 22 sporadic cases) with CN. To identify the mutation of FRMD7, we performed PCR-based direct sequencing using genomic DNA from the patient's peripheral blood.

Results:
In 13 (39%) of 33 patients, five mutations of FRMD7 were detected: start codon mutation c.1A>G, splice site mutation c.162+6T>C, and three missense mutations c.575A>C, c.722A>G, and c.875T>C. Four of them were novel mutations. In particular, the known mutation (c.875T>C) was identified in one family and six sporadic cases, and another two (c.1A>G and c.875T>C) were found in two independent families, respectively. Most mutations were identified in patients with idiopathic infantile nystagmus, but one patient with c.875T>C mutation had bilateral optic atrophy with a decreased peripapillary retinal nerve fiber layer thickness.

Conclusions:
Our study supports that FRMD7 mutations are the underlying molecular pathogenesis of congenital nystagmus. Furthermore, the missense mutation, c.875T>C within FRMD7 may be common mutation among Korean CN patients.

References: None.

Keywords: Nystagmus, Genetic Disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 265
Video head impulse test for follow up of cranial nerve 3, 4, or 6 paresis

Ali Saber Tehrani[1], David Newman-Toker[2], Jorge Kattah[1]

[1]University of Illinois, Peoria, Illinois, USA, [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Introduction:
Quantification of ocular misalignment is performed using prism-alternative cover technique in neuro-ophthalmology clinics. An objective device-based measurement of ocular misalignment that is not operator dependent would be the next step in improving evaluation of ophthalmoplegia due to cranial nerve palsies or strokes. vestibulo-ocular reflex gain measured by video-oculography is calculated by dividing eye velocity by head velocity during head impulse test. We seek to use the efferent arm of the VOR and measure the gain value of HIT to assess cranial nerve 3, 4, and 6 function.

Methods:
A prospective study on a convenience sample of patients with unilateral cranial nerve 3, 4, or 6 paresis diagnosed by a neuro-ophthalmologist at Illinois Neurological Institute Neuro-Ophthalmology clinic. Patients with prior history of vestibular disorders, unstable cervical spine, or history of rheumatoid arthritis will be excluded. Patients will be followed at 4, 8, 12 weeks. Participants will undergo thorough neuro-ophthalmologic examination, including prism-alternative cover test. We will measure HIT gain for all 6 canals, saccade velocity, and latency using video-oculography. Pearson correlation coefficient and regression analysis will be used to analyze the correlation between HIT gain and eye misalignment measured using prism-alternative cover test.

Results:
Plan to enroll 20 subjects as power calculations revealed it will be a sufficient sample to test the study hypothesis. The study is in preliminary phase. Full results will be available to report by NANOS meeting.

Conclusions:
We hypothesize the HIT gain is reduced in patients with cranial neve 3, 4, or 6 palsies, and correlates with the magnitude of phoria measured by prism-alternative cover test. Furthermore, improvement in HIT gain correlates with improvements in extra-ocular movement velocity and prism-diopters of misalignment in time. We are hoping to show HIT gain can be an objective, non-operator dependent alternative to prism-alternative cover test, with potential for numerous future applications.

References: None.

Keywords: Ocular Motility, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Ocular manifestations of vestibular disorders

Financial Disclosures: Interacoustics, Denmark, loaned their video-oculography device, EyeSeeCam goggles, for research purposes to our group; with plan for return of the product after study is done.

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Poster 266
Quantifying Severity of Ocular Myasthenia Gravis for Research Studies

Sui Wong[1], Aqsa Saleem[1]

[1]*Moorfields Eye Hospital, London, United Kingdom*

Introduction:
Ocular Myasthenia Gravis (OMG) causes ptosis and diplopia, which can be disabling. The rating scales currently recommended for MG research are arguably insufficiently sensitive for OMG, due to the limited ocular questions. A robust way of rating severity is important for research and prognostic studies on OMG (Wong et al 2016). This study aims to explore different methods of quantifying OMG severity, by physician- and patient-rated questionnaires.

Methods:
A prospective study of newly-diagnosed OMG patients seen through a neuro-ophthalmology service between July 2015-Nov2016. Severity was physician-rated using a modified version of an MGFA scale (Jaretzki et al 2000); an expanded Ocular Quantitative Myasthenia Gravis (Expanded Ocular-QMG) scale (Bhanushali et al 2008); and the MG Composite scale (Burns et al 2010). Patients rated symptom severity with the MG Quality of Life (MG-QOL); the National Eye Institute Visual Function (VFQ-25) and the Neuro-ophthalmic supplement of the VFQ-25 (NO-VFQ25) questionnaires.

Results:
62 patients (45% female) were included, median age at presentation 53y (range 17-81). Physician-rated MGFA severity: 3% spontaneous remission; 10% no symptoms but abnormal examination; 48% mildly symptomatic with no functional limitation; 39% moderately symptomatic with some functional limitation. Correlation was moderate between the modified MGFA and the Expanded Ocular-QMG scales (0.56); between MGFA and MG Composite scales (0.54); between MGFA and patient-rated MG-QOL scales (0.54). Correlation was poor between MG-QOL and Expanded Ocular-QMG; MG-QOL and MG Composite scales. Correlation was poor for the VFQ25 questionnaires with both MGFA rating and MG-QOL scales.

Conclusions:
The moderate correlations between physician-rated scales and patient-rated MG-QOL questionnaire suggest that a combination of both is required to accurately rate severity of OMG for research studies. Our experience of modifying the MGFA, Ocular-QMG and MG composite scales also highlight the potential for further improving these scales for OMG patients.

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Keywords: Myasthenia

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Poster 267

Visual Acuity at Different Thickness Levels of the Retinal Ganglion Cell Complex in Optic Neuropathies

Johanna Beebe[1], Aaron Fairbanks[1], Matthew Thurtell[2], Robert Mallery[3], Michael Wall[4], Randy Kardon[5]

[1]University of Iowa, Department of Ophthalmology, Iowa City, Iowa, USA, [2]University of Iowa Department of Ophthalmology & Neurology, Iowa City, Iowa, USA, [3]Neurology, Brigham & Women's Hospital & Ophthalmology MEEI, Boston, Massachusetts, USA, [4]University of Iowa Department of Ophthalmology & Neurology; Neurology, Iowa City VA, Iowa City, Iowa, USA, [5]University of Iowa Department of Ophthalmology; Ophthalmology, Iowa City VA, Iowa City, Iowa, USA

Introduction:
Structure-function correlations with optical coherence tomography (OCT) have been made for patients with optic neuropathies, which relate retinal layer thickness to contrast sensitivity, color vision, and visual disability. We investigated the relationship between best corrected visual acuity (BCVA) and macular ganglion cell complex (GCC) or ganglion cell layer + inner plexiform layer thickness in ischemic optic neuropathy (ION), demyelinating optic neuritis (ON), and compressive optic neuropathy (CON).

Methods:
Our institutions' electronic medical records was queried for patients between January 1, 2008 and August 3rd 2016 with a spectral domain Cirrus optic nerve OCT with GCC analysis. 719 patients were reviewed and patients with isolated ION, CON, or ON were identified. BCVA was recorded for each eye. OCT data was excluded if it was from the patient's acute presentation with associated optic nerve edema, and included if optic nerve pallor was note on exam.

Results:
54 patients with ION; 56 patients with CON; 15 with prior ON were identified. The 5th, median, and 95th percentile of BCVA (logMAR) were derived for several GCC layer thickness ranges: 40-49µm; 50-59µm; 60-69µm; 70-79µm; 80-89µm; for each type of optic neuropathy. The median and 95th percentile vision for the lowest GCC range was 20/63 and 20/20; 20/25 and 20/20; and 20/40 and 20/20 for ION, CON, and ON respectively. In 35 subjects who underwent measurement of visual fixation during OCT, mean GCC thickness in the region of fixation or in annuli centered at the fovea did not provide greater correlation with visual acuity than the global mean thickness.

Conclusions:
The broad range of visual acuity possible in eyes at the lower range of GCC thickness argues for an adaptive gain control mechanism of cortical visual processing in some patients which, allows the maintenance of normal visual acuity in spite of a significant loss of retinal ganglion cells..

References: Sabadia S et al, 20/40 or Better Visual Acuity After Optic Neuritis: Not as Good as We Once Thought?, J Neuroophthalmol. 2016 Dec;36(4):369-376 Lee T, Ji Y, Park S, Heo H, Retinal ganglion cell and axonal loss in optic neuritis: risk factors and visual functions. Eye. 2016 Nov 18. doi: 10.1038/eye.2016.253 Walter S et al Ganglion cell loss in relation to visual disability in multiple sclerosis. Ophthalmology, Jun;119(6):1250-7 2012. doi: 10.1016/j.ophtha.2011.11.032.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

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Poster 268
Chronic Optic Neuropathies Demonstrate Decreased Peripapillary Capillary Density on OCT Angiography

John Chen[1], Jackson AbouChehade[1], Raymond Iezzi[1], Jacqueline Leavitt[1], Randy Kardon[2]

[1]Mayo Clinic, Rochester, Minnesota, USA, [2]University of Iowa, Iowa City, Iowa, USA

Introduction:
Recent studies have demonstrated that patients with glaucoma have reduced peripapillary retinal capillary density on OCT angiography, but it remains unknown if these changes are the cause of glaucoma or secondary to the glaucoma. We used OCT angiography to compare the retinal peripapillary capillary network in a variety of chronic optic neuropathies to determine if all chronic optic neuropathies show a decrease in peripapillary capillary perfusion.

Methods:
This cross-sectional, observational case series (May 2015-May 2016), evaluated OCT angiography in 10 patients who suffered various kinds of chronic optic neuropathies, which included arteritic AION, NAION, optic neuritis, compressive optic neuropathy, traumatic optic neuropathy, and glaucoma (Optovue RTVue). OCT angiography images were acquired using a 4.5x4.5-mm scan focused on the optic disc. Split-spectrum amplitude decorrelation angiography algorithm was used to approximate blood flow. The density of the perfused peripapillary capillaries within the peripapillary retina was calculated using Optovue's automated software, AngioAnalytics, to create a flow density map. OCT angiography findings were compared to Cirrus OCT retinal nerve fiber layer measurements.

Results:
All 10 patients with chronic optic neuropathies showed a decrease in peripapillary capillary density on OCT angiography, regardless of the etiology of the optic neuropathy. The peripapillary capillary loss on OCT angiography correlated well with the areas of retinal nerve fiber layer thinning seen on OCT.

Conclusions:
All chronic optic neuropathies lead to a decrease in the peripapillary capillary density on OCT angiography. This is not specific to optic neuropathies that are thought to have an underlying ischemic mechanism, such as glaucoma. This does not rule out ischemia as a contributor to glaucoma but suggests that OCT angiography is unlikely measuring this process in the chronic setting. Future studies evaluating the time course and severity of peripapillary capillary density changes may still provide some ability to distinguish optic neuropathies.

References: None.

Keywords: Optic neuropathy, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 269

Perfused Large Vessel and Capillary Densities in Various Grades of Papilledema using OCTA Custom Software

David Fell[1], Sherief Raouf[1], Toco Chui[1], Patricia Garcia[1], Shelley Mo[1], Sarita Dave[1], Nicole Scripsema[1], Richard Rosen[1], Rudrani Banik[1]

[1]New York Eye and Ear Infirmary of Mount Sinai, New York, New York, USA

Introduction:

Optical Coherence Tomography Angiography (OCTA) Angioanalytics software has limitations in papilledema including: inaccurate autosegmentation, difficulty identifying the scleral canal border and inability to separate large vessels (LV) from capillaries. The purpose of this study was to apply customized software to overcome these issues and analyze perfused vessel density in various grades of papilledema.

Methods:

We performed a prospective cross-sectional analysis of eyes with papilledema using the RTVue XR Avanti OCTA. Images of choroid, radial peripapillary capillary (RPC), nerve head (NH), and vitreous layers were exported to MATLAB. The choroid image was used to center a 1.95-millimeter annular ring on the scleral canal opening, and a surrounding 0.75-millimeter peripapillary ring was analyzed. Custom digital subtraction analysis software separated LVs from capillaries and calculated mean perfused LV density (PLVD) and perfused capillary density (PCD) in RPC, NH, and vitreous layers. ANOVAs comparing the results of each layer by papilledema grade were performed, with post-hoc Tukey's procedure (PHTP) to examine individual relationships.

Results:

One eye from each of 56 subjects with papilledema, Frisén grades 0-5 and atrophic papilledema (n = 7, 14, 15, 4, 5, 2, and 9, respectively), was analyzed. ANOVA with LV subtraction analysis revealed significant changes in PCD throughout all three layers ($P \leq 0.04$). PHTP showed patterns of decreased PCD in high grade and atrophic papilledema compared to low grade. ANOVA of LV analysis showed significant changes in PLVD within the NH ($P=.01$) and vitreous ($P=0.002$) layers. PHTP showed decreased PLVD in high grades within the NH layer and increased PLVD in atrophic subjects within the vitreous layer, when compared to low grade papilledema.

Conclusions:

Customized OCTA post-processing software demonstrated significantly decreased PCD across high-grade papilledema and post-papilledema optic atrophy. LV analysis of NH and Vitreous layers may reflect changes in LV visibility secondary to changes in peripapillary retinal nerve fiber layer thickness.

References: 1. Frisén, Swelling of the optic nerve head: a staging scheme, Journal of Neurology, Neurosurgery, and Psychiatry, 45, 13-18, 1982

Keywords: Optic neuropathy, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 270
Utility of optical coherence tomographic angiography in evaluation of afferent neuro-ophthalmic disease

Eric Gaier[1], Aubrey Gilbert[1], Joseph Rizzo[1], John Miller[1], Dean Cestari[1]

[1]Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

Introduction:
Optical coherence tomographic angiography (OCT-A) is a powerful emerging tool for visualizing the microvasculature of the posterior pole in a laminar fashion with micrometer precision and in a non-invasive manner. OCT-A has been predominantly applied to the study of vascular retinopathies and glaucomatous optic neuropathy. We set out to explore the utility of OCT-A in the evaluation of non-glaucomatous optic neuropathies with the goal of providing pathophysiologic insight and advancing diagnostic capability.

Methods:
OCT-A (AngioVue, Optovue or AngioPlex, Zeiss) was performed on 1 patient with Leber hereditary optic neuropathy (LHON), 2 patients with visually significant optic nerve head drusen (ONHD), and 8 patients with acute ischemic optic neuropathy (4 arteritic and 4 non-arteritic). Normal-sighted subjects served as controls and fluorescein angiography was available for a subset of the ischemic optic neuropathy patients.

Results:
Optic nerve OCT-A findings varied across different etiologies of optic neuropathy. Temporal peripapillary capillary dilation was evident in both the acutely affected eye and the fellow eye of the patient with LHON. The patients with ONHD showed focal capillary drop-out in the areas associated with visually significant superficial drusen. Three of four optic discs affected by acute non-arteritic anterior ischemic optic neuropathy showed dilation, and one showed attenuation, of the peripapillary capillary network that corresponded to optic nerve head edema and visual field loss. The 4 patients with arteritic optic neuropathy demonstrated focal areas of capillary drop-out in a non-sectoral pattern.

Conclusions:
OCT-A analysis produced distinct findings between and within categories of optic neuropathy. These findings could provide new diagnostic utility in distinguishing overlapping clinical presentations of optic neuropathy. Continued work in this area could help further elucidate underlying pathophysiology and yield prognostic data for patients with optic neuropathies.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy, Vascular disorders

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Poster 271
The Ganglion Layer Analysis Trumps the Perimetry?

Oded Hauptman[1], Jennifer Hauptman[2]

[1]Royal Victorian Eye and Ear Hospital, East Melbourne, Australia, [2]Alfred Hospital, Melbourne, Australia

Introduction:
Computerised and Goldman Fields have been the backbone of afferent neuro-ophthalmology but require skill and patience by both the examiner and subject.. Ocular Coherence Tomography (OCT) Ganglion a Cell Layer (GCL) analysis and Nerve Fibre Analysis (RNFL) does not and may more efficiently serve the same purpose of diagnosis and monitoring and surveillance of disease process. A retrospective analysis of patient records that including serial RNFL and GCL OCT and perimetry going back over 8 years involving 500 glaucoma patients 12 patients with hemianopia and 20 patients with miscellaneous conditions including demyelinating optic neuropathy, optic nerve head drusen and compressive optic neuropathy.

Methods:
Big -Data Analysis of Humphrey perimetry XML data and OCT XML data by data by mining and programming a robotic windows tasking program to data mine numeric data which was cross referenced with patient historical data on the electronic medical record.

Results:
There is a close correlation of trend data between the Humphrey perimetry , enlargement of the disc cupping and OCT RNFL and GCL numeric data , For glaucoma, the GCL is more sensitive than the RNFL and Perimetry in all but late phases of the disease, The GCL reliable correlates hemianopia in stroke but is unreliable in diagnosing compressive optic neuropathy and chiasmopathy but is predictive is functional recovery after surgical decompression. Demyelinating disease, optic nerve head drusen and Lebers are sometimes easily monitored and diagnosed on OCT GCL despite often unreliable perimetry

Conclusions:
The GCL trumps Perimetry in early glaucoma, demyelinating disease, optic nerve head drusen and Lebers Optic Neuropathy ,. Late glaucoma is best tracked by perimetry. GCL OCT is unreliable in diagnosing compressive optic neuropathy and chiasmopathy. Used together to correlate structure and function the Perimetry and OCT GCL and NFL are symbiotic and complement each other.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields, Miscellaneous

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Poster 272

Efficacy of the Infrared Photograph with a Selective Wavelength Filter for Detecting Small Angle Esotropia

Jeong-Min Hwang[1], Yung Ju Yoo[1], Hee Kyung Yang[1], Nam Ju Moon[2]

[1]Seoul National University Bundang Hospital, Seongnam, Korea, Republic of, [2]Chung-Ang University Hospital, Seoul, Korea, Republic of

Introduction:
To determine the efficacy of the selective wavelength filter analysis with infrared photographs for diagnosing small angle esotropia in young children who had been recently diagnosed as pseudoesotropia in primary care hospitals.

Methods:
A total of 28 esotropes with an esodeviation of ≤ 25 prism diopters (PD) and 30 orthotropic controls under 4 years of age were included. All patients had been recently diagnosed as pseudoesotropia at a primary care hospital. Alternate prism and cover test or the Krimsky test was repeatedly performed to measure ocular alignment. Full-face infrared photographs were taken with a selective wavelength filter in front of either eye. The angles of esodeviation on photographs were measured with the three-dimensional strabismus photoanalyzer.

Results:
The mean angle of esodeviation was 14.1 ± 5.1 prism diopters (PD) by manual measurements and 18.9 ± 8.0 PD by the infrared photograph analysis. The sensitivity and specificity of the infrared photograph analysis for detecting esotropia was 100% and 93.8%, respectively, with a cutoff value of 4.5 PD.

Conclusions:
The infrared photograph analysis was simple and efficient for diagnosing small angle esotropia in young children.

References: None.

Keywords: Ocular Motility

Financial Disclosures: The authors had no disclosures.

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Poster 273

Optical Coherence Tomography RNFL analysis for studying axon loss in a relapsing NMOSD Venezuelan cohort

Emely Karam[1], German Chique-Alfonzo[2], jose Murcia[1], Javier Mendoza[1], Arnoldo Soto[1], Elizabeth Armas[2]

[1]Centro Medico Docente La Trinidad, Caracas, Venezuela, [2]Centro Médico Docente La Trinidad Hospital Universitario de Caracas, Caracas, Venezuela

Introduction:

Venezuela exhibits the highest frequency of NMO cases (43.3%) in South America. NMOSD has unique characteristics that could distinguish it from Multiple Sclerosis (MS). Optical coherence tomography is a useful tool that qualitatively and quantitatively measures the changes of the peripapillary RNFL optic nerve and axon lossTo first describe and characterize changes of the peripapillary RNFL in a relapsing, NMOSD Venezuelan population.

Methods:

In a cross-sectional study, 12 patients with relapsing Optic Neuritis and NMOSD from a multicenter data base from three center Venezuelan's institutions where studied. Optical Coherence Tomography Retinal Nerve Fiber Layer (RNFL) measurements were performed with Spectralis HRA-OCT (software version 6.0; Heidelberg Engineering GmbH.). Demographics, number of relapses, disease duration, Extended Disability Status Scale (EDSS), AQP4-IgG status were determined. We carried out all statistical analyses using SPSS version 23.0 (SPSS Inc.)

Results:

Mean: Age (34.17± 14.98). Age of onset (27.75± 13.18). Years of disease (7.42± 4.72). Number of relapses (6.17± 5.30). EDSS was 4.79 ± 2.21. AQP4-IgG positive 58.33%. All patients had bilateral optic neuritis, and average RNFL Thickness was (mean = 54.52 ± 34.77 µm). All RNFL quadrants measurements: Superior (74.57 ± 31.54 µm), Inferior (78.65± 38.45 µm), Nasal (38.78± 25.42 µm) and Temporal (41.70± 56.96 µm). In AQP4-IgG positive subgroup RNFL: Superior (71.38 ± 35.82 µm), Inferior (82.84± 46.25 µm), Nasal (40.23± 25.42 µm) and Temporal (45.15± 22.45 µm).

Conclusions:

Relapsing NMOSD optic neuritis in a disabled highly active disease population affected all peripapillary RNFL thickness quadrant measurements however this was most severe in the nasal and temporal quadrants.

References: Manogaran P, Traboulsee AL, Lange AP. Longitudinal Study of Retinal Nerve Fiber Layer Thickness and Macular Volume in Patients With Neuromyelitis Optica Spectrum Disorder.J Neuroophthalmol;36(4):363-368 2016 Jeong IH, Kim HJ, Kim NH, Jeong KS, Park CY. Subclinical primary retinal pathology in neuromyelitis optica spectrum disorder. J Neurol. 263(7):1343-8, 2016

Keywords: Demeylinating disease, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Optic neuropathy, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 274
Diagnosing Chiasm Tumors by SD- Optical Scanning Tomograpy

Umur Kayabasi[1]

[1]*Uskudar University, D- NO Visual Therapy Center, Istanbul, Turkey*

Introduction:
To detect bitemporal hemianopia with the help of visual field (VF) testing is diagnostically significant in the tumors of the chiasm. A study was performed to find out the reliability of SD- Optical Scanning Tomography (SD- OCT) in these conditions.

Methods:
20 patients who had compression of the chiasm diagnosed by MRI of the brain and VF tests underwent SD- OCT retina exams. The mean age was 51. Nasal and temporal macular ganglion cell layer thicknesses were examined by SD- OCT. 10 agematched healthy controls also had the same SD- OCT tests.

Results:
A mean thinning of 10 microns in bilateral nasal ganglion cell layer thickness was calculated in this patient group. The thinning of the bilateral nasal ganglion cell layer changed according to the dimension and duration of the chiasmal compression. Compared with VF testing, SD- OCT revealed more severe defects. The nasal and temporal ganglion cell layers were symmetrical in the control group. The thinning detected by SD- OCT was statisically significant (P< 0, 001).

Conclusions:
In this patient group, SD- OCT results were trustable and propabably more accurate in terms of revealing the severity of the compression.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Visual fields, Optic neuropathy

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Poster 275

Role of Ocular Ultrasonography to Distinguish Between Papilledema and Pseudopapilledema

Anita Kohli[1], Cesar Alfaro Cruz[2], Imran Jivraj[1], Sheila Bagchi[3], Grant Liu[4], Kenneth Shindler[1], Robert Avery[4], Ahmara Ross[1], Faisal Althekair[5], Jessie Chan[1], Dionne May[6], Maxwell Pistilli[2], Madhura Tamhankar[1]

[1]The Scheie Eye Institute, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA, [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [3]Robert Wood Johnson School of Medicine, Piscataway, New Jersey, USA, [4]Hospital of the University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [5]Massachusetts General Hospital, Boston, Massachusetts, USA, [6]Boston University School of Medicine, Boston, Massachusetts, USA

Introduction:
Differentiating between papilledema and pseudopapilledema can be challenging. The ability of ocular ultrasonography (OUS) to make this distinction has been studied retrospectively. Therefore, a prospective study was designed.

Methods:
Adult patients with suspected papilledema were enrolled in a prospective study and underwent OUS, fundus photography and Frisen grading of optic disc elevation. Positive OUS was defined as optic nerve sheath diameter ≥ 3.3 mm, with a positive 30° test, of either eye. Change in optic disc appearance of at least one eye on fundus photography, as determined by masked reviewers at any time between the initial and 6-month visits, was set as the standard to diagnose papilledema. If there was no change on fundus photography, pseudopapilledema was assumed. OUS results were compared to change or no change on fundus photography and to Frisen grading.

Results:
Forty-one patients were enrolled in the study, 20 with papilledema and 21 with pseudopapilledema. The sensitivity of OUS for detecting papilledema was 75% (15/20, 95% CI: 52-89%), and the specificity for detecting pseudopapilledema was 52% (11/21), 95% CI: 32-72%). The positive predictive value of OUS was 60% (15/25, 95% CI: 39-78%), and the negative predictive value was 69% (11/16, 95% CI: 41-88%). Overall, odds were increased (OR: 11.11, 95% CI: 1.19-104.81) of having positive OUS with Frisen grade ≥ 2, in the worse eye (p = 0.04), but not in Frisen grades 1 or 2.

Conclusions:
OUS is moderately sensitive to diagnose papilledema but is not specific for pseudopapilledema. The moderate positive predictive value may limit its use, especially in patients with mild optic disc elevation. A limitation of this study is the short follow-up interval between the initial and 6-month visit fundus photographs, which may have allowed some patients with papilledema to be characterized as having pseudopapilledema.

References: SB Carter, D Gold, N Volpe, K Shindler, GT Liu, MA Tamhankar. The Role Of Orbital Ultrasonography In Distinguishing Papilledema from Pseudopapilledema, Eye, 28, 1425-1430, 2014. DI Friedman, GT Liu and KB Digre. Revised Diagnostic Criteria for Pseudotumor Cerebri Syndrome in Adults and Children, Neurology, 81, 1159-1165, 2013.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Pseudotumor Cerebri

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 276
Optic Disc Drusen in Children: The Copenhagen Child Cohort 2000 Eye Study

Lasse Malmqvist[1], Xiao Li[1], Christina Eckmann[1], Anne Skovgaard[2], Else Olsen[2], Michael Larsen[1], Inger Munch[3], Steffen Hamann[1]

[1]Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark, [2]Department of Public Health, Faculty of Health and Medical Sciences, Copenhagen, Denmark, [3]Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

Introduction:
The etiology and pathophysiology of optic disc drusen (ODD) are still unknown even though the condition is found in up to 2.4% of the population. The purpose of this study was to examine the prevalence and risk factors of ODD in a population-based child cohort in early adolescence.

Methods:
Presence of ODD was assessed in enhanced depth imaging optical coherence tomography scans of 1306 children aged 11-12. Scleral canal diameter was measured in scans from children with ODD and in scans from 130 controls.

Results:
Of the 1304 participants with gradable scans, 13 (1.0 %) had ODD in one or both eyes. All but one of the cases were found in children with scleral canal diameter in the lowest quartile (1182 – 1399 µm). Children with ODD had a mean disc diameter of 1339 µm (interquartile range 30 µm), whereas it was 1508 µm (interquartile range 196 µm) in the 130 controls without ODD (P<0.001). No differences in gender, birthweight, refractive error and Tanner physical development stage were found between children with and without ODD.

Conclusions:
This prospective population-based study of a cohort of healthy children found ODD only in eyes with a narrow scleral canal. This is consistent with the proposition that ODD arise as a consequence of nerve fiber congestion in the scleral canal. The present study of healthy children adds substantial evidence to the theory that a small optic disc predisposes to the development of ODD.

References: None.

Keywords: Pediatric neuro-ophthalmology, Optic neuropathy, Orbit/ocular pathology

Financial Disclosures: The authors had no disclosures.

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Poster 277

OCT Angiography in Non Arteritic Anterior Ischemic Optic Neuropathy and co-relation with Visual Field Defects

Preeti Patil Chhablani[1], Uppal Gandhi[1], Ramesh Kekunnaya[1], Akshay Badakere[1], Jay Chhablani[1]

[1]L V Prasad Eye Institute, Hyderabad, Telangana, India

Introduction:

OCT angiography (OCT-A) allows the visualization of the peripapillary and optic nerve head (ONH) vasculature which may play a role in the pathogenesis of non-arteritic anterior ischemic optic neuropathy (NAION). This study aims to analyze OCT-A of the ONH in eyes with acute, unilateral NAION in comparison to normal fellow eyes and to find a possible correlation with visual field defects.

Methods:

Patients with acute, unilateral NAION without any other ocular pathology were included. The ONH was imaged using 6x6 mm scans using a swept source OCT system. OCT-A scans of the optic nerve head at the level of superficial, deep vessels and choriocapillaris level were analyzed. Disc edema was classified as diffuse / sectoral. Vascularity was qualitatively analyzed in four sectors (superior, nasal, inferior, temporal) around the disc and in the centre of the ONH in diseased eyes and was compared to normal fellow eyes.

Results:

Seventeen patients, (12 males) were included. Mean age was 56.6 years and the mean duration of presentation was 18.2 days. Four eyes (23.5%) showed sectoral disc edema and remaining twelve had 360 degrees disc edema. OCT-A demonstrated loss/thinning of the peripapillary vascular cuff in 16 eyes (94%) with NAION as compared to fellow eyes. Nine eyes (53%) showed an additional focal area of deficient peripapillary vasculature that co-related well with the visual field defect. Out of the remaining eight patients with no correlation with visual fields, five showed advanced field loss with no pattern, one had unreliable fields. A distinct decrease in the vascularity within the ONH was also noted in nine patients (53%).

Conclusions:

OCT-A detected distinct changes in vascularity of the ONH in patients with acute NAION as compared to the fellow normal eye and can shed further light on the pathogenesis of NAION and the contribution of peripapillary choroidal blood flow.

References: None.

Keywords: Optic neuropathy, Visual fields

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 278
Ganglion Cell Layer versus Retinal Nerve Fiber Layer Analysis for Detection of Retrograde Trans-Synaptic Degeneration

Bryan Pham[1], Michelle Yun[2], Marc Dinkin[1], Rebecca Chen[2], Cristiano Oliveira[1]

[1]Department of Ophthalmology, Weill Cornell Medicine, New York, New York, USA, [2]School of Medicine, Weill Cornell Medicine, New York, New York, USA

Introduction:
Segmental atrophy of the ganglion cell layer + inner plexiform layer complex thickness (GCL+IPLt) on spectral-domain optical coherence tomography (SD-OCT) has been demonstrated in vivo in cases of isolated post-geniculate visual pathway dysfunction, presumably through retrograde trans-synaptic degeneration (RTSD). Our goal with the present study was to investigate the differences in sensitivity and specificity between the analysis of the GCL+IPLt and the circumpapillary retinal nerve fiber layer thickness (RNFLt) on SD-OCT for the de novo recognition of RTSD.

Methods:
Twenty-seven non-neuro-ophthalmology trained physicians in our ophthalmology department, including residents, fellows, and attendings, were asked to examine the GCL+IPLt and RNFLt in a set of 37 de-identified and randomly coded SD-OCT studies, including 22 patients with RTSD and 15 controls. On a matching questionnaire, participants were asked if they suspected a brain lesion based solely on the scan reviewed and, if so, they were asked to predict the side of the lesion. The results of the survey were anonymized and statistically analyzed in Microsoft Excel. The overall predictive value (OPV), positive predictive value (for both the correct identification of a brain lesion, PPV-L, and the correct side of the lesion, PPV-S), negative predictive value (NPV), sensitivity, and specificity for detecting RTSD using the GCL+IPLt and RNFLt were computed.

Results:
In our cohort, the OPV, PPV-L, PPV-S, NPV, sensitivity, and specificity for detecting the presence of RTSD using the GCL+IPLt were 0.69, 0.94, 0.53, 0.57, 0.51, and 0.94, respectively, while the corresponding values using the RNFLt were 0.49, 0.77, 0.42, 0.45, 0.20, and 0.94, respectively.

Conclusions:
Among non-neuro-ophthalmology trained ophthalmologists, examination of the GCL+IPLt, as compared to the RNFLt, consistently and more accurately predicted the presence of RTSD. Except for the PPV-S and specificity, all differences studied were statistically significant.

References: 1. Mitchell JR, Oliveira C, Tsiouris AJ, Dinkin MJ. "Corresponding Ganglion Cell Atrophy in Patients With Postgeniculate Homonymous Visual Field Loss." J Neuroophthalmol. Volume 35, Issue 4. Pages 353-9. Dec 2015.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 279

Accuracy of Imaging Modalities in Differentiating Pseudopapilledema from True Optic Disk Edema (ODE) in children

Stacy Pineles[1], Melinda Chang[2], Federico Velez[2], Joseph Demer[1], Laura Bonelli[1], Peter Quiros[3], Alfredo Sadun[3], Anthony Arnold[1]

[1]Stein Eye Institute, UCLA, Los Angeles, California, USA, [2]Stein Eye Institute, UCLA; Doheny Eye Institute, UCLA, Los Angeles, California, USA, [3]Doheny Eye Institute, UCLA, Los Angeles, California, USA

Introduction:

Differentiation between pseudopapilledema and true optic disk edema (ODE) in children is challenging because drusen, the most common cause of pseudopapilledema, are often buried and non-calcified at this age. The optimal method for differentiating pseudopapilledema from ODE in children is unknown.

Methods:

We prospectively recruited children (5 to 18 years old) diagnosed with pseudopapilledema or ODE. All patients underwent imaging with: b-scan ultrasonography, fundus photography, autofluorescence (AF), fluorescein angiography (FA), optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL), spectral-domain OCT (SD-OCT) of the optic nerve, and enhanced-depth imaging OCT (EDI-OCT) of the optic nerve. Image interpretations by three masked neuro-ophthalmologists were compared to the clinical diagnosis to compute the sensitivity and specificity of each imaging modality for detecting ODE.

Results:

Twenty-one eyes (17 with pseudopapilledema and 4 with ODE) of 11 patients were included. Consistency of image interpretation by intraclass correlation coefficient ranged from -0.21 (ultrasonography) to 0.83 (FA). FA had the highest sensitivity (100%) and specificity (100%) for detection of ODE. Fundus photography had 75% sensitivity and 71% specificity. The other imaging modalities had low sensitivity (0 to 50%) but moderate specificity (75 to 88%).

Conclusions:

FA was the best imaging modality for differentiating pseudopapilledema from ODE in children. The other imaging techniques, except fundus photography, had low sensitivity for identifying ODE, due to irregularities in the images suggestive of drusen rather than ODE. Non-calcified and buried optic disc drusen in children are difficult to detect by any modality, and the distinction between pseudopapilledema and ODE in this age group may be best accomplished by evaluating for disk leakage indicative of ODE on FA.

References: Chang MY, Pineles SL. Optic disk drusen in children. Survey of Ophthalmology. 61(6):745-758, 2016. Pineles SL, Arnold AC. Fluorescein angiographic identification of optic disc drusen with and without optic disc edema. J Neuroophthalmol. 32(1):17-22, 2012.

Keywords: Pediatric neuro-ophthalmology, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Optic neuropathy

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Poster 280

Optic Nerve Head Morphology in Superior Segmental Optic Nerve Hypoplasia(SSOH), Primary Open-Angle-Glaucoma(POAG), and Healthy Patients

Lynn Shi[1], Jeffrey Odel[2], Ravivarn Jarukasetphon[3], Robert Ritch[3], Donald Hood[4]

[1]Columbia University College of Physicians and Surgeons, New York, New York, USA, [2]Department of Ophthalmology, Columbia University, New York, New York, USA, [3]Einhorn Clinical Research Center, New York Eye and Ear Infirmary of Mount Sinai, New York, New York, USA, [4]Departments of Psychology and Ophthalmology, Columbia University, New York, New York, USA

Introduction:
To compare the optic nerve head structures and blood vessel angles among SSOH, POAG, and healthy eyes.

Methods:
6 eyes with SSOH, 7 eyes with POAG, and 10 healthy eyes had swept-source OCT wide-field cube scans and 12 radial line scans centered on the disc. POAG eyes were selected to match the SSOH eyes; they had superior disc damage only and a similar pattern of field loss. On each radial line scan, we determined: circumpapillary retinal nerve fiber layer thickness (cpRNFL), Bruch's membrane opening-minimum rim width (BMO-MRW), lamina cribrosa thickness (LCT), anterior lamina cribrosa depth (ALD), minimum prelaminar thickness (PLT), and BMO-diameter (BMOd). The angles between the disc center and the superior (SBV) and inferior blood vessels (IBV) were measured on enface slabs derived from the wide-field scans.

Results:
Eyes with SSOH had significantly smaller BMOd (1422±176 vs. 1768±97um), larger LCT (285.6±21.2 vs. 201.4±28.3um), and smaller ALD (319.2±73.3 vs. 509.6±189.0um) than POAG eyes, all $P<0.05$. POAG eyes tended to have thinner PLT in comparison to SSOH (130.6±79.8 vs. 214.5±117.4um) and healthy eyes (243.7±147.4um), but this trend was not significant. In the superior disc, SSOH and POAG eyes had significantly smaller BMO-MRW and cpRNFL in comparison to healthy controls ($P<0.05$). There were no significant differences in SBV and IBV among the three groups.

Conclusions:
SSOH had similar LC thickness and location to healthy eyes, but similar BMO-MRW and cpRNFL thinning in the superior disc to POAG eyes. SSOH BMOd was significantly smaller than in both POAG and healthy eyes, while POAG eyes had thinned and posteriorly displaced LC compared to both SSOH and healthy eyes. The blood vessel locations (SBV and IBV) were similar among SSOH, POAG, and healthy eyes.

References: None.

Keywords: Optic neuropathy, Visual fields, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

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Poster 281

Reliability of Cyclotorsion Measurements using Scanning Laser Ophthalmoscopy Imaging in Healthy Subjects – CySLO study

Ghislaine Traber[1], Fabian Lengwiler[1], Daniel Rappoport[1], Gregor Jaggi[1], Klara Landau[1]

[1]*Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland*

Introduction:
This prospective methodological study evaluates inter- and intra-rater reliability of objective cyclotorsion measurements obtained in healthy subjects using the Heidelberg Spectralis Spectral Domain – Optical Coherence Tomography (SD-OCT) device.

Methods:
The retinal nerve fiber layer (RNFL) program by Heidelberg Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany) was used to measure cyclotorsion based on the inbuilt algorithm for the measurement of the foveo-papillary angle (FPA) on the scanning laser ophthalmoscopy (SLO) image. Repeated scans of the fixating and non-fixating right eye without and with eye tracker each were obtained by three different examiners.

Results:
Thirty-three healthy subjects (15 men, 18 women; aged 21-64 years) were enrolled and thirty-one right eyes examined. The mean FPA measured overall by all three examiners was 6.6°±2.8. The inter-rater reliability of the measured FPAs using the linear mixed effects model is estimated as p inter= 0.8803. The intra-rater reliability is estimated as p intra= 0.9589.

Conclusions:
There is excellent reliability of objective cyclotorsion measurements within and between observers using the Heidelberg Spectralis OCT. SD-OCT/SLO imaging is a reliable imaging technique to measure and study cyclotorsion.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Adult strabismus with a focus on diplopia, Ocular Motility

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 282

Fractal Analysis of Peripapillary Vasculature In Eyes With Papilledema Using Optical Coherence Tomography Angiography

Edmund Tsui[1], David Fell[2], Sherief Raouf[2], Nicole Scripsema[2], Sarwar Zahid[1], Sarita Dave[2], Patricia Garcia[2], Toco Chui[2], Richard Rosen[2], Rudrani Banik[2], Joshua Young[1]

[1]New York University School of Medicine, Department of Ophthalmology, New York, New York, USA, [2]New York Eye and Ear Infirmary of Mount Sinai, Department of Ophthalmology, New York, New York, USA

Introduction:

Optical coherence tomography angiography (OCTA) permits non-invasive evaluation of the retinal vasculature, optic nerve head, and peripapillary microvasculature. We aim to quantify the fractal dimension (FD) of eyes with papilledema compared with control eyes using OCTA.

Methods:

A retrospective study was performed in 49 eyes with papilledema and 40 control eyes. OCTA images were obtained using the RTVue XR Avanti (Optovue Inc., Fremont, CA, USA). Peripapillary scans of 4.5mm x 4.5mm diameter were obtained. Grayscale OCTA images were standardized and binarized using ImageJ (National Institutes of Health, Bethesda, Maryland, USA). Fractal box-counting analyses were performed using Fractalyse (ThéMA, Besançon Cedex, France). Statistical analysis was performed using one-way analysis of variance with post-hoc Tukey's multiple comparisons test and two-tailed t-test. Further analyses were performed on papilledema subgroups based on severity (Grade 0, n=12; Grade 1, n=15; Grade 2, n=13; Grade 3, n=5; Grade 4/5, n=4).

Results:

The mean FD of all eyes with papilledema (1.677, SD=0.075) was significantly higher (P=0.0021) than control eyes (1.630, SD=0.062). The FD in papilledema subgroups based on severity were Grade 0 (1.707, SD=0.047), Grade 1 (1.675, SD=0.046), Grade 2 (1.674, SD=0.090), Grade 3 (1.610, SD=0.139), Grade 4/5 (1.694, SD=0.060). Analyses between papilledema subgroups demonstrated a significant increase (P<0.05) in FD between Grade 0 papilledema and control eyes. There were no significant differences in pairwise comparisons between other subgroups.

Conclusions:

The FD in OCTA of eyes with papilledema was significantly higher compared to control eyes. When analyzed by severity, eyes with Grade 0 papilledema had a higher FD compared to control eyes. Since fractal geometry reflects the branching of the peripapillary microvasculature, an increased FD may correlate with an increase in perfused vessel density as identified by OCTA. Fractal analysis in OCTA has the potential to establish quantitative parameters for peripapillary microvascular pathology in papilledema.

References: None.

Keywords: Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, High intracranial pressure/headache, Miscellaneous

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 283
Plication of the Optic Nerve: A Mechanism for Rapid Vision Loss in Optic Nerve Glioma

Nailyn Rasool[1], Ashley Campbell[1], Michael Kazim[1]

[1]Columbia University, New York, New York, USA

Introduction:
Optic nerve glioma (ONG) is the most common optic nerve tumor of childhood presenting with gradual proptosis, strabismus and visual loss. Rarely, such patients may develop acute loss of vision with worsening proptosis which has been associated with new hemorrhage or mucoid substance into the tumor. We postulate that plication of the optic nerve may be an etiology for rapidly progressive vision loss in this population.

Methods:
A retrospective review of five patients with unilateral ONG was conducted. Both MRI imaging and surgical records were reviewed. MRI imaging of optic nerve caliber and "folding" was determined by analyzing the most acute angle present in the course of the optic nerve. In one patient, MRI resolution was insufficient to demonstrate folding of the optic nerve noted intraoperatively.

Results:
We reviewed 5 cases of unilateral ONG treated with resection of the nerve to prevent progression of the glioma to the chiasm. Three patients developed rapid loss of vision and proptosis over 6-8 weeks. The remainder had a more typical clinical course of gradually increasing proptosis and decreasing vision over months to years. MRI and surgical visualization of the ONG in patients with rapid visual loss demonstrated that all had an acute, 90 degree or less, fold in the optic nerve. Patients that did not experience acute vision loss had more obtuse bends in the optic nerve.

Conclusions:
Optic nerve tortuosity has been identified as a feature of "benign" gliomas. However, severe plication of the nerve as an etiology of rapidly progressive visual loss has not previously been discussed in the literature. Our cases demonstrate a new etiology for visual loss in patients with childhood ONG. Understanding of the degree of folding necessary to cause visual loss may enable us to determine which children are at risk for this complication and may warrant more proactive management.

References: 1. McLeod, A Reeves. Acute blindness in childhood optic glioma caused by hematoma. JPOS. 1983; 20(1): 31-33 2. Anderson DR, Spencer WH. Ultrastructural and histochemical observations of optic nerve gliomas. Arc Ophthal 1970; 83: 324-335 3. Levin MH, Armstrong GT, Broad JH, Zimmerman R, Bilaniuk LT et al. Risk of optic pathway glioma in children with neurofibromatosis type 1 and optic nerve tortuosity or nerve sheath thickening. Br J Ophthalmol 2016; 100: 510-514

Keywords: Neuroimaging, Pediatric neuro-ophthalmology, Orbit, Optic nerve trauma and treatment, Tumors

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 284

Clinical and Magnetic Resonance Imaging Characteristics of Post-Optic Nerve Sheath Decompression Pseudomeningoceles

Daniel Rubinstein[1], Leon Rafailov[1], Edward Wladis[2], Neena Mirani[1], Paul Langer[1], Larry Frohman[1], Roger Turbin[1]

[1]Rutgers New Jersey Medical School, Newark, New Jersey, USA, [2]Lions Eye Institute, Slingerlands, New York, USA

Introduction:

The clinical significance of post-operative pseudomeningocele formation following optic nerve sheath fenestration (ONSF) has not been fully characterized. A literature review identifies 9 previously published cases we believe represent pseudomeningoceles, and approximately 19 other surgical site findings that were either transient or less defined blebs.

Methods:

Sixteen-year single-center retrospective chart review of cases operated by two surgeons. Clinical data, radiographic imaging, and histopathologic review of cases with pseudomeningocele formation after ONSF are presented.

Results:

86 eyes in 57 patients underwent ONSF (28 unilateral, 12 bilateral sequential, 17 bilateral simultaneous).Forty-nine of 57 patients had documented high ICP, (41 IIH, 4 venous thrombosis, 2 meningitis, 1 AVM, 1 sarcoid). In 32 patients undergoing post-operative imaging, 4 eyes in 4 patients developed well-defined pseudomeningoceles (3 symptomatic, 2 revised surgically). Each developed in the setting of high ICP (350, 360, 430, 500mm H20). MRI/CT show sharply demarcated fluid filled cysts adjacent to the optic nerve. Cysts were hypointense on T1-weighted imaging, variably enhancing with contrast, hyper intense on T2-weighting, and dark on FLAIR. Histopathologic analysis of one cyst demonstrated an acellular, fibrocollagenized lining consistent with pseudomeningocele. Three eyes in three additional patients had less well defined findings interpreted as bleb-like or cystic-like change on scans.

Conclusions:

Pseudomeningoceles following ONSF may be asymptomatic, or act as a space-occupying orbital mass amendable to surgical excision. Post-ONSF cysts are identified on CT or MRI to occur at the locations of fenestration sites and contain cerebrospinal fluid communicating with the subdural space. These post-operative findings are found to be anatomically consistent with pseudomeningocele, which may act as a filtration bleb in some cases. The pseudomeningoceles may be symptomatic or asymptomatic, have a variable ability to filter CSF, and image findings may represent a spectrum spanning intraorbital CSF leakage, partial walling off of bleb, or fully developed cysts.

References: 1. Banta JT, Farris BK. Pseudotumor cerebri and optic nerve sheath decompression. Ophthalmology 2000;107(10):1907-12. 2. Hamed, LM, Tse, DT, Glaser, JS, et al: Neuroimaging of the optic nerve after fenestration for the management of pseudotumor cerebri. Arch Ophthalmol 1992; 110: 636-9. 3. Hawk MW, Kim KD. Review of spinal pseudomeningoceles and cerebrospinal fluid fistulas. Neurosurg Focus 2000;9(1):e5. 4. Seiff, SR and Shah, L: A model for the mechanism of optic nerve sheath fenestration. Arch Ophthal 1990; 108:1326-9. 5. Spoor TC, McHenry JG, Shin DH. Long-term results using adjunctive mitomycin C in optic nerve sheath decompression for pseudotumor cerebri. Ophthalmology 1995;102: 2024 –2028.

Keywords: Orbit, Neuroimaging, High intracranial pressure/headache

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 285
Likelihood of diagnosing neuroblastoma in isolated Horner syndrome

Nitza Goldenberg-Cohen[1], Avi Ben Shabat[2], Shifra Ash[3]

[1]Bnai Zion Medical Center, Haifa, Haifa, Israel, [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Pediatric Oncology Unit, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

Introduction:
To evaluate whether isolated Horner syndrome in children leads to a diagnosis of neuroblastoma (NB), and the incidence of NB in children diagnosed with anisocoria

Methods:
Review of the files of 125 children investigated for anisocoria between the years 2007-2015. Of them, 48 children had a positive cocaine test for Horner syndrome, 34 of them younger than 1 year old. Twelve were excluded because of lack of data. Complete evaluation included MRI of the brain and neck, abdominal ultrasound, and urine catecholamines. Data of follow up period and management were summarized. In addition, files of 173 children diagnosed with NB were reviewed for the existence of Horner's syndrome at presentation.

Results:
None of the 22 patients diagnosed with Horner syndrome had NB. Complete investigation was performed in 14 (64%) patients, partial investigation in 6 (27%) and observation only in 2 (9%). The leading etiology was idiopathic, followed by birth trauma and post-surgical. Of the 173 children diagnosed with NB, 5 (3%) had Horner syndrome detected after the diagnosis of NB was made, 4 of them post-surgical intervention. The remaining child was diagnosed due to the tumor symptoms and signs and the anisocoria was missed until a later stage.

Conclusions:
None of the children evaluated for Horner syndrome had NB, and none of the children with NB were diagnosed due to anisocoria. Even when Horner syndrome was noted, it was after NB diagnosis was made. These findings may suggest that anisocoria is not indicative of NB and investigation can be limited to abdominal ultrasound and urine catecholamines, whereas full investigation can be reserved for highly suspicious cases with other signs or symptoms of NB.

References: None.

Keywords: Pediatric neuro-ophthalmology, Pupils Retina, Tumors, Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease, Neuro-ophth & systyemic disease (eg. MS, MG, thyroid)

Financial Disclosures: The authors had no disclosures.

Grant Support: This study was partially supported by the Zanvyl and Isabelle Krieger Fund, Baltimore, Maryland, USA.

Poster 286
Characterization of Reflex Tearing Induced by Light Stimuli in Relation to the Post-illumination Pupil Response

Shaobo Lei[1], Xingqiao Chen[2], Marija Zivcevska[3], Herbert Goltz[4], Agnes Wong[1]

[1]The Hospital for Sick Children, University of Toronto, Toronto, Canada, [2]The Krembil Research Institute, Toronto Western Hospital, Toronto, Canada, [3]Institute of Medical Science, University of Toronto, Toronto, Canada, [4]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada

Introduction:
We hypothesize that light-induced tearing, a protective reflex associated with photophobia, is melanopsin-driven. This study tests this hypothesis by investigating whether light-induced tearing is more sensitive to blue light than red light and whether light-induced tear production is positively correlated with the melanopsin-driven post illumination pupil response (PIPR).

Methods:
11 visually normal participants completed the experiment, which consisted of 15 trials of 1-minute anesthetized Schirmer's test on the right eye while pupil response was simultaneously recorded from the left eye using a video-based eye tracker. Participants were seated in a darkened room with the head positioned in front of a Ganzfeld bowl with both eyes open. At 20 s into each trial, participants received either no light stimulation (baseline trial) or one flash of red (640±10 nm) or blue (467±17 nm) light stimuli of 400 ms duration. Light stimulation trials were presented in alternating fashion at 7 incremental steps of intensity (0.1, 1, 3.16, 10, 31.60, 100 and 400 cd/m2). PIPR was defined as the mean pupil diameter reduction from 10 to 30 seconds post illumination.

Results:
Tear production in response to 10 to 400 cd/m2 blue light was significantly greater than baseline, and it increased steadily with increasing light intensity. Red light did not induce significant tear production until 400 cd/m2. There is a high positive linear correlation between blue light induced tearing and PIPR, as confirmed by linear regression analysis ($R= 0.98$, $p<0.001$).

Conclusions:
The intensity-response function and spectral characteristics of light-induced tearing are highly consistent with the features of melanopsin phototransduction. This finding is the first in-vivo evidence supporting the idea that light-induced tearing is mediated primarily by melanopsin photoactivity, which provides valuable insight into the mechanism of photophobia.

References: None.

Keywords: Pupils Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: Supported by the Canada Foundation for Innovation, John and Melinda Thompson Endowment Fund for Vision Neuroscience, and the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children.

Poster 287
Efficacy of Digital Pupillometry for Diagnosis of Horner Syndrome

Jeong-Min Hwang[1], Yung Ju Yoo[1], Hee Kyung Yang[1], Nam Ju Moon[2]

[1]Seoul National University, Seongnam, Korea, Republic of, [2]Chung-Ang University Hospital, Seoul, Korea, Republic of

Introduction:
To evaluate the efficacy of digital pupillometry in the diagnosis of anisocoria related to Horner syndrome in adult patients.

Methods:
In this retrospective, observational, case control study, 19 patients with unilateral Horner syndrome (Horner group) and age-matched controls of 30 healthy individuals with normal vision and neither optic nerve dysfunction nor pupillary abnormalities were included. Pupillary light reflex (PLR) of the Horner group and controls were measured by a dynamic pupillometer (PLR-200; NeurOptics Inc., Irvine, USA). Pupil diameter, latency, constriction ratio, constriction velocity, dilation velocity, and total time taken by the pupil to recover 75% of maximal pupil diameter (T75) were noted. PLR were measured at baseline in both groups and at 30-45 minutes later after 0.5% apraclonidine (Iopidine®; Alcon Laboratories, Fort Worth, TX, USA) instillation in the Horner group.

Results:
In the Horner group, pupil diameter, constriction ratio, average dilation velocity, and T75 showed significant difference between the affected eye and contralateral unaffected eye at baseline (all $P<0.05$). Compared to controls, inter-eye difference values of pupil diameter and T75 were significantly larger in the Horner group (all $P<0.001$). After 0.5% apraclonidine instillation, changes of pupil diameter, latency, constriction ratio and velocity were significantly larger in the affected eye compared to the unaffected contralateral eye (all $P<0.05$). The area under the receiver operating characteristic curves for diagnosing Horner syndrome were largest for the baseline T75 and baseline inter-eye difference of maximal and minimal pupil diameter (AUC = 0.824, 975, and 994, respectively).

Conclusions:
Digital pupillometry is an objective method for quantifying PLR and provides valuable information for the diagnosis of Horner syndrome. Our results show that digital pupillometry is a reliable tool to diagnosing Horner syndrome.

References: None.

Keywords: Pupils Retina

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 288

Differences in pupillary light reflex between hereditary optic neuropathy and ethambutol induced optic neuropathy

Nam Ju Moon[1], Yung Ju Yoo[2], Hee Kyung Yang[2], Jeong-Min Hwang[3]

[1]Chung-Ang University Hospital, Seoul, Korea, Republic of, [2]Seoul National University, Seongnam, Korea, Republic of, [3]Seoul National University Bundang Hospital, Seongnam, Korea, Republic of

Introduction:
To evaluate the differences in pupillary light reflex (PLR) between ethambutol optic neuropathy (EON) and hereditary optic neuropathy (HON).Design: Retrospective, observational, case control study.

Methods:
This retrospective, observational, case control study included 13 patients with EON and 16 patients with HON whose PLR were measured by digital pupillometry (PLR-200; NeurOptics Inc., Irvine, USA). Age-matched control included 30 healthy individuals with normal vision and no optic nerve dysfunction. Pupil diameter, latency, constriction ratio, constriction velocity, dilation velocity, and total time taken by the pupil to recover 75% of maximal pupil diameter (T75) were noted. The differences in PLR measurements were compared between EON group and HON group and changes of PLR parameters in early phase and recovery phase in EON group was also evaluated.

Results:
Pupillary constriction velocity, constriction ratio, latency, and dilation velocity were all significantly decreased in EON group compared to HON group (all P 0.05). Average and temporal peripapillary and papillomacular bundle retinal nerve fiber layer thickness were significantly decreased in the recovery phase (P < 0.001, < 0.001 and = 0.001, respectively).

Conclusions:
Pupillary constriction ratio, latency, constriction velocity, and dilation velocity were significantly decreased in EON group compared to HON group and normal control. Decreased PLR in early phase of EON group were not recovered in recovery phase. Dynamic pupillometry may be a useful tool for differentiating patients with optic neuropathies.

References: None.

Keywords: Pupils Retina, Optic neuropathy

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 289

Novel Autoantibodies in Sjogren's Syndrome. Early recognition of this Autoimmune state prior to Neurological Complications

Norah Sydney Lincoff[1], Sandra Everett[1], Julian Ambrus[3]

[1]*Jacobs School of Medicine, Department of Neurology, SUNY at Buffalo*

Introduction:

The neurological complications of Sjogren's syndrome can be severe. This inflammatory condition is often considered "ruled out" in patients whose initial lab testing for anti-Ro and anti-La is negative. Novel autoantibodies have been discovered that are positive in many cases prior to the SSA ad SSB titers ever turning positive. These autoantibodies, which occur early in the course of SS, include Anti-salivary gland protein 1 (SP1), Anti-carbonic anhydrase 6 (CA6) and anti-parotid secretory protein (PSP).

Methods:

Patients from a dry eye clinic and normal controls were assessed by Schirmer's, and Tear Osmolality testing. Twenty seven patients with Schirmer's tests<3mm, 38 patient with Schirmer's tests<6mm and 35 normal controls were studied. Sera was assessed for autoantibodies using ELISA assays. The serologic studies performed on all groups included anti-Ro, anti-La, anti-Sp1, Anti-CA6 and Anti-PSP. Statistical analysis was performed with Prism 7 software and student's unpaired t-test. The Institutional Review Board at our institution approved these studies.

Results:

In this study 60% of the dry eye patients expressed one of these autoantibodies, while in comparison only 30% expressed one of the two more commonly tested autoantibodies SSA or SSB known to be associated with Sjogren's Syndrome. Also, patients with disease for less than 2 years and mild dry eyes did not express anti-Ro or anti-La, while 25% expressed at least anti-SP1.

Conclusions:

Because more than 50% of patients with neurological manifestations of Sjogren's never have the classic autoantibodies show up in there sera, it is imperative that these newer antibodies be tested. They have been shown to appear earlier and more often on testing. Autoantibodies to SP1, CA6, and PSP need to be studied further in patients with Sjogren's Syndrome. Testing for these antibodies will allow earlier recognition and treatment of patients with SS who may go on to suffer from neurological complications of the disease.

References:

1. Suresh L, Ambrus J et al, Investigation of novel autoantibodies in Sogren's syndrome utilizing Sera from the Sjogren's international collaborative clinical alliance cohort. Bmc Ophthalmol: 15, 2015
2. Meiners P et al, Abatacept treatment reduces disease activity in early primary Sjogrens syndrome (open label Phase II ASAP study). Annals of the Rheumatic Diseases 72: 89, 2013.
3. Morreale M et al, Neurological Involvement in Primary Sjogren's Syndrome. PLoS ONE: 9(1): e84605, 2014

Keywords: Neuro-ophth & systyemic disease (eg. MS, MG, thyroid), Diagnostic Tests (ERG, VER, OCT, HRT, mfERG, etc) Eyelid & adnexal disease

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

Poster 290
Infantile Horner's Syndrome due to Ectopic Thymus Gland

Milad Modabber[1], Christine Saint-Martin[2], Ayesha Khan[3], Helena Zakrzewski[4], Daniella Toffoli[3]

[1]McGill University, Montreal, Canada, [2]McGill University, dept of Radiology, Montreal, Canada, [3]McGill University, dept of Ophthalmology, Montreal, Canada, [4]Cumming School of Medicine, University of Calgary, Calgary, Canada

Introduction:
Horner syndrome results from a disruption of the sympathetic chain anywhere along the three neuron pathway from the hypothalamus to orbit. Common congenital causes include birth trauma, neoplasm and vascular malformations. We present a case of ectopic thymic tissue as a rare cause of congenital Horner syndrome.

Methods:
Literature review and case report.

Results:
A 19 month old child, known for left congenital fourth nerve palsy, presented with right pupillary miosis upon admission for asthma exacerbation. It was confirmed that the right pupil had been smaller than the left since birth. On examination, the anisocoria was greater in the dark. Right Horner syndrome was confirmed with topical cocaine 10% and apraclonidine 0.5% testing. Head and neck magnetic resonance imaging showed a 13.0 x 18.0 mm lesion in the neck inferior to the right lobe of the thyroid gland and medial to the common carotid artery with differential diagnosis including neuroblastoma and ectopic thymic tissue. Neck ultrasound confirmed that the solid lesion showed echotexture identical to that of the thymus but no direct communication with it, suggestive of ectopic thymic tissue ipsilateral to the Horner syndrome. Vanillylmandelic acid and Homovanillic acid urine testing were negative. Repeat MRI 6 months and 2 years later showed unchanged size of the lesion. The Horner Syndrome remained stable at follow-up.

Conclusions:
We present a rare case of Horner syndrome caused by ectopic thymic tissue. Thymic tissue rests occur due to failure of involution of thymic primordia found along the path of the embryologic thymopharyngeal duct in the neck. Solid thymic tissue rests are usually benign, however, they have been associated with dyspnea due to tracheal compression. Our case illustrates that ectopic thymic tissue can also cause compression of the sympathetic chain and should be considered in the differential diagnosis of Horner syndrome.

References: None.

Keywords: Pediatric neuro-ophthalmology, Neuroimaging

Financial Disclosures: The authors had no disclosures.

Grant Support: None.

North American Neuro-Ophthalmology Society

43rd Annual Meeting

April 1 – April 6, 2017
Washington Marriott Wardman Park • Washington, DC

Program Schedule

WEDNESDAY, APRIL 5

6:30 am - 5:30 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
6:30 am - 7:30 am	**Breakfast**	**Exhibit Hall C**
7:00 am - 7:30 am	**Annual NANOS Business Meeting**	**Thurgood Marshall Ballroom**
7:30 am - 11:15 am	**Afferent and Efferent Rehabilitative Strategies in Neuro-Ophthalmology [3.5 CME]** *Moderators: Sashank Prasad, MD and Paul H. Phillips, MD*	**Thurgood Marshall Ballroom**

After diagnosis and treatment, rehabilitation quickly becomes one of the most important aspects of the management of a patient with Neuro-Ophthalmic disease. There have been many important recent advances in rehabilitative methods for both afferent and efferent visual dysfunction. In this symposium, these methods will be reviewed, with an emphasis on both underlying neuroscientific principles and practical strategies.

Upon completion of this course, participants should be able to: 1) Examine recent data assessing the value of visual field stimulation to attempt to reduce a homonymous visual field deficit; 2) Recognize conceptual issues impacting the use of prisms and augmented vision to treat patients with visual field deficits; 3) Describe rehabilitation strategies for patients with visual loss from optic neuropathy; and 4) Appraise methods to treat convergence insufficiency.

		PAGE
7:30 am - 7:35 am	**Introduction and Overview,** *Paul H. Phillips, MD*	
7:35 am - 7:40 am	**Case Presentation: Homonymous Hemianopia,** *Sashank Prasad, MD*	
7:40 am - 8:00 am	**Update on Visual Field Expansion with Rehabilitative Training,** *Krystel Huxlin, PhD*	**451**
8:00 am - 8:20 am	**Fitting Peripheral Prisms for Hemianopia,** *Eli Peli, MSc, OD*	**457**
8:20 am - 8:40 am	**Driving Considerations in Teens with Optic Neuropathies,** *Judith E. Goldstein, OD*	**463**
8:40 am - 9:00 am	**Q & A**	
9:00 am - 9:15 am	**Coffee Break**	**Thurgood Marshall Foyer**
9:15 am - 9:35 am	**The Roles and Effects of Diplopia and Visual Confusion in the Treatment of Visual Field Loss***, Eli Peli, MSc, OD*	**469**
9:35 am - 9:55 am	**Rehabilitation Strategies for Optic Neuropathies in Adults (AION),** *Judith E. Goldstein, OD*	**481**
9:55 am - 10:00 am	**Case Presentation: Convergence Insufficiency,** *Paul H. Phillips, MD*	
10:00 am - 10:20 am	**Convergence Insufficiency: Review of Treatment Trials (Office versus Home Based Treatment**), *Susan Cotter, OD, MS*	**487**

10:20 am - 10:40 am **Convergence Insufficiency: Practical Pearls for Diagnosis and Treatment,** *Susan Cotter, OD, MS* **495**

10:40 am - 11:15 am **Q & A**

11:15 am - 11:20 am **NOVEL Update** **Thurgood Marshall Ballroom**
Presenter: Kathleen Digre, MD

11:20 am - 12:00 pm **Jacobson Lecture: Going with the Flow [.75 CME]** **Thurgood Marshall Ballroom**
Moderator: Patricia Johnston-McNussen, MD
Presenter: Randy Kardon, MD, PhD

A perspective will be provided on newly discovered aspects of ocular blood flow and how it relates to causes of vision loss seen by Neuro-Ophthalmologists.

Upon completion of this course, participants should be able to: 1) Describe disorders in which choroidal blood flow can be decreased; 2) Describe disorders in which retinal blood flow can be decreased; and 3) Recognize the relationship between retinal blood flow and metabolic activity of retinal neurons.

12:15 pm - 1:30 pm **Research Committee Meeting Luncheon** **Stone's Throw Restaurant**

1:30 pm - 2:30 pm **Women in Neuro-Ophthalmology (WIN) Forum: Gender Pay** **Exhibit Hall C**

Join your colleagues for a networking event where we will explore the evidence for, perspectives surrounding, and potential solutions to the gender pay gap in medicine. NANOS members, Dr. Lynn Gordon and Dr. Melissa Ko, will give brief presentations, and there will be small table strategy-focused brainstorming. All are welcome.

1:30 pm - 3:00 pm **My baby can't see! [1.5 CME]** **Thurgood Marshall Ballroom**
Moderator: Gena Heidary, MD, PhD
Panelists: Mark Borchert, MD, Grant T. Liu, MD, Paul H. Phillips, MD, & Stacy Pineles, MD

The purpose of this optional symposium, presented by members of the Consortium of Pediatric Neuro-Ophthalmologists (CPNO), is to review the assessment of vision during infancy, highlight important symptoms and signs of common Neuro-Ophthalmic conditions that cause visual dysfunction during infancy, and provide a framework for the diagnostic work up and management of these disease processes.

The workshop will begin with a brief overview of visual development during infancy to frame the discussion. After this overview, four topics including nystagmus in infants, congenital optic nerve anomalies, inherited retinal dystrophies/degenerations, and cortical/central visual impairment will be covered with an illustrative case presentation and a didactic talk.

The nystagmus in infants section will provide insight into the characteristic clinical features of infantile nystagmus syndrome, spasmus nutans, and latent nystagmus with a focus on diagnostic tools useful in clarifying the underlying etiology of nystagmus. The congenital optic nerve anomalies section will focus on novel insights into optic nerve hypoplasia. The retinal dystrophy/degeneration section will review the clinical presentation of an inherited retinal dystrophy/degeneration with a discussion on diagnostic evaluation in that setting. The cortical/central visual impairment section will review the clinical manifestations of this condition. In addition, data on the use of novel DTI-related imaging techniques to evaluate the neuro-anatomy of individuals affected with cortical/central visual impairment and recommendations for visual rehabilitation and management of these children will be highlighted.

Upon completion of this course, participants should be able to: 1) Develop an understanding of important milestones in visual development during the first year of life; 2) Review the clinical presentation of nystagmus during infancy and its diagnostic evaluation; and 3) Promote awareness of cortical visual impairment: its clinical features, epidemiology, and management.

1:30 pm - 1:35 pm **Consortium for Pediatric Neuro-Ophthalmologists brief overview,** *Grant T. Liu, MD*

1:35 pm - 1:40 pm **Case 1,** *Grant T. Liu, MD*

1:40 pm - 1:55 pm **Case 1, Discussant:** *Paul Phillips, MD*

1:55 pm - 2:00 pm **Case 2,** *Grant T. Liu, MD*

2:00 pm - 2:15 pm **Case 2, Discussant:** *Mark Borchert, MD*

2:15 pm - 2:20 pm **Case 3,** *Grant T. Liu, MD*

2:20 pm - 2:30 pm **Case 3, Discussant:** *Stacy Pineles, MD*

2:30 pm - 2:35 pm **Case 4***, Grant T. Liu, MD*

2:35 pm - 2:50 pm **Case 4, Discussant:** *Gena Heidary, MD, PhD*

3:00 pm - 3:30 pm **Consortium of Pediatric Neuro-Ophthalmologists Meeting (CPNO)**
Facilitator: Mark Borchert, MD **Thurgood Marshall Ballroom**

3:15 pm - 5:15 pm **Coding: A Day in the Life of a Neuro-Ophthalmologist** **Washington Rooms 3-6**
Moderators: Mark Moster, MD and John Pula, MD
Presenters: Jenny Edgar, CPC, CPCO, OCS
Coding Specialist, American Academy of Ophthalmology
David B. Glasser, MD
American Academy of Ophthalmology
Chair, Academy Health Policy Committee

For many practices, not only is correct claim submission a goal, making sure documentation meets medical necessity is a must, as audits are on the rise. This two hour course will walk through real-life Neuro-Ophthalmology cases focusing on how time is a factor for exams, plus how modifiers and bundling edits may impact services being submitted. The group will review testing service requirements providing what is necessary for both minor and major surgical procedures. Also present in the session will be David B. Glasser, MD, American Academy of Ophthalmology, Chair, Academy Health Policy Committee.

Upon completion of this course, the participant should be able to: 1) Recognize when to report and E/M vs Eye visit code; 2) Link CPT to ICD-10 to avoid claim denials; 3) Identify appropriate use of the Advance Beneficiary Notice; 4) Apply payer rules to testing services; and 5) Successfully avoid penalties under the MIPS program.

3:15 pm - 5:00 pm **Coding for Neuro-Ophthalmology with Interactive Case Studies**, *Jenny Edgar, CPC, CPCO, OCS*

5:00 pm - 5:15 pm **Q&A**

4:00 pm - 5:00 pm **International Relations Committee Meeting** **Hoover**

6:30 pm - 11:30 pm **Annual NANOS Reception and Banquet** **Thurgood Marshall Ballroom**

UPDATE ON VISUAL FIELD EXPANSION WITH REHABILITATIVE TRAINING

Krystel Huxlin, PhD

Flaum Eye Institute, University of Rochester
Rochester, NY

LEARNING OBJECTIVES

1. Recognize that it is possible to restore vision after primary visual cortex damage in adult humans
2. Distinguish visual restoration from visual compensation
3. Define what aspects of visual training are necessary to attain vision restoration in cortically blind fields
4. Define how recovered vision differs from normal vision in cortically blind fields
5. Explain how visual training impacts clinical perimetry and psychophysical measures of visual function

CME QUESTIONS

1. Localized vision discrimination training in cortically blind fields leads to:
    a. Complete restoration of vision across the entire blind field
    b. Partial restoration of vision across the entire blind field
    c. Partial restoration of vision inside the retrained blind field locations and along the blind field border
2. Which of the following rehabilitation therapies have been demonstrated to significantly reduce the size of the perimetrically defined blind field in cortical blindness?
    a. Compensation therapies (e.g. eye movement or saccadic training)
    b. Substitution therapies (e.g. prisms)
    c. Restoration therapies (e.g. visual discrimination training with controlled fixation)
3. What factors are most critical to attain measurable visual recovery in cortically blinded fields?
    a. Gaze-contingent stimulus presentation during training
    b. Gaze contingent stimulus presentation during testing
    c. Excluding patients with neurodegenerative conditions or eye disease
    d. Daily training for many months
    e. All of the above

KEYWORDS

1. Hemianopia
2. Quadrantanopia

INTRODUCTION

Damage to the primary visual cortex (V1) or its immediate afferents results in a loss of conscious vision in corresponding parts of the visual field in each eye – in essence, causing a "cortically-induced blindness" or CB. While blinding diseases are a significant scourge in our aging society, when it comes to cortical blindness, most of the sparse rehabilitation effort leans heavily towards substitution or compensation for the vision lost, rather than towards vision restoration. One contributing factor has been the mistaken belief that the adult visual system lacks the kind of plasticity inherent in other cortical [i.e., motor] systems, which underlies their ability to recover function after damage.

Research in our laboratory over the last 14 years has critically examined this problem first using an animal model of visual cortical damage, then using affected humans. In both cases, we found that gaze-contingent visual training can restore direction and orientation discrimination of both moving and static, simple and complex visual targets at trained, blind field locations, even in *chronic* stroke patients. Localized, discrimination training also generated large swaths of improvement in visual detection sensitivity measured by Humphrey perimetry, inside the original blind field border. The amount of improvement attained did not depend on patient demographics (age, time post-lesion, etc.), but instead, was directly proportional to the amount of training performed. However, both Humphrey perimetry and psychophysical measurements showed that recovered vision was not completely normal, with poorer sensitivity for luminance contrast. Visual psychophysics also demonstrated residual deficits in fine difference discriminations for both motion and orientation, which modeling revealed to be caused by abnormally high levels of internal processing noise.

Current research in our laboratory is focused on better understanding the nature and sources of this noise, and the neural mechanisms that underlie training-induced recovery. Together with our collaborators, we have also started manipulating training parameters and using

adjuvant therapies (both pharmacological and electrical) in an attempt to speed up the rate and magnitude of recovery and overcome residual visual deficits at trained, blind field locations.

Stroke is the main cause of damage to the primary visual cortex (V1) in humans, leading to loss of conscious vision in both eyes (Gilhotra et al., 2002; Pollock et al., 2011; Pollock et al., 2012). Other major causes include traumatic brain injury and tumors (Zhang et al., 2006). When the damage is unilateral, the resulting cortically induced blindness (CB) affects anywhere from a quarter (quadrantanopia) to a half of the visual field (hemianopia). Even when unilateral, CB impairs the ability to read, drive, and navigate; it impacts rehabilitation efforts and the capacity to live independently (Dombovy et al., 1986; Jongbloed, 1986; Jones and Shinton, 2006).

TRADITIONAL APPROACHES TO THE REHABILITATION OF CORTICALLY INDUCED BLINDNESS

The incidence of CB is high and likely increasing: according to the 2009 National Hospital Discharge Survey, the incidence of stroke in the United States approaches 1 million per year. Pollock and colleagues (Pollock et al., 2011; Pollock et al., 2012) estimated a 27% to 57% incidence of visual field defects following ischemic brain injury, suggesting that 270,000 to 570,000 individuals in the U.S. are affected by new onset of CB annually, due to stroke alone. The high incidence of visual loss and the dramatic impact on everyday functions highlight the importance of finding treatments that reverse the field defects. Yet CB is almost unique among the major types of brain damage because of the lack of accepted, validated vision rehabilitation treatments available to those afflicted. A 2011 Review (Pollock et al., 2011), performed by the Cochrane Collaboration - an independent, not-for-profit, non-governmental entity, which organizes and evaluates medical research information according to the principles of evidence-based medicine (see http://community.cochrane.org/about-us/our-principles) - examined three classes of interventions for CB: (1) **restitution therapies**, which aim to recover visual field deficits, (2) **compensation therapies**, which train saccadic eye movements to capture visual information that would normally fall onto blind portions of the visual field (e.g. Weinberg et al., 1977; Kerkhoff, 1999, 2000; Spitzyna et al., 2007), and (3) **substitution therapies,** which use prisms or other optical devices to present/overlay stimuli that would normally fall in the blind field, onto intact portions of the visual field (e.g. Rossi et al., 1990; Peli, 2000; Szlyk et al., 2008). Although a few of the studies examined by the Cochrane Review demonstrated benefits for reading and quality of life (Weinberg et al., 1977; Spitzyna et al., 2007), it was concluded that randomized, double-masked, controlled clinical trials conducted up to that point in time had failed to demonstrate the efficacy of any of the current interventions used in the clinic at improving vision in CB (Pollock et al., 2011; Pollock et al., 2012). Even today, several years after the Cochrane Review, CB patients are most often sent home and told to learn to live with their deficit because it cannot recover. Only a small fraction of patients are recommended for compensation or substitution therapies, assuming that they are available locally (which is not often).

CAN VISION BE RESTORED IN CORTICALLY-INDUCED BLINDNESS?

Surprisingly little basic research effort is being devoted at critically and rigorously evaluating whether vision restoration might actually be possible in CB. One reason for this may be the reputation garnered by the field of visual rehabilitation to date, and the fact that many professionals in both the clinical and scientific communities (Horton, 2005b, a; Plant, 2005; Reinhard et al., 2005) now question whether the damaged, adult visual system is capable of functional recovery. This sceptical attitude has led to the current situation, in which we know relatively little about the plastic potential of chronically damaged adult visual systems. This is in spite of the fact that the eyes (the input to the visual system) and many higher level visual cortical areas are intact in CB. In fact, these intact visual processing centres are known to underlie residual visual processing abilities - termed *blindsight* by Weiskrantz and colleagues in 1974 (Sanders et al., 1974; Weiskrantz et al., 1974) - inside cortically blind fields. Blindsight includes the largely unconscious ability to detect, compare and even discriminate stimuli in the blind field (for reviews, see Stoerig, 2006; Weiskrantz, 2009; Cowey, 2010).

Given what we know about blindsight, it should come as no great surprise that in the last 10 years, research by several teams worldwide, including ours, has identified one method that appears to reliably recover some of the vision lost in chronic CB patients: repetitive visual training to detect or discriminate stimuli presented at single locations in the blind field, while fixating a central target (Sahraie et al., 2006; Raninen et al., 2007a; Chokron et al., 2008b; Huxlin et al., 2009b; Sahraie et al., 2010; Das et al., 2014b; Vaina et al., 2014a; Cavanaugh et al., 2015; Turco et al., 2015). To date, our laboratory has specialized in retraining conscious visual discriminations and we have done so in over 60 chronic, CB patients. Trained participants uniformly exhibited recovery of coarse (left/right) direction discrimination abilities at trained, blind field locations (Huxlin et al., 2009b; Das et al., 2014b). Even more remarkable, trained individuals were able to relearn to perform static orientation discriminations *de novo* in their blind field (Das et al., 2014b), a surprising finding given that such stimuli are not normally discriminable in blindsight (Hess and Pointer, 1989; Weiskrantz et al., 1991; Morland et al., 1996; Sahraie et al., 2003b; Sahraie et al., 2008b). Importantly, training generalized to untrained stimuli and tasks (Das et al., 2014b). Although an exciting outcome, detailed characterization of the properties of recovered

vision also showed that while fine direction and orientation differences could now be discriminated at retrained, blind field locations, difference thresholds remained 3-5 fold higher than at corresponding locations in the intact field of vision (Das et al., 2014b; Cavanaugh et al., 2015). Combined with the fact that recovered contrast sensitivity was also about 10 fold lower than normal (Das et al., 2014b), it appears that using standard perceptual training methods, recovered vision is less accurate and sensitive than normal. This is something that patients confirm subjectively, and which research in our laboratory is actively trying to understand and overcome.

HOW DOES VISUAL TRAINING IMPACT THE VISUAL FIELD IN CORTICAL BLINDNESS?

In addition to characterizing the quality of vision recovered as a result of perceptual training, we also asked whether improvements on the trained task(s) translated to improved perimetry. Perimetric visual field measurements are the primary clinical method used to diagnose and evaluate visual field defects in CB. There has been surprisingly little exploration of this question in the literature, and results have tended to vary markedly (Raninen et al., 2007b; Chokron et al., 2008a; Sahraie et al., 2008a; Bergsma and van der Wildt, 2009; Huxlin et al., 2009b; Raemaekers et al., 2011; Bergsma et al., 2012; Vaina et al., 2014b).

To begin addressing this question, we conducted a small, retrospective, pilot study, evaluating the impact of visual discrimination training on Humphrey automated perimetry. We examined 23 patients with chronic CB from stroke, 16 of whom trained using our motion and/or orientation discrimination paradigm and whose results were previously published by our group (Huxlin et al., 2009b; Das et al., 2014b; Cavanaugh et al., 2015). Humphrey visual field tests (HVF) were performed both before and after training. They were contrasted with repeated HVFs collected on 5 chronic CB subjects who did not train. Among other factors, we examined changes in perimetric mean deviation (PMD) and the area of the HVF that increased or decreased in sensitivity by more than 6dB (twice the test-retest variability of the system). The area of the HVF was computed using Matlab from interpolated maps of visual sensitivity across the two eyes and all visual field locations sampled in the 10-2 and 24-2 HVFs at each time-point examined. Several main findings emerged:

- First, training chronic CB subjects to discriminate global motion, static orientation, or both, improved performance on the trained tasks *and* shrank perimetrically-measured field defects. Trained subjects exhibited a significant improvement in PMD and showed significant increases in sensitivity (≥6dB) over ~100 deg^2 or 6% of the total HVF area (~1,600 deg^2). Critically, HVF improvements were not influenced by the type of training, the subject's age, the time since their stroke, or initial deficit size (suggesting that lesion size may not be a significant factor). Thus, any patient with chronic CB capable of performing rigorous training with controlled fixation may be able to recover some lost vision, even on stringently performed HVF tests. Critically, the number of training sessions and locations correlated significantly with the area of HVF improvement. In fact, we ascertained that meaningful recovery (~75 deg^2) can be attained with ~150 consecutive training sessions (of 300 trials each) at 2-3 blind field locations. Assuming two sessions/day, such training should take ~3 months to complete. However, since continued training may generate continued improvement, patients should probably train for as long as improvement is observed. Of course, our research has generated many new questions, which future studies will need to answer: (1) is there a limit on how much of the blind field can recover vision in chronic CB? (2) Can greater recovery be attained if we start training patients in the acute or sub-acute phases after V1 damage? (3) Does the recovered vision persist indefinitely? (4) Can we modify training methods or use adjuvants (brain stimulation, pharmacology) to increase the rate and quality of vision recovery in CB?
- A second important finding of this pilot study was that without training, HVFs did not remain stable – instead, they exhibited a significant decrease in PMD, as well as relatively large areas where sensitivity decreased by ≥6dB. Whether this represents a form of "visual disuse atrophy", a consequence of retrograde degeneration of neurons in the dorsal lateral geniculate nucleus (dLGN) and retina (Cowey and Stoerig, 1989; Cowey et al., 1989; Porrello and Falsini, 1999; Jindahra et al., 2009; Cowey et al., 2011; Millington et al., 2014), and/or because subjects learn to ignore weak, unreliable vision near their blind field, remains to be determined. That worsening was not systematically reported previously may be due to HVF analyses in prior studies lacking the sensitivity to measure such changes. Nonetheless, our results also suggest that visual discrimination training, even when started >6 months post-stroke, may reverse or compensate for losses in visual sensitivity in chronic stroke patients.
- A third important observation was that improvements in the HVF were not restricted to trained, blind field locations, but appeared to extend along the original blind field border. That HVF improvements should occur within trained locations is unsurprising. This is because visual training to detect or discriminate stimuli in the blind field is known to improve contrast sensitivity (Sahraie et al., 2003a; Das et al., 2014a) and HVFs are, in essence, a luminance contrast detection task with broadband

stimuli (Carl Zeiss Meditec, 2010; Kraft et al., 2010). However, improvements in trained discrimination tasks are typically restricted to trained locations in CB subjects (Sahraie et al., 2003a; Huxlin et al., 2009a). Therefore, our results suggest that recovery has different spatial distribution, depending on which visual function is measured. They also suggest that the blind field border may be a region of enhanced plasticity in the adult, post-stroke visual system.

POSSIBLE MECHANISMS UNDERLYING TRAINING INDUCED CHANGES IN HVF

While largely speculative, a possible substrate of training-induced visual improvements in CB fields is engagement of extra-geniculo-striate pathways to mediate recovery. Projections from the dorsal lateral geniculate nucleus that bypass V1 provide direct input to higher level visual cortical areas such as V2/V3 (Bullier and Kennedy, 1983; Hendry and Reid, 2000; Schmid et al., 2009), V4 (Cowey and Stoerig, 1989) and MT/MST (Sincich et al., 2004). It has been postulated (Schmid et al., 2010) that these pathways mediate blindsight. Such pathways are thought to rely primarily on koniocellular (K-cell), as opposed to parvocellular (P-cell) and magnocellular (M-cell) geniculate neurons, partly because K-cells appear to be more resistant to retrograde degeneration than P-cells (Dineen et al., 1982; Cowey et al., 1989). K-cells also possess contrast sensitivity and spatial frequency preferences that match the responses seen in blindsight (Ajina et al., 2015) and in our patients post-training (Das et al., 2014a). Moreover, it has been suggested that K-cell pathways can switch from a "modulatory" to a "driving" role following damage to V1 (Schmid et al., 2009). Repeated, directed activation of these pathways through visual discrimination training could strengthen their driving role. This in turn, may allow the residual visual system to better utilize information bypassing V1, measurably improving conscious vision both perimetrically and in visual discrimination tasks.

CONCLUSIONS

Scientifically, our findings are exciting for a number of reasons. First, they confirm that visual discrimination training at a few distinct locations in the blind field can recover the ability of patients with chronic cortically-induced blindness to correctly discriminate motion direction and orientation at the trained, blind field location. In addition, trained patients also exhibit a boost in luminance sensitivity, even though neither luminance nor contrast was varied during training. Moreover, this boost in sensitivity can be reliably reported by CB subjects during perimetry, extended over large swaths of the Humphrey Visual Field and could therefore be used in their day-to-day lives. Third, the amount of perimetry improvement attained did not depend on major demographic parameters such as patient age, lesion age or deficit size. Instead, it was directly proportional to the amount of training performed. Finally, training-induced visual sensitivity improvements occupied previously impaired regions along the blind field border. Taken together, our findings provide compelling evidence against the prevailing dogma in the field by showing that visual discrimination training in chronic CB fields appears to improve visual performance on both the trained tasks and Humphrey perimetry. We posit that the present finding of a substantial, positive impact of visual discrimination training on perimetry motivates designing a controlled, randomized clinical trial to further elucidate this phenomenon in a larger patient population.

CME ANSWERS

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FITTING PERIPHERAL PRISMS FOR HEMIANOPIA

Eli Peli, MSc, OD

Schepens, Mass Eye & Ear, Harvard Medical School
Boston, MA

LEARNING OBJECTIVES

1. Describe the theoretical concepts of the peripheral prism design
2. Define the relative roles of optical image-shift, visual confusion, apical scotoma, and total internal reflection as factors that affect the use of prisms as field expansion devices
3. Explain the basic procedures for fitting peripheral prisms (frame selection, fitting, positioning the prisms) and describe the variety of fitting options

CME QUESTIONS

1. Apical scotoma in field expansion prisms is:
    a. Always bad, as it blocks part of the field of view
    b. Sometimes bad, as it may reduce confusion which is needed for field expansion
    c. Sometimes good, as it can reduce or eliminate diplopia
2. Because peripheral prisms are fitted above and below the pupil they can operate at all position of gaze equally, unlike prism that are fitted right or left of the pupil.
    a. True
    b. False
3. Spurious reflections may be bothersome especially in conditions of extreme range of light. These may be controlled to some extent by limiting the prism size only to the range that provide useful direct imaging.
    a. True
    b. False

KEYWORDS

1. Field expansion
2. Apical scotoma
3. Peripheral double vision
4. Binocular vision confusion
5. High power prism effects

INTRODUCTION

The lecture presents the background and procedures for fitting prisms for hemianopia. We will start with reviewing the effects and limitations of the main prior techniques, then present the motivation and rationale for the peripheral prism designs, and finally review the evidence base for their use from a growing body of clinical studies. We will also cover recent developments in analyzing the effects of very high power prism in the context of field expansion. Most recent prescription formats, including magnetic clip-on designs, offer numerous advantages; and a fitover design permits inexpensive and simple in-office demonstration and immediate dispensing.

Prism corrections for hemianopia have been in use for many decades and increased in popularity with the introduction of the press-on™ Fresnel prism by 3M. Earlier designs of prism for treatment of homonymous hemianopia (some still in use by many today) can be classified as bilateral or unilateral and as overall or sector designs. All of the known designs fit the prism with the base towards the field loss, i.e. base right for right hemianopia. This is based on the assumption that the image shift in the direction of the prism apex will provide a view in the functioning side. The overall bilateral yoked prism fits such prism over the whole spectacle lens on both sides. Whatever effect is achieved with this approach cannot be considered field expansion; for example, the patient with left hemianopia is not able to see anything left of fixation with the yoked prism. Only moderate power prisms are fitted in these designs because they all require central fixation through the prisms. In addition to the increase thickness and weight of high power prisms, the image quality deterioration through high power prisms is unacceptable to patients when it is applied centrally. With a prism of 20Δ the shifting effect is only about 10°. If the prisms are fitted as sector prism only on half of each spectacle lens, with the apex a few millimeters from the pupil in the direction of the field loss, the prisms have no impact in primary position of gaze or when the gaze is directed in the direction of the intact field. However, the gaze is likely to be directed to the intact field as visual stimuli in that direction are seen and can attract attention and saccadic exploration. Only when the patient is intentionally gazing or responding to a sound or tactile stimuli to the blind side do the prisms have any visual effect. In the case of bilateral sector prisms the result is a shift of the field of view. The patient is able to see further into the blind side than would be possible with the same eye movement without the prism. However, the segment of the field of view that is about equal to the shifted view but more centrally is lost to the apical scotoma. The apical scotoma is an optical phenomenon that occurs at the apex of any prism.

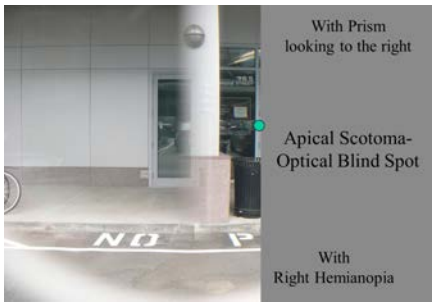


Figure 1.

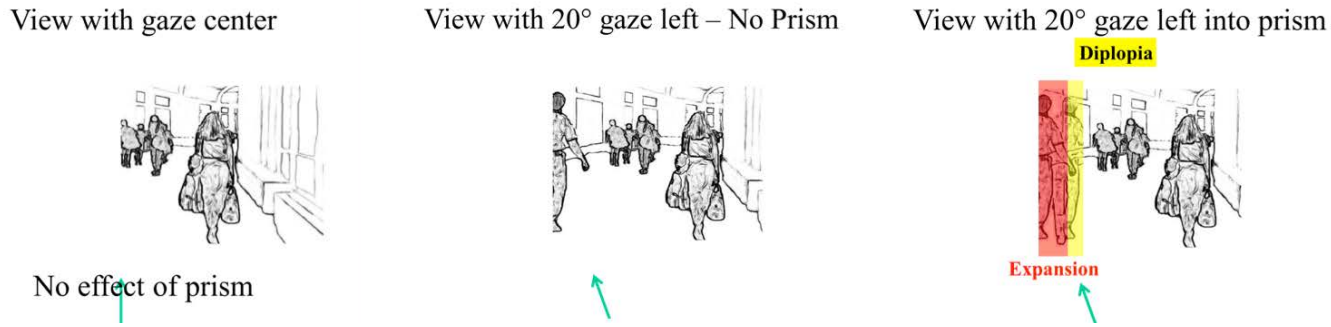
Simulated view of a scene with right hemianopia and with bilateral sector prisms fitted slightly to the right. With central fixation at the sign post no effect of prism.

Simulated view of the same scene with a fixation shifted to the right.

The same scene photographed through a sector prism. An expanded view to the right is apparent; together with the impact of the apical scotoma centrally that obscures the blue sign.

The effect and consequences of a unilateral sector prism is much more complex. It was addressed in detail by Apfelbaum et al.[8] The main difficulty is that the effect of the monocular prism is induced centrally or pericentrally and is thus bothersome. With a large magnitude scan into the prism, i.e. 20°, there is some field expansion. The true expansion in this case, as in all other designs discussed here is accompanied by binocular visual confusion (seeing two different objects in the same direction). Central confusion is annoying and bothersome. The limited expansion achieved with this design is accompanied also by a similar magnitude of central binocular diplopia (seeing two images of the same object in two different directions). Central diplopia serves no purpose and is quite bothersome.

Figure 2.



Simulated view of a patient with left hemianopia in a walking situation. The fixation is assumed to be straight ahead (primary position of gaze).

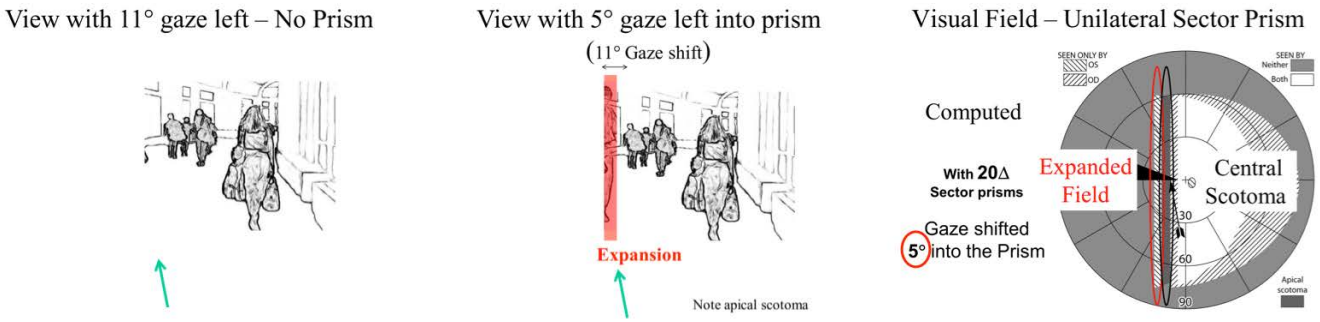
Simulation of the same view with the patient looking 26° to the left. Only the right leg of the man is visible.

The same view with the patient gaze 26° to the left (20°) into the 20Δ prism. The color is to delineate areas. The visible left leg is clear expansion.

Eye movement as large as required to get to 20° into the sector prism which is placed 2 mm from the pupil (~26° in totoal) is not impossible but uncommon. In walking most eye movements are less than 15° in magnitude. The illustration below shows the effect of a more likely gaze of 5° into the prism which requires an eye movement of 11° from the primary position of gaze. In this case in addition to the field expansion (via **central** binocular visual confusion) there is no diplopia but there is a pericentral apical scotoma. The main limitations of the sector prism designs are: a small field expansion only on gaze shift to the blind side, central confusion and central diplopia on large gaze shift, and pericentral apical scotoma on realistic gaze shifts. It appears that patients are discouraged from scanning towards the blind side with these prism designs, though there is no eye tracking data showing that to be the case.

Since the year 2000 we have been developing and evaluating a new optical treatment for hemianopia aimed at addressing the main limitations of the prior designs. We use peripheral prisms mounted above and below the line of sight on one lens on the side of the field loss[1]. The clear area between the prism segments (Fig. 4) permits continuous single undisrupted central binocular vision while

Figure 3.



Simulated view of the scene with a gaze shift of 11° to the left. Only the right hand of the man is visible without the prism.

The same view with the same gaze shift which is 5° into the prism. The field expansion is clear. The apical scotoma is revealed by the man's missing right arm and hand.

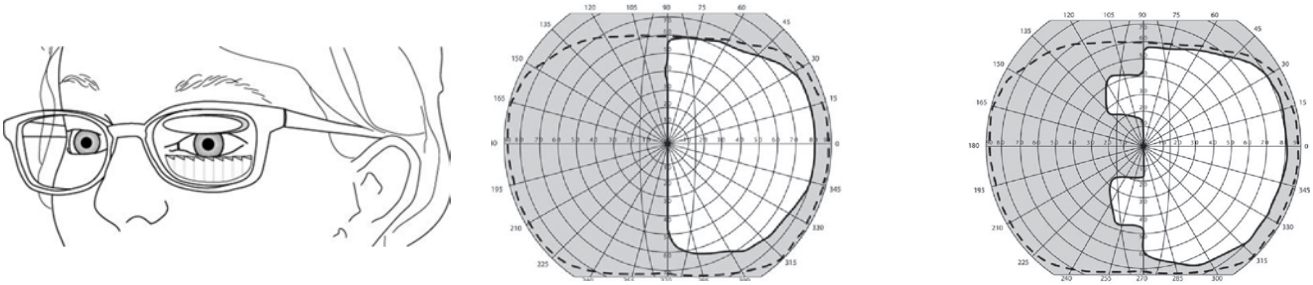
Computed / simulated dichoptic binocular perimetry under the same conditions. About 5° of field expansion and a similar size apical scotoma are shown.

the extent of the prism across the lens provides measurable peripheral field expansion at all (horizontal) positions of gaze. This last statement is true only if the high power prisms are fitted with the serrations towards the eye, as typically done with the press-on Fresnel prism. A series of studies including Multi Center Community Based clinical trials have confirmed that many patients with hemianopia find the field expansion helpful for obstacle avoidance when walking.[2-5, 9] A randomized control trial has shown that the prisms are effective also in improving driving performance.[6] Recent study has shown an improved performance in pedestrians detection task with the peripheral prism in a driving simulator study (submitted).

The peripheral prisms were initially implemented in a "horizontal" design using temporary 40Δ press-on™ Fresnel prisms (providing about 20° lateral field expansion (Fig. 4 center)). A fitting procedure for the press-on prisms was developed[1] and later refined in a multi-center community-based clinical trial.[2] The initial fitting position is centered vertically on the pupil / primary line of sight and the gap between the prisms is about 12 mm, leaving a prism free zone of over 30° vertically. This multi-center trial demonstrated that community-based practitioners, with little or no prior experience of the peripheral prism system, could successfully fit the press-on prisms using the protocol we developed.

With Chadwick Optical, Inc. we developed a permanent 40Δ PMMA Fresnel prism insert embedded in the spectacle lens (Fig. 5), which provides better optical quality and durability than the temporary press-on prisms. More recently a 57Δ high power prism, providing about 30° of field expansion, has been implemented in the permanent prism glasses. Other more recent developments include a new patented "oblique" design that enables expansion of the (vertical) peri-central field despite the peripheral placement of the prisms (Fig. 5 center). While the position of the oblique

Figure 4.



Peripheral prisms fitted for a patient with left hemianopia. The prisms are fitted base-out on the left lens. Shown here with ophthalmic prism above and Fresnel prism below the pupil.

The binocular visual field plot (Goldmann V4e) of a patient with left hemianopia. The gray area represents regions of the visual field that are not seen. The dashed line represents the binocular visual field of a normally sighted person.

The binocular visual field of the same patient with the peripheral prism system using press-on prism of 40 prism diopters. Two areas of about 20° x 20° of visual field expansion are seen.

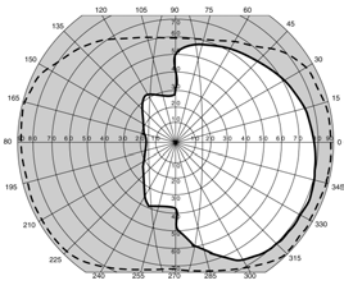
prisms is identical to that of the horizontal design and thus the single binocular vision is maintained centrally, the image shifted by the prism covers the central portion of the lost field (Fig. 5 below). This is considered advantageous in general and particularly for the possible use in driving. With this design the area through the windshield of a car is expanded despite the position of the prism segments themselves are above and below the windshield.

We further conducted a controlled randomized clinical trial in which the "horizontal" and the "oblique" designs using the 57Δ power prisms were compared.[4] This trial has enrolled 73 patients.[9] A simplified fitting procedure developed for that study was found effective and easy, which will be the basis of the fitting technique taught at the workshop. An independent third party study claimed even higher success rate than we have found.[5] We have also published a paper reporting the outcome of a controlled

Figure 5.

Spectacles with permanent 40Δ Fresnel prism segments in the "horizontal" design developed by Chadwick Optical, Inc. Shown for a patient with right hemianopia.

Spectacles with permanent 40Δ Fresnel prism segments in the "oblique" peripheral prism design. Shown for a patient with left hemianopia. The prisms are now routinely dispensed with 57Δ power.



Binocular visual field of patient with left hemianopia wearing peripheral prisms in the oblique design. This design enables expansion of the central field despite the peripheral placement of the prisms.

trial in which a real prism was compared to a sham prism during on road driving evaluation.[8] We have continued to analyze and study the various effects of the prisms addressing secondary effects that have been ignored or neglected in the past.[8,10] With these analyses we have uncovered many novel considerations that are important for implementing clinical decisions. For example we now understand that people with incomplete hemianopia will not benefit fully from the high power prism fitted in the typical design with the serration pointing away from eye. For these patients fitting with the prism serration towards the eye may be more beneficial, although the effective prism power and thus the magnitude of the expansion are smaller. We also realized that under specific luminance conditions such as with bright patches of sun light and in nights with car headlights or other bright sources of lights the patient may be impacted by spurious reflection seen in the prisms coming from unintended directions that may create false alarms for the patients (Fig. 6 see page 461).

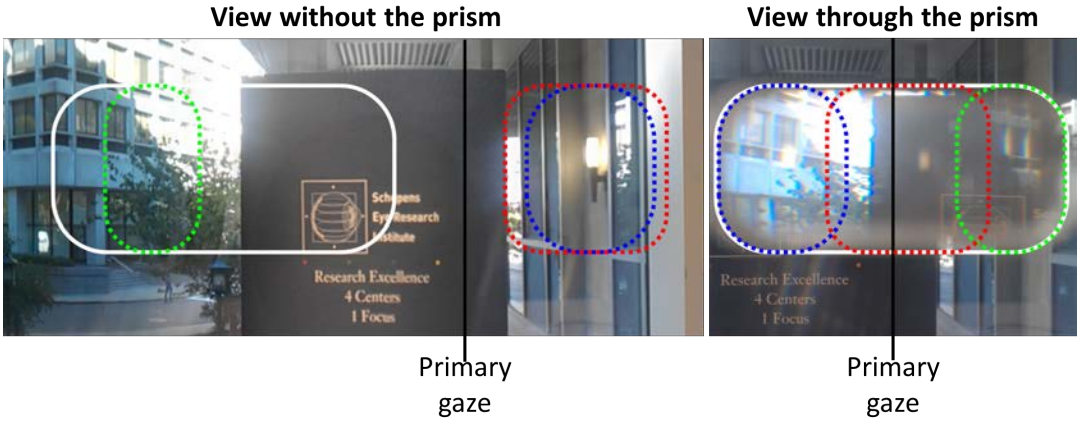
The difference in prism distortion level between the two fitting configurations is also very large with extremely high power prisms. The OPS design results in wider field expansion but much of it is due to the minification (distortion effects). With this configuration the effect of prismatic total internal reflection starts playing a meaningful role with increased scanning into the hemiblind side Fig. 7 top). This limits the field expansion for patients who do scan into the blind side. On the other hand with EPS configuration the field continues to expand with scanning and there is slight magnification rather than minification (Fig. 7 see page 461). However, the overall field expansion is not substantially different, and as mentioned above the spurious reflections problem is heighten with the EPS design. Thus choosing between the two designs requires careful analysis of the patient characteristics, needs and environments, and should be considered only when substantial experience has been gained. We have not yet gained this understanding. Instead of studying these effects we are trying to develop new devices that will overcome these limitations.

As can be seen from the list of references we continue to explore both basic science[11] and applied[12-14] aspect of these treatments in continuous effort to increase our understanding and provide better designs, fitting and instructions. Stay tune.

Acknowledgements: Supported in part by NIH grants R24EY12890, R01EY12890, and R01 EY023385 and DoD grant DM090420. JaeHun Jung created many of the images.

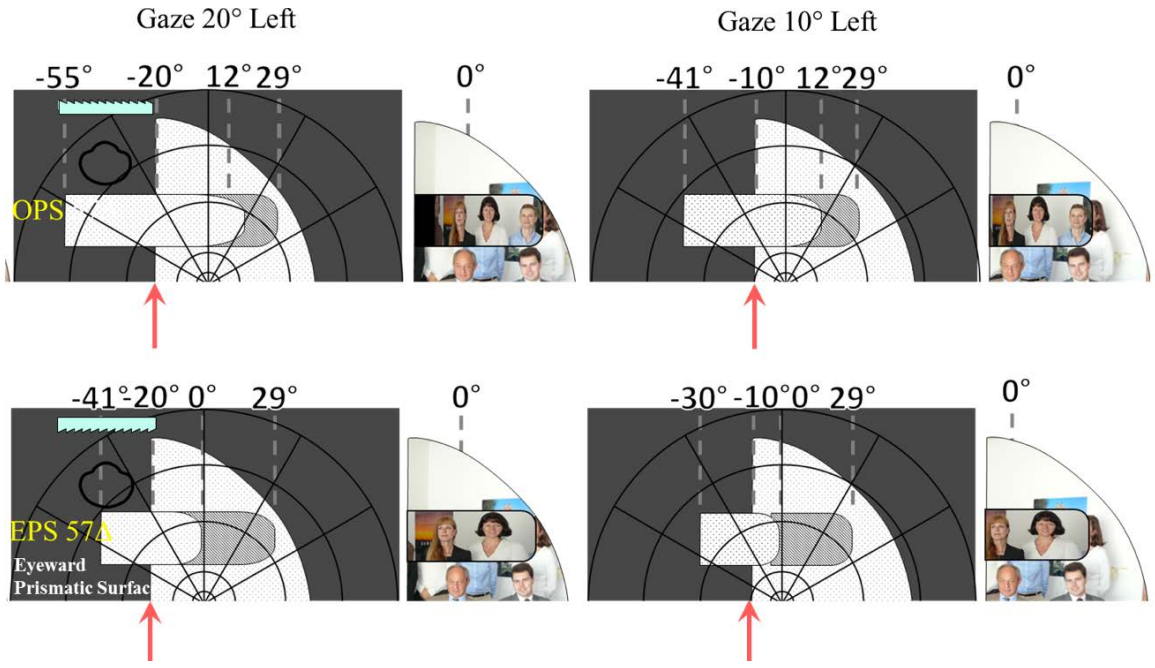
Dr. Peli has a patent assigned to MEEI licensed to Chadwick optical related to the peripheral prisms. He has received modest unrestricted research support from Chadwick Optical & MultiOptical.

Figure 6.



Spurious reflections with 57Δ prism using eyeward prism serration (EPS) fitting. On the left a natural scene with bright light sources locally. On the right the view of that scene photographed through the prism. Note the coding of the same areas highlighted on both sides with the same color framing. With the outward prism serration (OPS) the level of spurious reflection is reduced but distortions are increased.[10]

Figure 7.



Variation with field expansion, distortion and lack of transmission due to total internal reflection as a function of angle of scanning to the blind side (left) with the OPS (top) and EPS (bottom) configurations, respectively.

CME ANSWERS

1. c
2. a
3. a

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DRIVING CONSIDERATIONS IN TEENS WITH OPTIC NEUROPATHIES

Judith E. Goldstein, OD

John Hopkins School of Medicine
Baltimore, MD

LEARNING OBJECTIVES

1. Discuss and review 2 cases of teen drivers with optic nerve dysfunction
2. Review the visual and comorbid considerations when evaluating potential teen drivers
3. Describe the role of vision impairment measures and their impact on driving ability
4. Describe processes, criteria, and the variability in the requirements for teen driving licensure

CME QUESTIONS

1. Visual acuity should be the predominant factor in judging whether teens should be driving
   a. True
   b. False
2. Being monocular precludes a teen from achieving licensure in most states
   a. True
   b. False
3. There is significant variability in vision requirements for driving licensure between states
   a. True
   b. False
4. New driver readiness, effectiveness and licensure is most likely predicted by:
   a. VA and VF findings meeting state criteria or specialized program
   b. Insight into the responsibility of driving
   c. Supportive home environment
   d. All of the above
5. Studies comparing different states show that the most effective legislation in reducing crash rate involves the following except:
   a. a mandatory waiting period of at least six months before a driver with a learner's permit can apply for a provisional license
   b. a requirement of at least 50 hours of supervised driving
   c. a minimum age of 18 for a full license
   d. driving weekdays only

KEYWORDS

1. Visual ability
2. Contrast sensitivity
3. Graduated drivers licensing
4. Functional domains

INTRODUCTION

Driving is often the primary presenting concern in high school age students presenting for low vision rehabilitation services. The issues of social equality and independence are paramount for the teen, as are the typical parental concerns surrounding issues of safety, and the impact on future vocation and career options. Given that effective driving requires attributes other than adequate visual reserve, a careful assessment of visual ability and surrounding comorbidities, maturity, and judgment must be performed.

CASE INTRODUCTION #1

A 16 yo man with a history of familial Dominant Optic Atrophy (DOA) presented to the Vision Rehabilitation Service for an initial evaluation with his mother and father. He was interested in determining whether he could qualify for driving licensure. He lives in rural Maryland and feels he is capable of driving as he has driven his friend's car a few times. He is a junior in high school and is a "C" student. He readily admits he doesn't like academics and prefers to work with his hands. Additionally, he carries a diagnosis of Attention Deficit Hyperactivity Disorder. His father is a longstanding patient of the Low Vision Service and shares the diagnosis of DOA. His father was able to obtain licensure several years ago through a special program in

Maryland that allows training and assessment of patients who don't meet standard state licensure criteria. Clinical findings of the teen include best-corrected visual acuity of OD 20/100+ and OS 20/100-. Contrast sensitivity measured 1.25 log units (mild to moderate reduction), and visual fields as measured by Goldman were peripherally intact (Figure 1 and 2) with evidence of a centro-caecal scotoma OS. Although a central scotoma could not be detected by Goldman visual field testing in the right eye, microperimetry by MP1 testing confirmed centro-cecal scotoma OD (Figure 3)

Figure 1

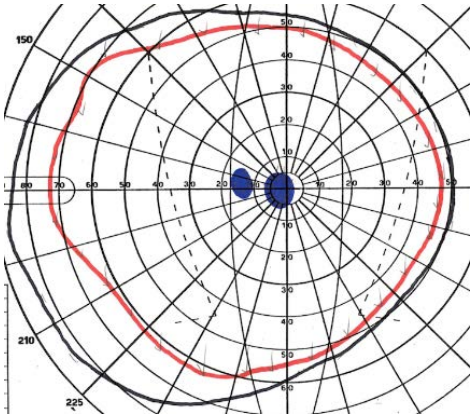


Figure 2

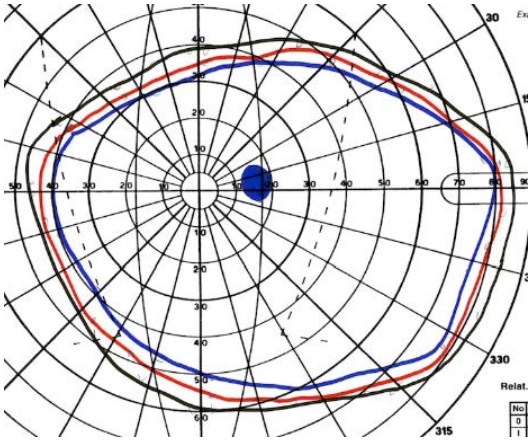
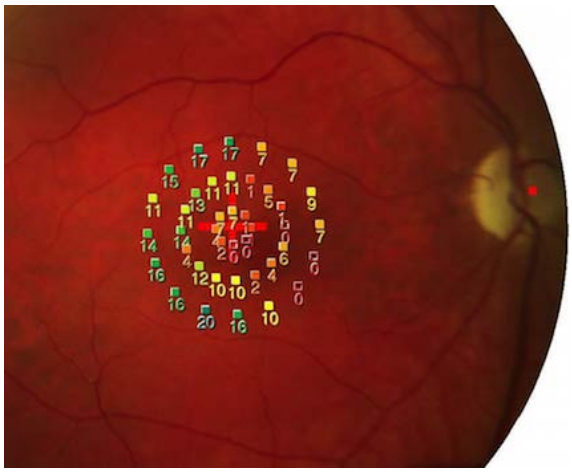


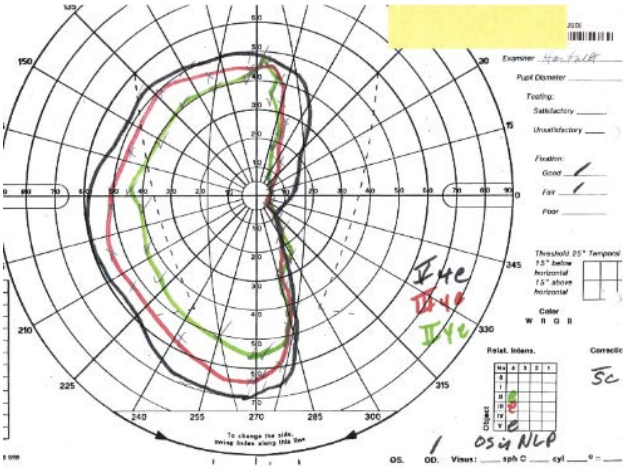
Figure 3



CASE INTRODUCTION #2

A 20 yo man with a history of resection of cystic astrocytoma 2004 which compressed the left optic nerve presented to the LVR clinic wanting to be approved for his driving license. He presents with his father for the appointment and reports that "my dad thinks I shouldn't drive"; "I feel I can drive". In addition to his visual loss, he carries a diagnosis of Asperger's disorder. Clinical findings include best-corrected visual acuity OD 20/40 and OS NLP. Visual field OD showed nearly complete right-sided loss (Figure 4).

Figure 4



BACKGROUND ON DRIVING RESEARCH IN TEENS

There is little research to date on teens with visual impairment and the ability to drive. Most all research has been qualitative.[1] Additionally, most of the research on driving effectivity and safety surrounds the older driver, the younger healthy driver and risky behavior, and crash risk in teens. Motor vehicle crashes are the greatest single public health threat to teens in the US and teen drivers have the highest crash rate per mile of any age group.[2-3] Male teens have an especially high rate of fatal crashes and an even higher rate of non-fatal injury crashes. Although crash rates are highest among the youngest drivers, they generally decline with each year of increasing age, but not reaching the lowest levels until after age 30.

Factors that increase teen crash risk include driving with passengers, driving on weekends, drinking and driving, and non-use of seat belts. Teens who have access to and use tobacco, ETOH, and marijuana, tend to show riskier driving behavior and are more likely to experience crashes, as do teens with hostile or aggressive behavior tendencies. To achieve effective driving requires skill development with vehicle control, visual scanning, practice, and observation over an extended period of time. Less risky driving behavior is seen in teens living with both parents, and teens with better grades in school. With experience behind the wheel, visual scanning behavior is believed to become more developed which is an essential part of being an

effective driver. Environmental factors including how the parent(s) drive, parental oversight, the use of graduated license programs (GDL) and peer impact are all thought to contribute to shaping teen driving practices.

GRADUATED DRIVERS LICENSING (GDL)

GDL programs dramatically reduce the rate of teen driver fatal crashes among 16 to 17 year-olds and some form of a GDL program has been adopted by most all states.[4] GDL programs compose a three-stage approach to granting young drivers full license privileges. The stages are (1) *supervised learning period* which requires the new driver to drive only with a supervising adult in the car for a minimum time or number of hours before earning an intermediate license; (2) *intermediate license* which allows the teen to drive without supervision, however, other restrictions such as a curfew, the number of passengers allowed in the car and cell phone use may be limited; (3) *full-privilege license*. Studies comparing different states show that the most effective legislation in reducing crash rate has a least 5 of seven key elements: (1) a minimum age of 16 for learner's permit; (2) a mandatory waiting period of at least six months before a driver with a learner's permit can apply for a provisional license; (3) a requirement of 50 to 100 hours of supervised driving; (4) a minimum age of 17 for a provisional license; (5) restrictions on driving at night; (6) a limit on the number of teenage passengers allowed in the care; (7) a minimum age of 18 for a full license.

ADHD AND DRIVING CONSIDERATIONS

There have been several published reports on the increased risk of driving injury and crash in ADHD drivers as well as varying observations and recommendations on use of stimulants while driving.[5-6] A meta-analysis in 2006 pointed to an increased risk in driving incident of individuals with ADHD.[7] However, in 2013, another review pointed to limited rigor in evidence quality to support such a predictive associations.[8] The possibility exists that symptoms associated with ADHD, such as hyperactivity and impulsivity may lead to riskier driving behaviours' and increased incident, however, like many of the other variables reviewed, ADHD in isolation alone should not rule out the possibility of licensure.

VISUAL EXAMINATION AND CONSIDERATIONS

HISTORY, OCULAR EXAMINATION

Patient history is key to evaluating insight, motivation and expectations of the teen and parent(s). In addition to understanding the ocular disorder, medical and developmental history, it is useful to obtain functional, family, social, academic, and driving history.

FUNCTIONAL DOMAINS

Functional history should explore the 4 functional domains. This includes (1) reading, (2) visual information or "seeing", (3) visual motor, and (4) mobility function. Reading ability and appropriate adaptations can be relevant when students take the written component of the permit and driving test. Depending on the test administration, accommodations may need to be provided (e.g., large print or computer administration). The teens understanding of their visual information or "seeing" ability can be explored by questioning their ability to see the smart board in school (with consideration to their classroom seating position). This provides insight into their ability to read street signs, view road work in the distance, and resolve traffic light detail. This will likely impact the decision to drive only in familiar areas or routes. Although commonly used global positioning system (GPS) can provide tremendous benefit when navigating unfamiliar areas, it requires adequate divided attention and may create anxiety when the information is inaccurate. Visual motor function (e.g., hand-eye coordination), although typically intact in everyday activities when the deficit is congenital, may be impaired in patients with acquired conditions (e.g., compressive and ischemic). Mobility function history should include a discussion regarding the teen's ability to walk and navigate in lighted, dim and dark environments. Performance under different luminance conditions provides the clinician insight not only into the teen's ability to manage day versus night driving, but also potentially in managing different weather conditions (e.g. bright sun vs shady or overcast days). The teen's ability to navigate steps, stairs, curbs and uneven pavement in familiar and unfamiliar environments should also be explored, as this can provide information on scanning ability and judging depth when behind the wheel.

ACADEMIC

Academic history should include school performance (e.g., types of classes, grades) and whether a specialized education plan is in place (e.g., Individualized education plan or 504 plan). If a plan is in place, an understanding as to intent of service provision should be clarified (e.g., vision problems, behavior concerns or both). If applicable, the types of accommodations in the plan should be reviewed (e.g., frequency of interaction with vision teacher, orientation and mobility services, modified physical education, etc.), and whether the services are in fact accessed. This information provides the clinician with an overall picture of how the teen manages the demands and responsibilities of high school, considering the seriousness of taking on the responsibility of driving. Additionally, it may provide helpful insight into the student's adaptation to their vision loss. For example, orientation and mobility training may have been discontinued despite visual field loss as the student may scan their environment very effectively and have no further need for training.

INSIGHT

It is useful to ask unlicensed teens if they have driven already. It is not uncommon for teens with vision impairment to satisfy their curiosity about their ability to drive, and when asked, will share that they have driven a friend's car, or taken their parents car out. This provides the opportunity to ask the teen about their perceived driving ability, specifically their comfort and confidence behind the wheel. For a teen with good insight, this information coupled with all of the findings can be invaluable in understanding "readiness for driving" and help the clinician make a determination. Additionally, gaining an insight into the teen's plans after completing high school (e.g., continued education, job placement, vocational training, etc.), informs the clinician regarding the necessity of the teens transportation demands in the near future.

VISUAL ACUITY

Relevant visual impairment findings primarily include visual acuity and visual field. Visual resolution is primarily predictive of reading road signs and interpreting upcoming changes and obstacles in the distance (e.g. construction ahead, cones, etc.). As the level of resolution required to adequately judge a given situation varies, it is not surprising that there is significant variability in visual acuity criteria for licensure between states. There are no federal standards for unrestricted noncommercial passenger vehicle drivers' licenses in the United States. Individual states have their own vision requirements for initial and renewal licensing.[9] In several states there are visual acuity "cut-offs" for unrestricted and restricted licensure. Additionally, there are states which provide special licensure or programs to individuals who do not meet the required VA criteria, that can result in a restricted or modified license once patients are tested behind the wheel and demonstrate "fitness to drive". This may or may not involve the use of bioptic telescopes while driving, of which approximately 40 states allow.[10]

VISUAL FIELD

Visual field considerations are further subdivided into central and peripheral loss. Discreet central VF loss (including central and/or paracentral scotomas), is not a standard part of state driving licensure criteria and the impact of central VF loss on driving performance remains unclear. Understandably, central VF is most likely to impact performance when the losses are larger and absolute, thus also likely translating to an increase in loss of VA. As scotomas and VF loss can affect making efficient scanpaths, compensation and good scanning ability is key to good driving ability. As is typical for any impairment, the earlier the onset, the more likely effective adaptation will occur. Most teens with optic neuropathy interested in gaining driving ability show central scotomas as opposed to peripheral VF loss. The central loss is commonly due to hereditary etiologies including Leber's hereditary mitochondrial optic neuropathy and Kjers (or Dominant) optic neuropathy.[11]

Peripheral VF loss in teens can be due to traumatic, ischemic and compressive causes. Quadrantanopsia and hemianopsia present different challenges in observing and testing patients. Key considerations must include stability of the deficit and associated comorbidities. Goldman VF testing can provide useful data on the far periphery, and if not, careful confrontation VF's are invaluable. As part of assessing patients, the response time to stimulus and awareness are both important variables in visual attention. The Useful Field of View Test (UFOV), a computer-based program can be very helpful in measuring responsiveness to peripheral stimuli and divided attention ability.[12]

Most, if not all states permit individuals with one eye to obtain driving licensure. As the VF's of both eyes show significant overlap, a loss of one eye has minimal impact on the binocular VF. Nearly one-third of states however have no requirements for VF for non-commercial drivers. What remains unclear is how much VF, which portions of the VF, and the level of sensitivity required to be an effective driver. Several studies have not found a correlation between crash rate and VF deficits, but deficits do remain difficult to quantify.[13] In a small sample of drivers ages 53 to 81, increased horizontal and vertical constriction (as measured by Goldman perimetry) was associated with poorer skills in driving manoeuvres (e.g., changing lanes) that likely require a larger field of view.[14] Like VA measures, the VF requirements for unrestricted driving varies from state to state ranging from 30-140 degrees and there is no treatment corollary to the bioptic (e.g., field minifying or reverse TS to address loss in VF). In most cases the VF requirements is defined in terms of the extent of the binocular field along the horizontal meridian, however the method of VF measurement (e.g., confrontations, automated, Goldman) in order to meet criteria also varies from state to state and internationally.

CONTRAST SENSITIVITY/LIGHT SENSITIVITY/ COLOR VISION

A significant portion of driving research has focused on contrast sensitivity and its importance in predicting an effective driver. Despite that, contrast sensitivity is rarely, if ever, used as a criterium for driving licensure in the U.S.; the prevailing view is that contrast sensitivity plays a predictive role in driving ability. Although moderate correlation (r = -0.52) exists between log CS and log MAR acuity in the low vision clinic population (median age 77 years), anecdotally, we find that in younger individuals with congenital or early onset acquired VA and/or VF loss, contrast sensitivity remains normal to near normal in most.[15]

Light sensitivity or glare can be ambiguous and difficult to measure. It can be observed during examination of pupillary testing or biomicroscopy. Understanding the patient's ability to visually cope with bright sun and recover when transitioning from a bright to dim environment (e.g., travelling into tunnel) helps guide determination as well as considering different glare control options (e.g., tinted

window, sunglasses). There are no specific metrics in testing (e.g., photostress test) that are used to be predictive and in practice, these symptoms vary by patient. Among teens with optic neuropathy, it is common for there to be heightened sensitivity to bright conditions and this is typically managed with tinted lenses. On occasion, tinted windshields are requested, and regulations surrounding use vary by state.

Color vision is not widely thought to increase crash-risk involvement but is commonly tested or requested in many states. Some research points to a longer reaction time to traffic control devices (e.g., traffic lights), but other cues such as luminance, position and pattern provide adequate information to interpret directional signal. Color vision loss alone should not be a deterrent for considering capacity to be an effective driver.[16]

EDUCATION AND COUNSELING

For many teens, gaining driving privileges is a "rite of passage", rather than a privilege, and the decision as to whether they gain privileges has significant consequences on their future, including vocational choices, type and location of residency and independence. As such, any discussion with the teen should consider the emotional impact of the conversation and determination. If a teen appears to have the visual reserve but the current vision criteria of the state of residence doesn't support the opportunity, a focus on the big picture is helpful, explaining variability in state vision requirements, as teens may move to a different state for higher education, employment, etc. Additionally, the discussion should involve alternative transportation options available including public transportation, state/county mobility services, reduced fare taxi programs, Uber, Lyft, etc. When the examination findings show concerns beyond vision alone, e.g., impulsivity, risky behavior, poor insight, etc., it can be helpful to defer consideration for a few years to monitor and evaluate changes in maturity and need for driving. If it is clear that the visual, physical or cognitive reserve precludes driving currently, it is critical to be forthright with the teen and parent(s), that independent driving is not possible and other forms of transportation and ultimate living and work situations will need to accommodate this lifestyle.

SUMMARY

Driving is a complex skill that requires adequate visual ability, executive function and physical ability. Individuals with optic neuropathy considering driving are typically faced with issues of loss in VA, VF and CS which first must be evaluated in the context of visual ability; essentially how effective the individual is in using their visual reserve based on their individual adaptations. In teens, particular attention should be placed on issues related to new drivers, specifically the lack of experience and insight into taking on the practice of driving responsibly. As states have variability in their driver's licensure requirements, teens interested in gaining driving privileges should be counselled on their individual state laws and the existence of variability in laws. Counselling and education on alternative transportation options should always also be part of treatment.

CME ANSWERS

1. False
2. False
3. True
4. d
5. d

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THE ROLES AND EFFECTS OF DIPLOPIA AND VISUAL CONFUSION IN THE TREATMENT OF VISUAL FIELD LOSS

Eli Peli, MSc, OD

Schepens, Mass Eye & Ear, Harvard Medical School
Boston, MA

LEARNING OBJECTIVES:

1. Describe the phenomenology of double vision
2. Describe the interaction of field loss with double vision
3. Explain prism apex scotoma
4. Describe prismatic field expansion as a binocular phenomenon

CME QUESTIONS:

1. Besides confusion what other mechanism can expand the visual field?
2. Exophoria in bitemporal hemianopia results in horizontal diplopia. Hyperphoria results in vertical diplopia true or false?
3. When diplopia exists-every object of fixation is doubled. When confusion exists-every object of fixation is confused with another object. True or false?
4. Converting ipsilateral exotropic HH patient to ipsilateral esotropic eliminates central diplopia yet; it does not relieve the symptoms of double vision. Why?

KEYWORDS

1. Field expansion
2. Diplopia
3. Visual confusion
4. Hemianopia
5. Tunnel vision

INTRODUCTION

Misalignment of the eyes results in double vision. It is important to recognize the two coexisting components of double vision: diplopia (seeing the same object in two different directions) and binocular confusion (seeing two different objects in the same direction). Patients primarily report the diplopia rather than the binocular confusion; this may be a result of the statistics of natural images. One reason clinicians should be aware of binocular confusion is that it is the main tool used for prismatic expansion of visual fields in cases of field loss. With visual field loss alone, and with use of partial prism segments for field expansion, the two phenomena may be separable: diplopia without confusion, and confusion without diplopia. The roles both play in vision rehabilitation will be explained for common and rare conditions. Understanding this separability offers new insights into binocular function that should lead to better rehabilitation techniques and individual patient care.

Double vision occurs when eyes are not aligned. The eyes are not aligned in strabismus, or if a prism is placed in front of one eye (horizontally or vertically). Double vision occurs because images of objects fall on different, non-corresponding, retinal loci in both eyes. Non-corresponding retinal loci are associated with different perceived directions. Double vision is composed of two phenomena – Binocular Diplopia and Binocular Visual Confusion. Diplopia refers to seeing/perceiving the same object in two different directions. Obviously, this means seeing two copies of the object, hence the name diplopia. Binocular visual confusion is an equally important result of ocular misalignment, referring to seeing/perceiving two different objects in the same direction (superimposed on each other). As the two eyes' views are shifted relative to each other, the double vision affects every point in the image equally. As it may appear in Figs 1 & 2, see page 470, diplopia affects each and every object within the field of view, though it may be less apparent that confusion similarly affects each and every object and point in view. These figures also show how, generally, diplopia and confusion always coexist and each view of a diplopic object is also being confused with other objects. While most objects appear to be diplopic, one or even both copies do not always appear to explicitly be confused with another object. This, however, is merely a result of the statistics of the image where the object may be perceived in the same direction as part of the image which, in the cartoon presentation, is blank. This may happen in

a natural (non-cartoon) image as well, if the object is being confused with a blank wall or other low contrast surface. The difference in prevalence of diplopia and confusion across natural scenes may account for the fact that diplopia rather than confusion is frequently reported spontaneously.

It is also likely that the difference in spontaneous reporting is a result of the fact that every attended (fixated) object is always diplopic when the eyes are misaligned, however, the attended object may frequently not be confused.

Fig. 1. Typical "simulation" of double vision using transparency functions in imaging applications. The low contrast appearance of both images is not representative of the patient's view, in which both images are perceived in full contrast. This can be appreciated easily by holding a prism in front of one eye. In such pictorial simulation the magnitude of the diplopia is equal everywhere.

Fig. 2. Illustration of double vision using cartoons. The cartoons maintain the full contrast of both images, as perceived in real double vision. The cartoons format also supports better illustration of visual fields loss. The two colors are not representative of the real views; the blue lines are used here and below to help mark the left eye's view.

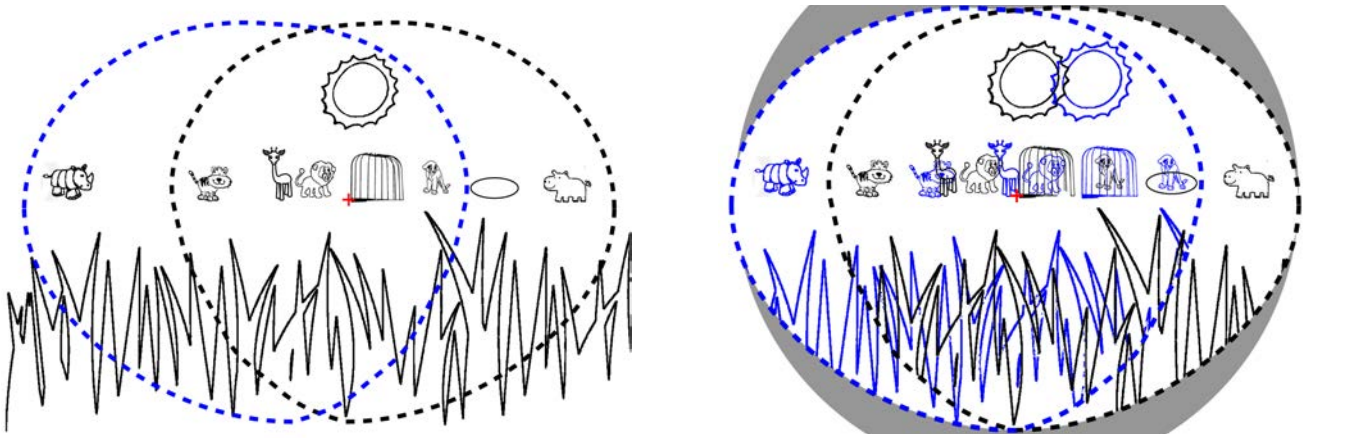


Figure 3. A cartoon of a savannah scene. A) Marking the visual fields of a patient with 20° (40Δ) left exotropia and full visual fields. The fixation point of the right eye is marked with a **+** symbol. The field of the deviating left eye is marked with blue. B) A perception diagram[1] of the savannah as seen by that patient with double vision. Objects seen by the left eye are marked with blue. Many animals are seen twice (diplopic) and many of them appear superimposed on others (confusion). The rhinoceros on the left and the hippopotamus on the right are not diplopic or being confused as they fall in the monocular non-overlapping temporal crescents. The elliptical pond seen by right eye is confused (superimposed on) the (blue) cub seen by the left eye, but while the cub is also diplopic the pond is seen only once. The tiger seen by the right eye is also seen by the left eye (diplopic) but the right eye copy appears to not be confused. This is not the case, it is confused with an area of the background seen by the left eye but that confusion is not apparent in the cartoon illustration.

It is generally true that diplopia and confusion coexist and are not separable everywhere. Though, as illustrated in Fig. 3, even with normal fields both eyes fields do not fully overlap and the binocular overlap area may shrink when the eyes are not aligned. This creates situations where even with full visual fields some objects (that fall into the non-binocularly overlapping parts of the field) are not diplopic or confused. It is also possible to have objects (which fall near the edge of the field) that are confused but not diplopic. In this case of a full/normal field, however, we do not find diplopia without confusion. The separation of diplopia from confusion can occur to a larger extent with visual field loss and with the use of partial prism. Partial prism segments are frequently used as field expansion treatments in cases of field loss. As will be seen below, with field loss or partial prisms some sections of the field may include diplopia and confusion while others may include only one of the two (i.e., confusion without diplopia or diplopia without confusion).

The illustrations in Figs 1 through 3, see page 470, deal with two-dimensional views only. In this simpler case the disparity between both eyes images is only a function of the misalignment of the eyes and it is uniform across the image. The diplopia is the perception that occurs if the disparity is large enough to exceed Panum's fusional area.[2] Thus diplopia may be thought of as the manifest/apparent disparity. In the three-dimensional (3D) world the situation is more complex. In this case the binocular disparities of different objects' images vary with objects distance from the object of fixation. Those disparities exist even without misalignment of the eyes. When a person fixates an object in 3D space that object and other objects that fall within the (horizontal and vertical) horopter[3, 4] are seen singly. Objects outside of the horopter are seen in double vision. This so-called 'physiological diplopia'[5] affects the perception of peripheral objects that happen to be at a sufficiently different distance than the fixated object, exceeding the limits of the horopter. Most of these objects are also being confused with other objects (creating peripheral confusion). Peripheral physiological diplopia is rarely reported spontaneously by people, though it is very easily demonstrated for every person with a patent binocular system. Occasionally a patient may notice the diplopia spontaneously and seeks care for the double vision. The spontaneous observation of peripheral confusion is extremely rare. The low awareness of peripheral double vision indicates that the annoyance and disturbance of diplopia and confusion is much more impactful when applied to attended/central/fixated objects.

Maintaining single binocular vision is one of the most difficult tasks of the visual system. As stated above it is only possible within a very small fraction of the visual world volume. Single vision is necessary because double vision is annoying and can be confusing (in the literal sense of the word) and thus affect performance. The two components of double vision (diplopia and binocular visual confusion) have different roles in achieving single binocular vision. Confusion has no role in driving convergence, as it provides no information regarding the direction or magnitude of the eye misalignment. Confusion, however, when it is noticeable, may be even more disturbing and unnatural than diplopia. There is nothing inherently unnatural about seeing two trees, two tigers in the savannah, or two identical children. However, seeing two animals in the same direction/position is indeed unnatural and physically improbable.

In normal vision, confusion results in binocular rivalry where one of the two images predominates at a time. This can be global, where the image of one eye predominates over the whole field-of-view or it can be local where one eye's image predominates at one place and the image of the other eye predominates at other places in the field at any instant. Thus rivalry eliminates the confusion aspect of double vision at every instant and every location even when the disparities exceed the fusional range. However, rivalry does not affect diplopia in fact it may be enhancing its perception. Suppression of confused images from one eye may be thought of as an extreme case of rivalry where one image/eye predominates almost all the time. This may be the stimulus for the suppression seen in constant tropia in young children.

Diplopia is the signal that potentially can drive convergence to reestablish fusion. Convergence (or divergence) reduces the magnitude of diplopia (the separation of all the diplopic images) and the direction is indicated by the diplopia being crossed or uncrossed. By eventually eliminating the diplopia, when the two images are fused, the system achieves single binocular vision. Without diplopia the visual system does not have the control error signal needed to reduce the convergence error. Such a situation may arise with "tunnel vision", a severely reduced peripheral visual field of both eyes, commonly occurring in retinitis pigmentosa and affiliated diseases and in glaucoma. With sufficiently small residual fields, if the two eyes become misaligned for some reason (most likely a decompensated phoria), and the misalignment is large enough so that the two eyes fields are not (or just barely) overlapping (Fig. 4, see page 472), the patient is faced with binocular confusion but no diplopia (Figs. 4 and 5, see page 472-473). The two eyes residual fields are pointing to non-overlapping portions of the visual scene (Fig. 4A, see page 472) so no objects can be seen in both eyes, and thus diplopia (the signal for convergence) is missing. Under this situation the patient would manifest a tropia even if with full visual field the same patient is simply heterophoric.

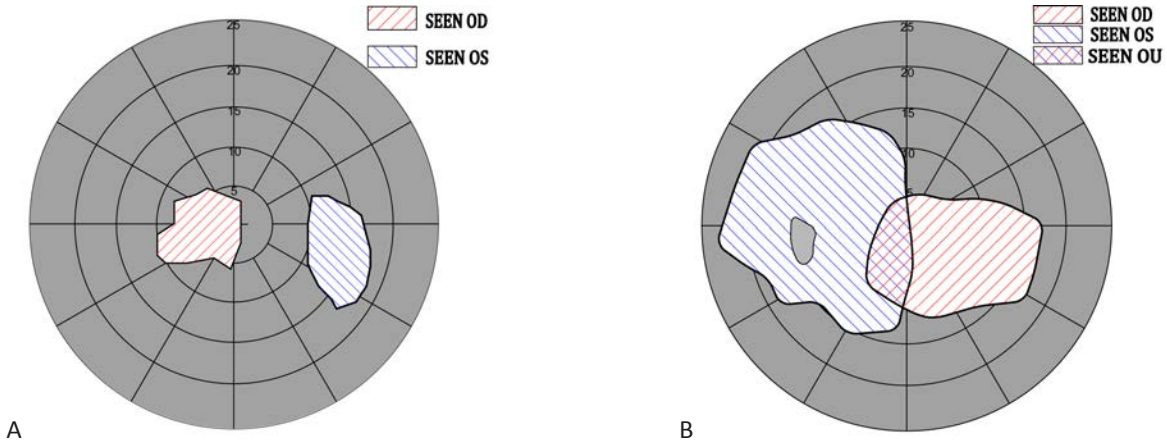


Figure 4. Confusion without diplopia. A) Dichoptic binocular visual field of a patient with RP and left esotropia of about 15° degree obtained with a dichoptic perimeter[6] Since the two eye's residual fields are non-overlapping, the result of the eye deviation is (central) confusion with no diplopia. B) A dichoptic field of a patient with right HH and right exotropia of about 16° (the patient also has significant peripheral field loss in both eyes). Here most of the field is non-overlapping resulting also in confusion without diplopia but the small overlapping areas (cross hatched) will give rise to diplopia of the object fixated by the left eye. Note that the right eye diplopic image of an object fixated by the left eye is perceived at the direction of the left eye blind spot and thus is never confused. This may be the exotropic analog of the esotropic blind spot syndrome.[7]

The patient depicted in Fig. 4A faces binocular confusion without diplopia. The confusion is central and is likely to be noticeable if and when it is manifested, which is when both eyes are aimed at two (different) salient objects. The patient depicted in Fig. 4B has the same confusion peri-centrally, but due to the partial overlapping of the two fields the left eye fixated object is seen in diplopia (and confusion). However, because the second copy of that image is seen by the right eye at about 16° temporarily (the direction of the left eye's physiological scotoma), that second diplopic copy is not being confused. Central to our interest here is that these situations result in expansion of the field of view (e.g., Fig. 5, see page 473). Assuming that the area of the residual central field in both eyes is about equal this strabismus doubles the area of the field-of-view available simultaneously. As the patient may be searching using scanning eye movements with his dominant eye, other objects which may be of interest may fall into the field of the deviating eye and be detected, substantially reducing the search time. As illustrated in Fig. 5, see page 473, this may also help the patients avoid collisions with objects near his walking path.

This situation emphasizes two important principles; 1) that in order to expand the visual field using prism one may need to have (binocular) confusion and 2) that diplopia is of no value for field expansion as the diplopic object is already seen by the fixating eye. Thus effective field expansion prism devices should be designed to induce confusion and avoid diplopia, when possible. We implemented such a prism device for patients with tunnel vision and found it to be beneficial; 25% of the RP patients fitted continued to wear it for extended period.[8] In that design the power of the prism was explicitly designed to assure non-overlapping of the two eyes fields, assuring the lack of diplopia. Yet, even the patients who continue to wear the device commented that the central double vision (central confusion) was disturbing and annoying. Note that the field expansion was effective only when the confusion manifested (when there was an object of interest within the residual field of the deviated eye).

An important clinical consideration in these cases is the great difficulty in measuring the deviation. Most subjective clinical techniques for measuring magnitude of phoria or tropia require diplopia or at least "split diplopia" (explained below). Faced with confusion without diplopia these techniques do not work. To be able to measure the deviation one has to first reduce the deviation using a prism to the point that the field overlap significantly (this requires a good estimation of the deviation first). This reestablishes diplopia within the residual fields and enables refining the measurement with the standard techniques.

The appearance, at two time instances, of the terminal scene to the patient, whose field is depicted in Fig. 4A, are illustrated in Fig. 5B & C, see page 473. At the instance illustrated in Fig. 5A & B, see page 473, the largely blank right wall of the terminal seen by the left eye is confused with the 3 people seen by the right eye but the impact of that confusion is minimal. As the patient gets closer to the people ahead, a few seconds later, the "magnified" scene brings the woman on the right into the left eye's residual field making it possible for the patient to detect her presence and avoid colliding with her. This illustrates the utility of the field expansion nature of this situation. The percept diagram in Fig. 5C, see page 473, illustrates that at this later time instance the central confusion is indeed highly noticeable and may be disturbing even though it may be helpful.

Figure 5. The field expansion effect of confusion in the case of tunnel vision with esotropia. A) The terminal scene with the outlines of the residual central fields of both eyes of the patient depicted in Fig. 4A, see page 472, superimposed. At that instance in time the patient is fixating the group of 3 passengers ahead with his dominant right eye and may not be aware of either the man or the woman on the left and right between him and the 3 passengers. B) The perception diagram (patient's view) at that instance. While the 3 passengers seen with the right eye (black edges) are superimposed (confused) over the terminal right wall and columns (blue edges) seen by the left eye, the lack of details there makes this confusion inconsequential. C) If the patient is walking forward faster than the other people in the terminal a few seconds later the patient will be closer to the people and the "magnified" scene will move the woman into the left eye residual field demonstrating the field expansion effect. This will also result in a much more noticeable/disturbing central confusion.

DIPLOPIA WITHOUT CONFUSION IN PATIENTS WITH BITEMPORAL HEMIANOPIA (BTH)

Diplopia without confusion may and does occur in cases of complete bitemporal hemianopia[9]. Patients with a preexisting exophoria who suffer from bitemporal hemianopia will manifest exotropia, as shown in Fig. 6A. Because there are no corresponding points in the two eye's retinas, there is no way for any convergence movements to null the diplopia through fusion. This misalignment of the eyes results in true diplopia, as illustrated in Fig. 6B. The diplopia in this case is limited to a relatively narrow vertical stripe of the visual fields. The width of the diplopic section is equal to the angular magnitude of the phoria/tropia (highlighted in Fig. 6B), which is also the angular separation between every pair of diplopic objects. It is important to note that unlike the diplopia experienced with normal visual fields, where most if not all of the diplopic pairs of images end up in one cortical hemisphere or the other, here the two diplopic images are always represented in separate hemispheres.

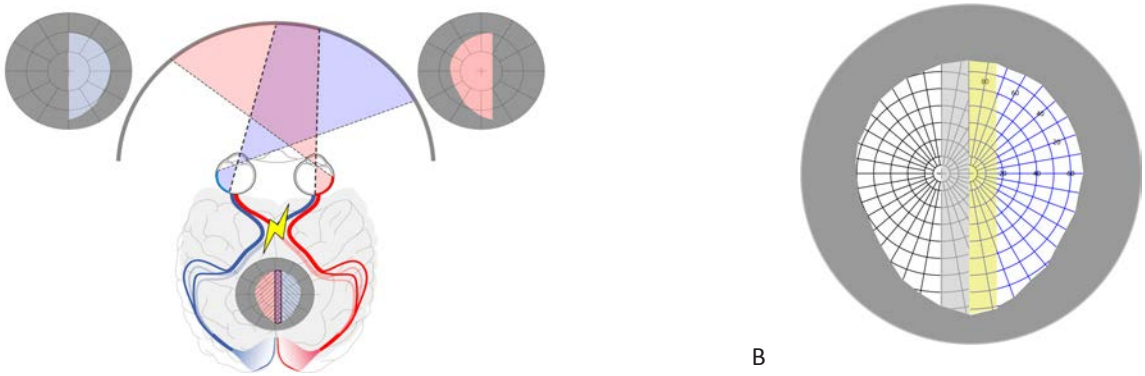


Figure 6. Diplopia without confusion in bitemporal hemianopia with exophoria. A) An illustration of optical neural pathway with the chiasm severed, resulting in both eyes losing the temporal fields. If the patient had exophoria prior to the damage to the chiasm it is manifested as (right) exotropia. Vertical stripes areas of the visual fields of both retinas (as wide as the angular magnitude of the phoria/tropia) are overlapping and thus pointing to the same objects that are perceived in diplopia. B) The percept diagram illustrating the view seen by the patient in (A) who is fixating with his left eye at the center of a perimeter graph paper. The right eye nasal view (in black) is shifted to the right and duplicates a section (highlighted in grey) of the same view seen by the nasal field of the left eye (blue, highlighted in yellow). Every object within the highlighted sections is seen in diplopia, but there is no confusion anywhere in the field-of-view of the patient.

The impact of this horizontal hemi-retinal slip results in frank diplopia where the same object is perceived (twice) in two different directions. That diplopia is limited to a small section of the field (Fig. 6B and Fig. 7, see page 473) and there is no confusion anywhere in the field. In addition to this relatively common condition of horizontal diplopia without confusion, vertical frank diplopia (without confusion) is possible in very rare cases of anti-symmetric altitudinal hemianopia[10] if it is combined with preexisting vertical heterophoria.

If bitemporal hemianopia is combined with a preexisting vertical heterophoria the effect is different. Here too the lack of corresponding points makes it impossible to overcome the phoria and a vertical tropia is manifested. However the perceptual effect of the vertical hemislide is different. The lack of corresponding points between the two eye result in complete lack of confusion despite the misalignment of the eyes. However there is also no frank diplopia present, as no object is seen by both eyes and no object is perceived twice in two different directions. Instead the views of both eyes are displaced vertically from each other (Fig. 8). With this displacement different parts of the same objects are seen at different directions. In general two halves of the same object are seen at two different directions which is conceptually a very close percept to diplopia. I call this percept "Split Diplopia". The split diplopia illustrated in Fig. 8 is corrected[9] from the original illustration in Shainberg, et al.[11], where the frame of the face was not split but the internal portions of the face were. In both types of hemi field-loss (bitemporal or anti-symmetric altitudinal hemianopia), if the preexisting heterophoria has both horizontal and vertical components a frank diagonal diplopia will result over a limited portion of the field, yet no confusion will be present anywhere.

Note, however, that the diplopia that drives convergence has to be within one hemisphere to enable fusion. If the diplopic images are falling each on a different hemisphere, as in the case of bitemporal hemianopia, the diplopia may not drive convergence, or if it does, the convergence may be able to eliminate the diplopia but not achieved single fused vision. The single fused vision provides the signal of zero error in convergence and without it the system apparently is not able to sustain the required convergence angle. This may be because the convergence error signal is unipolar only indicating cross disparity due to exotropia. Once convergence exceeds the value needed to null that error, uncrossed disparity is not possible; instead, a central field loss stretching the full height of the field occurs[9], leaving the binocular system with no error signal at all. Further discussion of this issue is beyond the scope of this paper, it does, however, point to the potential value of such natural experiments to the understanding of binocular vision in general.


The New York Times

CITY

Unknown's Painting Hangs Out at Modern for a Weekend

By JAMES BARRON

Paul Rebhan with one of his paintings. He hung another of his works on a wall at the Museum of Modern Art last Friday.

Figure 7. Diplopia without confusion in bitemporal hemianopia. The image shows the view of newspaper page seen by a patient with bitemporal hemianopia and exotropia. The area highlighted in yellow in the view of the left eye (nasal field) is also seen by the right eye (highlighted in grey). While this part of the field-of-view is diplopic there is no confusion anywhere in the field. This is an example of frank diplopia within part of the field with no confusion anywhere.

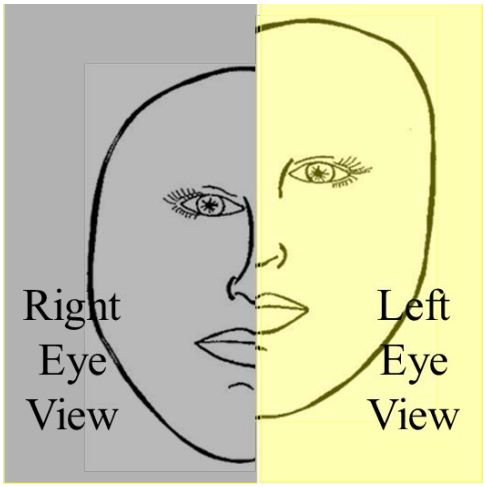


Figure 8. Vertical hemi-retinal slide resulting in this type of view when bitemporal hemianopia is combined with vertical heterophoria (in this case left hypophoria). No object is actually seen twice, but different parts of the same objects (i.e., nose or mouth) are seen at different direction creating an impression of vertical diplopia over the whole field. This is not frank diplopia and I call it "split diplopia".

FIELD EXPANSION IN HOMONYMOUS HEMIANOPIA (HH) VIA IPSILATERAL EXOTROPIA (OR CONTRALATERAL ESOTROPIA)

Natural expansion of the field-of-view occurs when HH is combined with ipsilatral exotropia (i.e., right exotropia with right HH, see Fig. 9A, see page 476).[12, 13] The magnitude of the field expansion is equal to the angle of deviation. The peri-central field expansion also occurs with contralateral esotropia (not shown), though in that case the same magnitude of field-of-view is being lost in the contralateral far peripheral field.[1] In both cases the non-expanded field-of-view includes both confusion and diplopia everywhere and of all objects, except for the temporal crescent conditions excluded in Fig. 3A, see page 470. In both cases the field expansion is achieved via intermittent occasional confusion and it is accompanied by central and peri-central constant diplopia that provides no beneficial aspect as illustrated in Fig. 9A, see page 476. The constant central and peri-central diplopia is very annoying and adult patients who develop this syndrome rarely feel that the field expansion is of sufficient benefit to compensate for the annoyance of the double. They seek some way of eliminating the diplopia and confusion; via surgery, prism correction, or in many cases by occluding the deviating eye. While diplopia is what is mentioned by these patients it is not clear that the central diplopia is more bothersome than the central confusion in these cases. The diplopia, however, is constant and therefore more noticeable. If the adult patient had the strabismus since early childhood and has adapted by suppressing either the fovea of the deviating eye (eliminating the central confusion) or the peripheral retina area of the deviated eye directed at the same object as the fixating eye's fovea (eliminating the central diplopia) or both, they may benefit from the peripheral field expansion above and below the fovea[14] and may not need to correct the deviation or occlude the eye. In a number of cases young patients with this syndrome were reported to develop abnormal retinal correspondence (ARC)[15,16]. This adaptation is optimal as it provides the field expansion and avoids the diplopia. It has been named "Panoramic Vision", although the magnitude of the field expansion is typically modest, on the order of typical strabismus deviation. In a recent review of charts at Boston Children Hospital, we identified 103 patient records with both HH and strabismus.[17] From the 75 with exotropia, 53 (70%) had a deviation that potentially expanded the field, while from the 28 with esotropia only 9 (32%) had the field expanding deviation. It is important to note that the field expansion effect of the strabismic horizontal eye deviation is effective at any position of gaze.

THE ROLE AND IMPACT OF PERI-CENTRAL CONFUSION IN HH

While the field expanding strabismus that may accompany HH is arguably helpful, there are other two possibilities that do not provide any field expansion: HH with ipsilateral esotropia (Fig. 9B, see page 476) and HH with contralateral exotropia. These situations create diplopia and confusion peripherally, but peri-centrally they manifest, for the fixating eye, only intermittent confusion and no diplopia. This observation also highlights the fact that while confusion is necessary for field expansion, confusion is not sufficient on its own to expand the field. In fact, in this situation the peri-central confusion offers no apparent benefit and only the potential for annoyance. Unlike diplopia that is apparent and annoying for any fixated object in the field expanding variant of the syndrome, the confusion may frequently not be manifested. As the patient is fixating an object, the fovea of the deviating eye may fall on a blank or low salience area of the scene resulting in no apparent confusion (cf the tiger in Fig. 3, see page 470). The intermittent peri-central diplopia that occurs in these cases is related to the non-fixated unattended objects and the more central copy is seen by the deviating eye, all making it less noticeable. The observation that ipsilateral esotropia avoids central diplopia has led some clinicians to suggest that it may be advantageous to convert patients with HH and ipsilateral exotropia who are bothered by the diplopia to esotropia either by surgery or by using of prisms. Such a change will largely relieve the patient from the central and peri-central diplopia. However, I have found that while the initial response to such a change is one of relief, as the patient immediately notices the lack of central diplopia, however, soon thereafter situations emerge that result in central or peri-central confusion of two salient objects (i.e. the faces of two persons seating across the table from the patient may be superimposed). This confusion is no less, and possibly more, annoying than seeing one person in diplopia. The confusion in such case may appear like the one depicted in Fig. 5C, see page 473, but here without the field expansion benefit. Of course the ipsilateral exotropia (or contralateral esotropia) variants do not eliminate the confusion in addition to the diplopia but in these cases the patient at least enjoys a benefit of field expansion when the confusion is manifested. In the patients record survey we conducted[17] only 30% of patients with HH and exotropia vs. 68% of patients with HH and esotropia exhibited this non-expanding variant of the syndrome. The reason for that asymmetry is not clear.

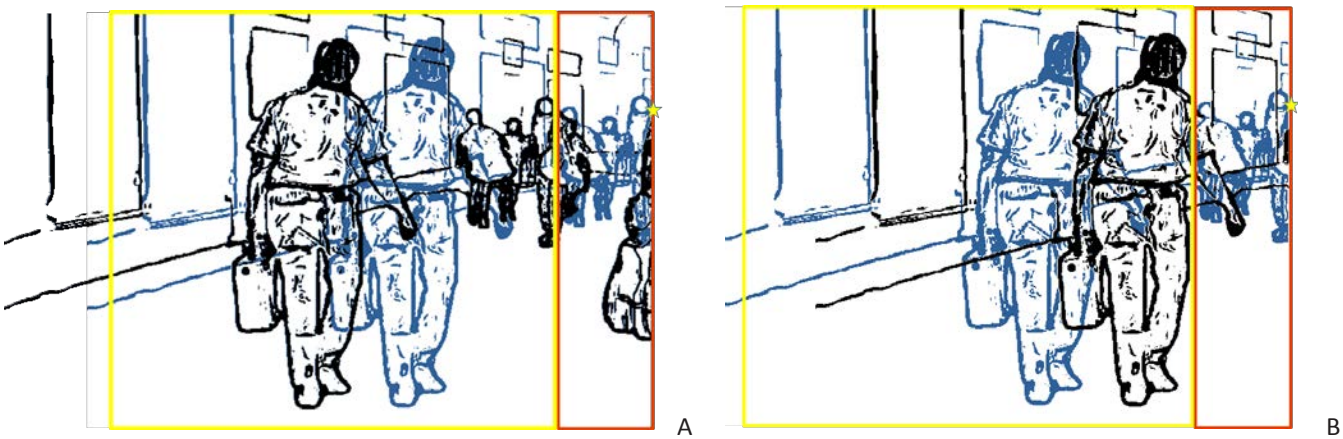


Figure 9. Right homonymous hemianopia (HH) combined with A) ipsilateral (right) exotropia, and B) ipsilateral esotropia. The left eye view is shown in blue and right eye view in black. The left eye fixation point is marked with the yellow star. The area outlined with yellow in both images indicates the peripheral section of the field-of-view seen with both diplopia and confusion. The right eye view (black) in the section highlighted in red in (A) represent the field expansion achieved via confusion (e.g., the woman's bag visible only by the right eye). The fixated object in (A) and all objects seen by the left eye to the left of fixation are diplopic. Peri-central diplopia is bothersome. The objects seen with the right eye only in this area are confused but are not diplopic. In the case shown there is peripheral (lower field) confusion but not central confusion (by chance only, a larger deviation, or moving forward, would bring the woman head into central confusion as shown Fig. 5C). In (B) the left fixating eye's view within the red highlighted section includes attended objects seen in confusion, when it is manifested (e.g., the left of the 3 passengers ahead is confused with the man's right arm) but no diplopic objects at all. Salient objects within the deviated right eye's view in this section which are confused with the left eye's view may be diplopic with farther peripheral left eye's view objects (e.g., the man's right arm). However, in this case the confusion does not provide any field expansion, as all objects seen by the esotropic right eye are already seen by the fixating left eye.

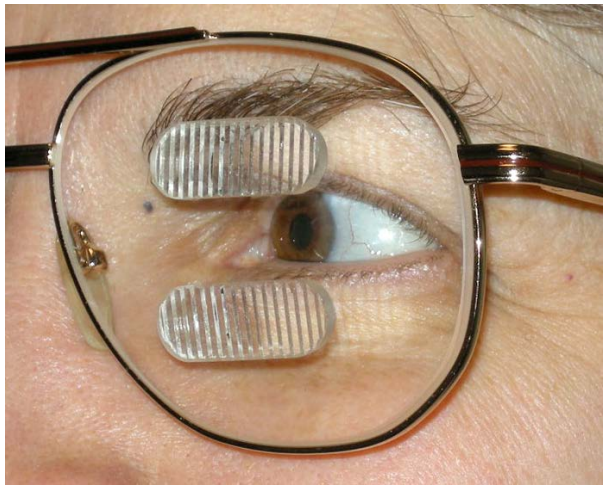
PRISM BASED FIELD EXPANSION FOR HH

While it is frequently stated that prisms are used for field expansion because they shift the view from the blind hemifield to the seeing side, in fact image shifting per se does not expand the field-of-view as we clearly explained[1]. As in Fig. 9A the field is expanded via confusion caused by misalignment of the two eyes. The confusion is a result of presenting a view of object not seen without the prism superimposed over another view seen without the prism. Such superposition is needed to expand the field (the only other known way to expand the field is minification, and minification does not expand the field in HH). The confusion that results from naturally occurring strabismus can therefore be substituted with prism induced strabismus. If a prism of large enough power is introduced in front of one eye the patient will not be able to fuse and will end up in a manifest strabismus. A base-out prism placed in the spectacle lens in front of the right eye of an adult patient with right HH will result in the same effect as the natural exotropia depicted in Fig. 9A. The field is expanded with the disturbing side effects of this treatment; central and peri-central diplopia and confusion are never accepted. Here too the field expansion is effective at all positions of gaze, and so are the disturbing side effects of diplopia and confusion over the whole field. In distinction from the naturally occurring strabismus the prism induced strabismus is also affected by the prism distortions.[18]

Since the full time/full field double vision that accompanies HH field expansion with adult onset of strabismus either naturally occurring, or prism induced is unacceptable, a number of designs have emerged that limit the prism extent. A sector prism which limits the prism to the blind hemifield side of the spectacle lens is commonly used. These sector prisms may be fitted bilaterally or unilaterally. A major limitation is that most of the time, when the patient is in primary position of gaze or is looking in the direction of the seeing hemifield, these prisms have no effect, as they are fully enclosed within the blind hemi field. A detailed review of their other limitations, in particular the occurrence of central and peri-central diplopia and the scope of confusion with the unilateral fitting as a function of gaze movement have been provided[1]. Typically prism powers of only about 20Δ (10°) are used in these designs. The prism power is limited by the thickness and weight of the prisms and by the reduction in visual acuity due to the high color dispersion of high power prisms. The same paper[1] also explains the impact of the apical optical scotoma (that is present in any prism) in the context of the use of the prism for field expansion, and in particular the impact of the apical scotoma on the use of sector prisms. This material is also covered in part by another paper presented in this symposium.

PERIPHERAL PRISMS FOR TREATMENT OF HH

Many of the limitations of the sector prisms and other prism treatment designs can be overcome by our peripheral prisms (Fig. 10A).[19,20] First and foremost this design keeps the central field free of prism effects at all positions of gaze, eliminating the disturbing and annoying central diplopia and confusion. It limits the effective field expanding confusion (and possible diplopia) to the upper and lower peripheral fields (Fig. 10B), where they are much easier to be accepted and adapted to. With the peripheral position, where acuity is naturally poor, it is not difficult for the patient to accept the slightly reduced image quality, color dispersion, and spatial distortions that come with high power prisms. This enables us to use high power prisms and in particular Fresnel prisms that have many desirable mechanical and cosmetic properties such as low weight and thickness, but poorer optical quality. We currently routinely use prisms as high as 57Δ (providing field expansion of more than 30°). The field expansion areas are seen in confusion. The possible peripheral diplopia seen is rarely noted by the patients spontaneously. With proper design this useless diplopia can be eliminated at least at primary position of gaze.[18]



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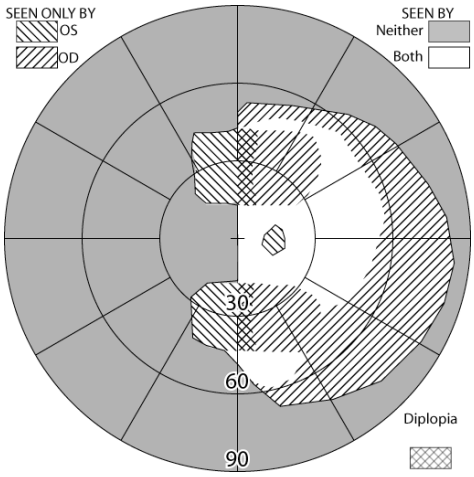

B

Figure 10. Peripheral prism for HH. A) A PMMA Fresnel prisms of 40Δ embedded in the spectacle lens. For a patient with left HH the prisms segments are placed in the left lens with base left (base-out). In typical clinical use, as shown here, the Fresnel prism serrations are pointing outwards from the eye. The clear area between the upper and lower prism segments enables maintaining clear and single binocular vision. The impact of the prisms is limited to the upper and lower periphery. B) Combined monocular Goldmann fields of a patient with left HH wearing the prism shown in (A) illustrating two 20° x 20° sections of field expansion (seen by the left eye only) through the upper and low prism segments. The corresponding sections seen by the right eye only are in fact the apical scotomas blocking the views from the left eye. The crossed hatched areas seen by both eyes are diplopic. The patients typically do not report or notice this peripheral diplopia.

INTERACTION OF PRISM CONFIGURATION WITH DIRECTION OF GAZE AND THEIR INFLUENCE ON THE RANGE OF DIPLOPIA

The apical scotoma (shown in Fig. 10 B) is equal in angular extent to the deflection power of the prism at the apex.[1] The deflection power at the apex varies with the eccentricity (incident angle) which depends on the position of the apex on the spectacle carrier lens relative to the pupil.[18] The prism apex with its apical scotoma is placed in the peripheral prism design at the lateral periphery on the seeing side, while in the sector prism design it is located peri-centrally and may cause peri-central scotoma.[1] In the peripheral prism design the apical scotoma may actually plays a positive role by reducing or even completely eliminating the diplopia. As shown in Fig. 11B for the eyeward prism serrations (EPS) configuration with the current prism design shown in (Fig. 10A), using the higher power (57Δ) Fresnel, the apical scotomas block the diplopic areas completely when the eyes are at primary gaze, since the deflection power of the prisms at the apex is equal to the lateral eccentricity of the apex in the visual field (29°). With the outward prism serrations (OPS) configuration in Fig. 11A, the apical scotoma is smaller (only 20°), and that leaves a 9° of diplopia in the upper far periphery because of the reduced prism power at the apex (20°). The diplopia at such far eccentricity is hardly noticeable and easy to adapt to for the patient. As shown in Fig. 11C & D with a 20° gaze shift to the left, the eccentricity and the angle of incident at the apex increases, resulting in a lower deflection power, reduced extent of the apical scotoma, and a consequent increase in the extent of the peripheral diplopia. While the variation in the extant of diplopia and confusion with gaze

movements are large, they probably have little impact on the functionality of the prism and the patient with them, because all this action is taken place in the far periphery. Yet, understanding all these considerations, as well as others, such as the compression (minification) depicted in Fig. 11, total internal reflection (Fig. 11C), and the spurious reflections[18] not addressed here at all, is all needed for proper design and implementation of these treatments.

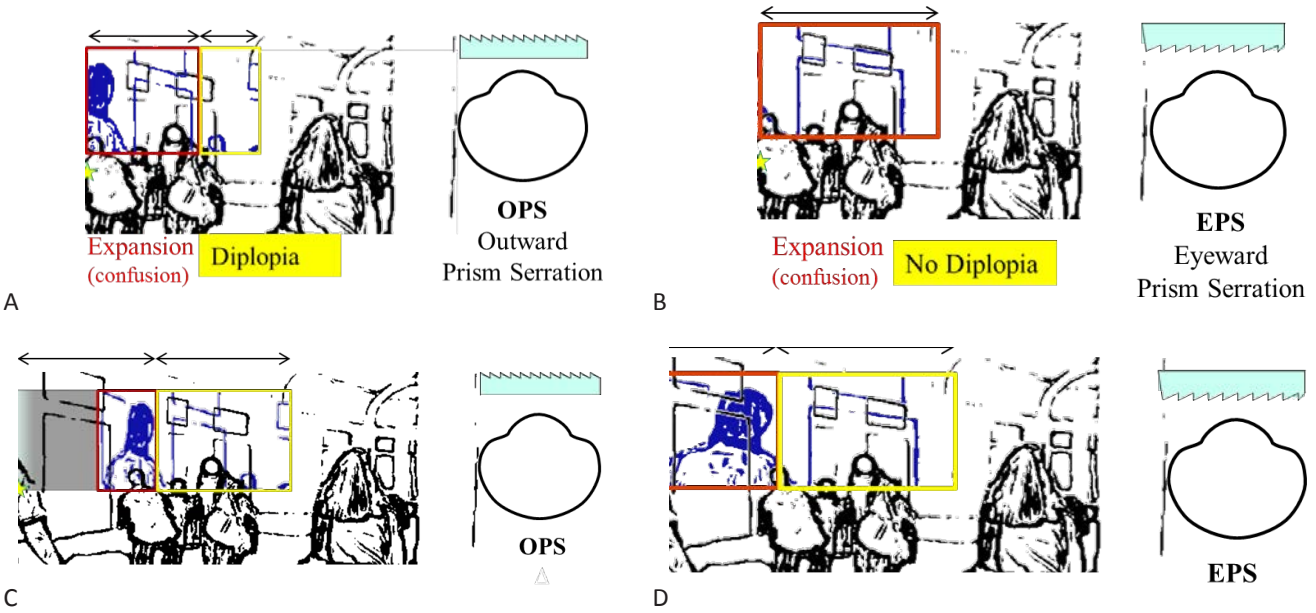

Figure 11. Interactions of prism configuration with direction of gaze and their influence on the extent of diplopia with high power (57Δ) peripheral prisms for HH. The images here only show the effects of the upper prism segment in front of the left eye (blue) with the uncorrected right eye (black). The lower segment effects are not different. Top row is for the primary position of gaze; bottom row is when the patient is fixating 20° to the left (blind side). The yellow star represents the point of fixation by the right eye. A) With outward prism serration (OPS) configuration at primary position of gaze, using the standard prism dimensions results in 39° of confusion (red & yellow outlines) out of which 9° of diplopia (yellow outline) does not contribute to the expansion (30° red outline) B) With the prism serrations towards the eye (EPS) the prism deflection power and consequent field expansion is reduced to 21° but there is no diplopia at all. C) With gaze shifted 20° to the left the area of diplopia is substantially increased to 29° and the overall expansion area including the confusion and diplopia is 60° (giving just 31° of field expansion with minification beyond the shifted gaze position). Note the compression of the man's head as a result of the prism distortion18. The dark grey area represents the area of total internal reflection (TIR) of 15° in this case. D) For the EPS configuration with 20° gaze shift the extent of diplopia is 20° while the full expansion is 41° (or 21° beyond the shifted gaze and there is no TIR or image compression in this case.

SUMMARY

Diplopia and confusion are separate components of the double vision effect. Normally they coexist, yet diplopia is much more noticeable than confusion. This is due to the fact that with normal field all fixated objects appear in diplopia but not necessarily in confusion. The latter effect depends on the image statistics. Diplopia and confusion play different roles in maintaining single binocular vision and in adaptation to the loss of binocular vision in children and adults. The interaction of these phenomena with the loss of visual field and with partial prism may provide experimental tools to better understanding of the properties and roles of diplopia and confusion in normal and in binocular dysfunction and disease. Better understanding can lead to better treatments and better implementation of current devices.

ACKNOWLEDGEMENTS

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Dr. Peli has a patent assigned to MEEI licensed to Chadwick optical related to the peripheral prisms. He has received modest unrestricted research support from Chadwick Optical & MultiOptical.

CME ANSWERS

1. Minification
2. False. Vertical hemislide results in split diplopia but not frank diplopia, since no object is actually seen twice.
3. False. The other eye's fovea may be pointing into a blank part of the field where there is no salient object to be confused with the object of fixation.
4. Peripheral double vision may still be noticeable and central confusion when it occurs is as bothersome or even more bothersome than diplopia.

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REHABILITATION STRATEGIES FOR OPTIC NEUROPATHIES IN ADULTS (AION)

Judith E. Goldstein, OD

John Hopkins School of Medicine
Baltimore, MD

LEARNING OBJECTIVES

1. Describe the traits of patients seeking vision rehabilitation services
2. Interpret the role of visual acuity, visual field loss and comorbidities in visual ability function
3. Illustrate vision rehabilitation strategies in the management of chronic vision loss in AION

CME QUESTIONS

1. The majority of patients seeking outpatient vision rehabilitation services have visual acuity that is categorized as:
    a. Mild to moderately visually impaired
    b. Severely visually impaired
    c. Profoundly visually impaired
    d. Totally visually impaired
2. Nearly half of patients with NA-NAION maintain VA greater than or equal to 20/30.
    a. True
    b. False
3. Low vision rehabilitation in patients with NA-NAION focuses primarily on management of scotomas, visual field loss and contrast enhancement.
    a. True
    b. False
4. As most patients with NA-NAION don't meet the legal blindness standards, they are ineligible for disability.
    a. True
    b. False
5. Visual ability is affected by:
    a. emotional health
    b. physical ability
    c. vision state
    d. all of the above

KEYWORDS

1. Visual ability
2. Contrast sensitivity
3. Scotoma(s)
4. Reading ability

INTRODUCTION

NA-AION occurs in working-age adults where high visual demands are typically present. [1] Management is challenging, as currently there is no effective medical or surgical intervention. With bilateral involvement and vision impairment, low vision rehabilitation (LVR) remains the primary intervention to improve visual ability.[2] Despite stable visual impairment findings over time (visual acuity, contrast sensitivity, visual field), patients with AION may perceive worsening of vision and visual ability over time making ongoing LVR tailored to the individuals needs beneficial for the motivated patient.

CASE INTROCUTION: MEDICAL FINDINGS (2011)

A 53 yo woman presented for a second opinion to the neuro-ophthalmology division at Johns Hopkins regarding a diagnosis of NA-AION. Approximately 10 weeks prior, she noticed loss of vision in the left eye and 8 weeks later, experienced a similar event in the right eye. She visits from Roanoke, VA and is accompanied by her sister who is a physician. Her past medical history is significant for hypertension, primary hypothyroidism, DMx2yrs (last A1c 6.9%), hypercholesterolemia (not under tx, but elevated labs), TMJ, asthma without exacerbations x 9 years, Meniere's disease, mild depression, and chronic UTI's. Her surgical history is significant for total abdominal hysterectomy, appendectomy, abdominal herniorrhaphy, carpel tunnel surgery, gastric bypass (2003). She denies history of smoking and ETOH abuse. Ocular Hx: Strabismus surgery (1960 and 1961).

Examination findings revealed visual acuity (VA) with her current correction of OD 20/60 ph 20/50 and OS 20/200 ph 20/50-. Color vision 4/10 OD and OS 5/10. Visual field (VF) findings OD showed a dense inferior altitudinal defect and

VF OS showed inferior loss appearing more arcuate. Results were stable compared with prior VF's. There was a right RAPD and mild abduction deficits bilaterally. Cover testing showed 18 PD esotropia with preferred OS fixation. Retinal findings showed optic nerve pallor OU. The diagnosis was confirmed as bilateral sequential NA-AION. No medical intervention was recommended other than managing the hypercholesterolemia and DM.

The patient was referred for low vision rehabilitation (LVR) at this visit and presented for initial LVR evaluation 6 weeks later.

BACKGROUND ON AION IMPAIRMENT

AION is the most common acute optic neuropathy in individuals over 50 yo. The disorder is presumed to result from circulatory insufficiency, or infarct, to a portion of the optic nerve head that is supplied by the short posterior ciliary arteries. The majority of scientific research has focused on diagnosis and medical/surgical management. Currently there are no well-accepted medical or surgical treatments and there is limited to no evidence on effectiveness of low vision rehabilitation (LVR) strategies in NA-AION. Despite LVR attention in improving visual ability (*the ability to perform activities that depend on vision*) in homonymous hemianopia secondary to stroke, there are significant differences in VA, scotomas and peripheral VF effects between NA-AION and stroke, warranting attention on LVR management practices in NA-AION. As expected, vision impairment typically affects visual ability when there is bilateral involvement.

NA-AION results in reduced visual acuity and visual field loss. Vision loss often involves the fovea, impacting steady, central fixation, primarily affecting reading ability. Epidemiologic data shows that nearly half of patients maintain VA greater than or equal to 20/30, however, measurements are commonly classified as the best line read and therefore don't consider the impact of scotomas and contrast sensitivity loss, potentially minimizing the profound functional effects of the disorder.[3] When scotomas are close to fixation, reading speed and fluency can be severely impacted, affecting visual ability. As such, visual acuity often overestimates visual ability. This is evident in the marked discrepancy between perceived quality of vision and VA, since more than three fourths of low vision patients with VA >20/60 rate the quality of their vision as fair or poor.[4]

Descriptions and prevalence of visual field loss in NA-AION vary depending on attention to classification systems and to the method of VF testing (e.g., automated 24-2 or 30-2 Vs. Goldman). VF type and analysis may impact size, location and sensitivity of defect(s) observed (e.g. relative vs. absolute defect). Inferior altitudinal VF loss was considered to be the classic VF defect (reported prevalence varying from 25% to 79%). However, further careful study shows that the most common (22.4%) pattern of VF loss observed is a combination of relative inferior altitudinal defect with relative or absolute inferior nasal sector visual loss.[5] Functionally, peripheral visual field loss affects mobility function, visual-motor skills and visual information processing.

VISUAL ABILITY, LOW VISION AND REHABILITATION

The visual ability construct, *the abiity to perform activities that depend on vision*, is likely governed primarily, by two factors.[6,7] One factor is related to visual acuity or resolution ability, while the other factor is less well understood, and likely related to preview area or visual field. A large body of work has explored patient-reported deficits in function, and through factor analysis, the visual ability construct has identified 4 functional domains. These domains are reading, visual information processing ("seeing"), visual motor function, and mobility. These factors are essential, supporting the goal-directed approach in rehabilitation and in organizing treatment plans for patients.

Low vision typically is defined as chronic visual impairments that limit the person's ability to perform his or her usual daily activities and is a major cause of functional limitations and disability.[8-10] Loss in ability to read, drive, and perform other vision-dependent daily tasks often causes dependency on others and increases the risk of depression, injury, and decline in general health. Depending on the visual acuity criterion used, <20/70 or <20/40, epidemiological studies show that 1.5 to 3.5 million Americans, respectively, older than 40 years of age have low vision.[11,12]

Low vision rehabilitation (LVR) is the primary intervention for chronic vision impairment. LVR improves *visual ability*, through patient-centered, goal-directed therapy via incorporating vision-assistive equipment, sensory substitution strategies, education and counseling. Given the prevalence of low vision and the effectiveness of LVR, the American Academy of Ophthalmology (AAO) recognized the importance of educating the ophthalmic field to ensure that patients are identified and referred for LVR services. As such, the AAO established the SmartSight initiative.[13] As part of the AAO's Preferred Practice Patterns, the SmartSight initiative encourages ophthalmologists to discuss LVR services and provide an educational handout when VA drops below 20/40, or when there is loss in contrast sensitivity or visual field loss. Like physical medicine and rehabilitation, LVR services are typically provided in a team approach, encompassing multiple providers including the ophthalmologist, optometrist, occupational therapist, rehabilitation therapist, orientation and mobility instructor, assistive technology specialist, psychologist, psychiatrist and social worker.

Outpatient LVR services across the U.S. are effective in improving overall visual ability in nearly half (47%) of patients, with large average effect sizes (Cohen's *d* = 0.87). At the functional domain level, effect sizes are moderate (Cohen's *d* = 0.4 to 0.51) with 28% to 45% of patients meeting the minimum clinically important change criteria.[14] Results from VA Blind Rehabilitation Center, which offers an intense 4 to 6 week inpatient LVR program with full coverage of visual assistive equipment (VAE) costs have shown much larger effects with LVR intervention (Cohen's *d* = 1.96).[15] Because LVR is impacted by the person's overall health state, it is essential to factor patient traits besides VA and VF into the rehabilitation plan.[16] Therefore individual LVR plans consider the patient's co-morbidities, co-disabilities, living arrangements, available resources and personal preferences in order to set rehabilitation goals and determine the patient's rehabilitation potential.

CHARACTERISTICS OF PATIENTS SEEKING OUTPATIENT LVR SERVICES

Based on a large observational study, the population seeking private outpatient LVR services in the U.S. is primarily older (median age 77 years with a range 19 to 98 years) and female (66%).[4] Macular disorders compose 55% of all patients seeking outpatient services and mild VA loss (>20/60) is present in approximately one-third of patients (37%). For the 50% of all patients for whom contrast sensitivity (CS) was measured, mean contrast sensitivity was 0.96 logCS (moderately reduced) and log CS is significantly correlated with log MAR acuity (r = -0.52, p < 0.0001). Of the population studied, 16% of patients seeking LVR services had a primary diagnosis of glaucoma, optic atrophy or optic neuropathy. It is commonly observed in patients with optic neuropathy, that VA can be near normal while CS is severely reduced.

Most patients seeking LVR services consider themselves in good to excellent general health, particularly those 71 to 80 years of age. However, over one third (39%) of patients reported that physical disabilities limit their ability to perform daily activities. Mobility adaptations are reported by 37% of patients seeking LVR services, manifested through the nonexclusive use of supportive aids, primarily straight cane (23% of all patients) and walker (16% of all patients). Over one half (52%) of all patients report that they had suffered a fall during the previous 2 years, and 39% of those individuals who had a fall reported it to be vision related. This is particularly relevant in the population of AION patients where the inferior VF is primarily affected. Given the age of onset of NA-AION, the expected decline in proprioception with age, coupled with inferior VF loss, make this group particularly at high risk for falls and fractures. Dim and unfamiliar environments with "drop-off's" often call for use of a mobility aid.

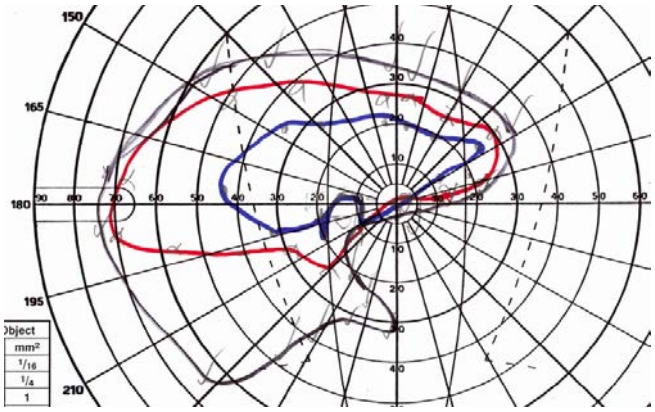
Emotional health can be significantly affected in the low vision population.[4,17-19] Depression, anxiety, and difficulty coping are common. Nearly half (42%) of low vision patients report "frustration"; consistent with the inability to perform activities with ease and efficiency. Performing everyday activities take longer. The limitations and inability to drive adds to the loss of independence and potentially raises the risk of depression. Many with AION are in the workforce at the time of vision loss, challenging the rehabilitation process with considerations of work-place adaptations and/or disability.

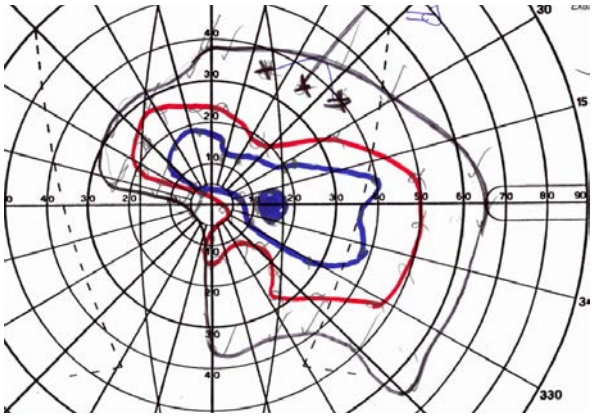
CASE PRESENTATION (CONTINUED): REHABILITATION FINDINGS (2012-2016)

Visit 1 focused on the primary concerns of vision loss affecting reading and computer ability. She is bothered that her vision fluctuates. She feels she reads with her right eye and the print is not clear. She tries to read on her mom's kindle. She works full-time in an OB-GYN practice coordinating ultrasound reports with testing orders. She is no longer able to perform ultrasounds and continues to assist with office management and billing. Work has supplied a large monitor for computer tasks. Regarding her visual information processing, "seeing", she cannot read the scroll text on TV. She had mono-vision glasses from prior, but now she is not wearing them as they don't help. She is licensed to drive but discontinued driving after she lost vision in the second eye. She has not had any falls and is always accompanied when leaving the home as she relies on others for transportation. When walking, she notes she "has to watch out and put out her hand" sometimes. Glare and certain lighting conditions are bothersome and her amber sunfilters help. She is single, lives with her mom in a condominium (elevator building) and has support from her mother, sister and friends. She maintains some responsibility for cooking, shopping, and managing personal finances. She reports her everyday activities are mild to moderately difficult and her physical health does not limit her activities. Psychologically she is managing well.

Entering VA (sc) OD was 20/80-2 with a dense scotoma to right of fixation and OS was 20/125. Binocularly she measured 20/80-/+ with a head turn. Manifest refraction improved VA to OD 20/50- and OS 20/50-. Contrast sensitivity was moderately reduced at 1.30 log units. Near evaluation showed slowed and threshold reading at moderate to small print (2.5M/1.6M @ 37cm). With a +3.25 Add, near VA improvement to 0.8M with OD preference. 8-10 D of magnification with illumination – provides maximal VA 0.5M.

Pupillary finding showed a right RAPD, cover testing revealed an Alt ET without observed fixation preference. Goldman VF's showed bilateral inferior nasal loss splitting fixation. Optic nerves were pale OU with 0.25 cupping.





Rehabilitation goals identified included (1) maximize spot and continuous text reading, (2) improve endurance on computer, (3) minimize discomfort form indoor and outdoor glare, (4) mobility safety, (5) maintain employment, (6) improve management of activities of daily living. LVR visits in February 2012 involved modifying spectacles to maximize visual information, eliminating the monovision approach, Rxing first bifocal ever with consideration given to writing, viewing food on plate and mobility (e.g., +2.50). We prescribed an occupational bifocal for computer and desk work with the plan to modify work distance to screen from 23 inches to 18 inches and incorporate a magnification mouse. The low vision occupational therapist evaluation and treatment focused on use of electronic magnification with a high-definition closed circuit television with reverse polarity for sustained continuous text at work (e.g. documents). We worked to incorporate a tablet with reverse polarity for book reading. A+10.00D LED hand magnifier was prescribed for spot reading and we observed a preference for use of tints such as yellow 465, light amber, dark amber preference for different luminance levels. We provided education and counselling on permanent driving cessation which was anticipated by the patient.

Over the next year we added a distance only pair of spectacles to be used when she was a passenger in the car (as opposed to lined-bifocal), given her sensitivity to motion and perception of experiencing nausea when wearing a bifocal while in fast motion. We ultimately changed her occupational bifocal to single vision only as well for the computer and added a sun Rx as a distance only with amber polarization tint. We referred her to the Department of the Blind and Visually Impaired in Virginia to initiate orientation and mobility (O&M) training given her uncertainty in walking in unfamiliar environments. She observed over time that her eyes tire easily and she must take frequent rest breaks at work (5-10min) after 15 minutes of reading; When exercising at the gym with a trainer, she sometimes visually loses his location and must take time to visually located him. She continued to have concerns when navigating from a parking lot to a place of interest and the detail on television remained inadequate. She started to use her white cane regularly during the work day. Best corrected VA remained in the 20/60 to 20/80 range with eccentric viewing in each eye. We completed paperwork for a handicap placard for when she is a passenger, loaned a 2.5x clip monocular telescope OS for TV viewing and considered trial occlusion to limit visual fatigue. We initiated use of zoomtext software (magnification and speech output) for work demands.

2013 - VA remains stable at follow up visits but the patient continues to notice visual fluctuations. DM remains controlled with metformin and A1c remains around 6.0%. Snellen VA measures do fluctuate between 20/70 and 20/100. CS showed slight reduction to 1.05 log units over the year. Rehabilitation has involved increasing the LED HM power to 16D to increase accuracy of spot reading numbers. Iphone accessibility using voice over and portable electronic magnification for “hands-free” document reading have become useful in work and everyday activities. Zoomtext software mag @ 1.5x to 1.75x coupled with single vision only computer specs work best.

2014 – Vision is noticeably becoming hazier indoors; stumbles a lot in and outside. Uses white cane as needed. More cautious when walking outside. Receiving IV Fe infusion for Restless Leg Syndrome. VA and CS stable. Recommended initiating use of yellow 465 nm filters for indoor haziness and overcast outdoor conditions, minimize home safety hazards, including tacking down rugs, and switch to iphone 6+, and add illuminated 8D pendant. Adaptive and sensory substitution strategies focused on continued use of voice-over, initiating use of speak screen, and practicing with 3 new ipad apps.

2015 – Light sensitivity worsening; 1 fall since last visit (“feet go tangled up”)

Using white cane with increased frequency. Computer work manageable with SVO computer specs and zoomtext @ 1.75x to 2x. Recent initiation for tx of depression – Effexor, for which she feels helps. Best-corrected VA OD 20/60- with EV and VA OS 20/100- with EV. CS remains unchanged. Ocular health shows mild cortical and nuclear sclerotic cataracts, 2+ pallor OD and 3+ pallor OS without any evidence of diabetic retinopathy. Because of the mobility concerns and mild depression, we discussed use of service dog (re: depression) and guide dog (unlikely to qualify).

Exploration of new optical character resolution technology and head mounted electronic magnification were explored, but not indicated.

2016 – Struggling more with vision but lost bifocals recently. Glare more bothersome (tries to keep all lighting very dim); wearing darker sun Rx in meetings and at store. Must use hand magnifier now when placing blood on strip to check blood sugar. She has had 3 falls within the last 6 months despite use of cane. VA remains stable at OD 20/60- with EV and OS 20/70- with EV, CS and VF also unchanged. Extensive discussion at visit regarding disability should patient feel she no longer can keep up at work. Patient feels she can still continue to stay in the workplace with the accommodations in place.

CME ANSWERS

1. a
2. True
3. True
4. False
5. d

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CONVERGENCE INSUFFICIENCY: REVIEW OF TREATMENT TRIALS (OFFICE VERSUS HOME BASED TREATMENT)

Susan Cotter, OD, MS

Southern California College of Optometry, Marshall B Ketchum University
Fullerton, CA

LEARNING OBJECTIVES

1. Describe the results and discuss the clinical implications of the large-scale CITT study comparing treatments for children with symptomatic convergence insufficiency.
2. Identify the strengths and limitations of the large-scale CITT study comparing treatments for children with symptomatic convergence insufficiency.
3. Identify and discuss questions that still need to be answered in regard to the management of symptomatic CI.

CME QUESTIONS

1. The treatment regimen that was prescribed for the office-based vergence/accommodative therapy group (OBVAT) consisted of 12 weeks of:
    a. Bi-weekly 30-minute therapy sessions, with no home therapy
    b. Weekly 1-hour therapy sessions, supplemented with 15 minutes of home therapy 5 days per week
    c. Twice monthly, 30-minute therapy sessions, supplemented with 30 minutes of home therapy 3 days per week
    d. Once monthly 1-hour therapy sessions, supplemented with 15 minutes of home therapy 5 days per week
2. Which of the following was not part of the treatment regimen the pencil push-up therapy group in the CITT trials?
    a. Once weekly phone discussions with the therapist
    b. Monthly in-person therapy appointment in the office with the therapist and an examination by a masked examiner
    c. A written home log for tracking the amount of therapy completed per day
    d. A small letter to stimulate accommodation and the use of a physiological diplopia control
    e. Performing 30 minutes of push-ups 5 days per week
3. The goal of the CITT trials were to determine:
    a. the comparative effectiveness of commonly prescribed treatments as presently used in clinical practice
    b. the comparative effectiveness of equal dosages (time) of pencil push-ups and office-based vergence/accommodative therapy
    c. if office-based computerized therapy was better than home-based computerized therapy
    d. the comparative effectiveness of base-in prism reading glasses and low-plus reading glasses

KEYWORDS

1. Convergence insufficiency
2. Vision therapy
3. Vergence/accommodative therapy
4. Orthoptics
5. Pencil push-ups

INTRODUCTION

Convergence insufficiency (CI) is a binocular vision disorder that is characterized clinically by a larger-sized exodeviation at near than at far, a remote near point of convergence (NPC), and deficient positive fusional vergence (PFV) (i.e., convergence amplitudes) at near. It is of clinical consequence because it is associated with a plethora of symptoms, ranging from mild to severe, that when present, are directly related to reading or other near activities. Commonly reported symptoms include diplopia, blur, headaches, eyestrain, tired eyes, words moving on the page, loss of place, and poor concentration with reading and close work.

CI is non-discriminatory when it comes to age – school-aged children and adults of all ages can be affected. Most studies reporting prevalence rates of CI in children are based on school-based samples and thus have not used sampling methods that allow precise prevalence estimates representative of the overall population. Prevalence rates from these school-based samples have used the presence of 2 or 3 clinical signs (exophoria at near greater than at far in addition to a receded NPC or insufficient positive fusional vergence) and have been substantial ranging from

12% to a surprising 31% in a population of school-age Native American children.[1] Clinical signs of CI, however, are not always in sync with associated symptoms. The most recent study, reporting a prevalence 31%, noted that the prevalence of "symptomatic" CI was considerably less at 6.2%.[1] The prevalence of CI in young and older adults is unknown, but it is commonly noted in patients with Parkinson disease and those who have suffered traumatic brain injury or concussion. A recent cross-sectional study of 100 adolescents with the diagnosis of concussion reported that 49% met the diagnostic criteria for CI.[2]

TREATMENT INTERVENTIONS

The treatment of CI is typically nonsurgical with various treatment modalities available. The two main categories of treatment consist of either performing some version of convergence exercises designed to improve fusional convergence or wearing base-in prism glasses for reading, albeit some clinicians prescribe a plus add at near. Most ophthalmology and optometry textbooks state that 'convergence exercises' are the most appropriate treatment for CI. However, 'convergence exercises' mean different things to different people, and range from having the patient look and maintain fixation on the tip of a sharpened pencil as it moves closer and closer to the eyes (i.e., pencil push-ups) for a specified duration or number of times (e.g., 10 minutes or 100 times) per day at home to more intensive therapy consisting of weekly 1-hour office-based therapy sessions supervised by a therapist and supplemented with daily therapy performed at home. Other types of convergence therapy include orthoptics (that can range from simple to more intense exercises and be performed in the office or at home), home-based convergence exercises, and home-based computerized therapy.

THE CONVERGENCE INSUFFICIENCY TREATMENT TRIALS (CITT) – A BIT OF HISTORY

While CI had long been recognized as a relatively common binocular vision disorder encountered in ophthalmology and optometry practices, there was a lack of consensus regarding the most effective treatment for the condition. The results from two surveys provided insight and corroborated the clinical impression that pencil push-up therapy performed at home was a commonly prescribed treatment for CI. Table 1 provides the results of a survey of US eye care professionals who were asked to indicate their usual prescribing patterns given an 18-year-old patient with symptomatic CI who was highly motivated and willing to comply with any treatment approach.[3] Pencil-push up treatment was prescribed by one half and more than a third of the responding ophthalmologists and optometrists, respectively.

Table 1. Treatment That is Often or Always Prescribed for Symptomatic CI

	Pencil Push-ups	Office-based VT*/ Orthoptics	Home-based VT†/ Orthoptics	Base-In Prism	Reading Glasses	No Treatment
OD	36%	16%	22%	15%	13%	3%
MD	50%	5%	21%	10%	4%	10%

* Regular office visits during which an OD or therapist performs therapy with vectograms, tranaglyphs, stereoscopes, lenses, prism, computer-assisted therapy, etc.

† Treatment only at home with prism, stereoscopes, or other devices

In another survey, specific to pediatric ophthalmologists, 53% of the respondents (72% response rate of 100 surveyed) indicated that they usually or always recommended pencil push-ups as the sole treatment for children with symptomatic CI, with treatment typically prescribed for 5 to 15 minutes per day for 5 to 7 days per week.[4]

Interestingly, while pencil push-up therapy was the most commonly prescribed treatment modality by optometrists and ophthalmologists alike, there was no evidence in the literature to support its effectiveness as a treatment for CI. The only published report was a pilot study of 25 subjects with no control group and a 50% loss to follow-up; it did not provide any supportive evidence for the use of a 6-week pencil push-up treatment regimen.[5] Thus, the clinical popularity of pencil push-ups as a treatment for CI presumably had been based on clinical impression and advice passed from mentor to mentee, likely because of the treatment's simplicity and nonexistent cost. Contrary to studies evaluating pencil push-up treatment, there were numerous papers reporting on the effectiveness of orthoptic or vergence/accommodative vision therapy for the treatment of CI; however, all of the studies had one or more design limitations and thus did not provide convincing evidence that orthoptic or vergence/accommodative therapy was an effective treatment.

Despite the popularity of pencil push-up treatment, there was no general consensus within the ophthalmology or optometry professions in regard to the most effective treatment for symptomatic CI (Table 1). There was agreement, however, that there were significant differences in terms of complexity, dosage, mode of administration, time commitment, and cost among the different modes of non-surgical treatment for CI. Recognizing that determining the effectiveness of non-surgical treatment interventions would be beneficial to the eye care community and patients affected with symptomatic CI, a multidisciplinary group of investigators, the Convergence Insufficiency Treatment Trial (CITT) Group, sought to determine the best treatment for symptomatic CI. Because of the considerable differences in cost and ease of implementation, it was imperative to determine if a simple, no-cost procedure like pencil push-up treatment was as effective as the more costly and time consuming treatment of office-based vergence/accommodative therapy.

To compare the treatment effectiveness of these two therapeutic approaches, it was necessary to conduct a rigorous clinical trial that included a placebo therapy with equal provider-patient interaction for the office-based vergence/accommodative therapy group (at that time called office-based VT/orthoptics). This was the impetus for the first CITT randomized clinical trials evaluating treatments for CI – two concurrent trials that compared home-based pencil push-ups, office-based VT/orthoptics, and office-based placebo VT/orthoptics in 9 to 18-year old children[6] and 19 to 30-year-old young adults.[7]

The data from the initial CITT trial for children were then used to design a subsequent large-scale clinical trial for children. Because of the increasing popularity of home-based computer treatment for CI, this mode of therapy was added as a fourth treatment arm.[8,9] In addition, a separate randomized clinical trial was conducted to evaluate the effectiveness of prism reading glasses for children with symptomatic CI.[10]

THE CONVERGENCE INSUFFICIENCY TREATMENT TRIALS (CITT) RESULTS

The goal of the CITT trials were to determine the effectiveness of commonly prescribed treatments "as presently used in clinical practice." The prescribed therapy dosages were designed to mirror clinical practice, meaning that the dosage of office-based treatment (with weekly 1-hour in-office therapy visits) was greater than the dosage of the simpler home-based treatments not requiring weekly office visits. It was thought that equalizing therapy dosage and face-to-face provider contact time would limit the clinical utility and negate the primary advantages (simplicity and low cost) of home treatment.

Table 2 summarizes the CITT comparative effectiveness trials for non-surgical treatment modalities for individuals with symptomatic CI. Symptomatic CI for these studies was diagnosed when a patient exhibited the following despite correction of refractive error: exodeviation at near at least 4Δ greater than at far, a receded NPC break ≥6 cm, insufficient positive fusional vergence at near (PFV) [i.e., failing Sheard's criterion (PFV less than twice the magnitude of the exodeviation) or minimum PFV of ≤15Δ base-out blur or break], a CI Symptom Survey (CISS) score ≥16 for children and ≥21 for adults. Patients having had prior treatment for CI, wearing BI prism or a plus add at near, or an accommodative amplitude less than 5 D were not eligible for the study.

Table 2: Summary of CITT Randomized Trials for Children with Symptomatic CI

N	Treatment Groups	Key Results
A RCT of Treatments for Convergence Insufficiency in Children Ages 9-18 Years[6]		
47	• Home-based pencil push-ups (HBPP) • Office-based VT/orthoptics (OBVT) • Office-based placebo VT/ orthoptics (OBPT)	• OBVT more effective than HBPP & OBPT in reducing symptoms & improving clinical signs • Neither HBPP nor OBPT effective in improving symptoms or signs
A RCT of Treatments for Convergence Insufficiency in Young Adults Ages 9-30 Years[7]		
46	• Home-based pencil push-ups (HBPP) • Office-based VT/orthoptics (OBVT) • Office-based placebo VT/ orthoptics (OBPT)	• Statistically significant improvements found for CISS, NPC & PFV for all 3 groups, but OBVT group greater improvements on NPC & PFV vs. other groups • Only OBVT within normal range on CISS, NPC, & PFV; however, >58% still symptomatic on CISS
Effectiveness of Base-in Prism Reading Glasses vs. Placebo Reading Glasses for Symptomatic CI in Children Ages 9-17 Years[10]		
72	• Base-in prism reading glasses • Placebo reading glasses	• Base-in prism reading glasses no more effective in alleviating symptoms or improving clinical signs than placebo reading glasses; significant decrease in symptoms only, but same in both groups
Treatments for Symptomatic CI in Children Ages 9-17 Years[9]		
221	• Home-based pencil push-ups (HBPP) • Home-based computer VT & pencil push-ups (HBCVAT+) • Office-based vergence/accommodative therapy (OBVAT) • Office-based placebo therapy (OBPT)	• OBVAT when compared to HBPP, HBCVAT+, & OBPT resulted in significantly greater: - Improvement in symptoms (CISS) - Clinical signs (NPC & PFV) - Greater percentage of subjects reaching predetermined success criteria
1-Year Follow Up of Successfully Treated Symptomatic CI in Children Ages 9-17 Years[11]		
70	• Home-based pencil push-ups (HBPP) • Home-based computer VT & pencil push-ups (HBCVAT+) • Office-based vergence/accommodative therapy (OBVAT) • Office-based placebo therapy (OBPT)	• % remained asymptomatic and % remained successful or improved - HBPP: 67% (10/15) and 67% (10/15) - HBCVAT+: 80% (8/10) and 80% (8/10) - OBVAT: 84% (27/32) and 88% (28/32) - OBPT: 77% (10/13) and 69% (9/13)

- Symptomatic CI defined as an exodeviation at near at least 4Δ greater than far with a receded NPC break ≥6 cm and insufficient positive fusional vergence at near (PFV) (i.e., failing Sheard's criterion or minimum PFV of ≤15r base-out blur), and a CI Symptom Survey (CISS) score ≥16 for children and ≥21 for adults.
- Primary outcome measure was the CISS score and secondary outcomes were clinical measures of NPC & PFV, and success criteria based on a composite outcome classification of the CISS score, NPC, and PFV.

STRENGTHS & LIMITATIONS OF THE LARGE-SCALE CITT TRIAL

The strengths and limitations of the large-scale clinical trial[9] are noted in Table 3.

Table 3. Treatments for Symptomatic CI in Children Ages 9-17 Years[9]

Study Strengths
• Study design was a prospective randomized clinical trial • Both optometrists and ophthalmologists participated in the planning, implementation, and oversight of the study • A prior pilot randomized trial was conducted to pilot test study procedures and therapy implementation, and to determine the standard deviation estimates necessary for calculating sample size for the trial • Subjects were randomly assigned to treatment groups, thus controlling for known and unknown confounding variables and avoiding treatment assignment bias • A placebo-control group for the active therapy group was included • Evidence that subjects assigned to the 2 office-based treatment groups were masked to their treatment assignment, as were the masked examiners • The CI Symptom Survey (CISS) was developed and its validity and reliability established so that it could be used as a primary outcome measure to determine whether a change in symptoms occurred post-treatment • The secondary outcome measures were defined a priori • All outcome measures were collected by an examiner masked to subject treatment group • There was sufficient sample size to detect a statistically significant difference between the treatment groups with 90% power • Outstanding follow up – 99% of 221 subjects completed the 12-week outcome exam
Study Limitations
• There were no control groups for the home-based therapy groups (HBPP and HBCVAT+); thus, it is not known if the improvements found in these groups were due to placebo effects, regression to the mean, or natural history of CI • Adherence with the prescribed dosage of home-therapy performed (in all treatment groups) was determined by home logs and subject self-report • Subjects assigned to the two home-based therapy groups (HBPP and HBCVAT+) received weekly phone calls from the therapist to discuss therapy progress, answer questions, and promote adherence with therapy; this is not typical of clinical practice • There was not a “no treatment” group; thus, it is not known if some subjects (in all treatment groups) would have improved anyway

UNANSWERED QUESTIONS & FUTURE STUDIES

There are still a number of questions of interest that need to be answered in regard to symptomatic CI, some of which are listed in Table 4.

Table 4. Convergence Insufficiency Wish List

- Establish the natural history of CI
- Determine precise estimates of the prevalence CI in children and adults, reporting separately the rates of those who have symptomatic CI
- Determine why some patients with clear signs of CI are not symptomatic
- Determine if and how symptomatic CI affects reading performance and attention, and if improvements occur with treatment
- Determine why the combined home-based computerized therapy & pencil push-up therapy (HBCVAT+) was no more effective than placebo therapy in the CITT study
- Be able to monitor and verify adherence with prescribed home therapy so one can determine dosage effects and if treatment failure is related to failure to do treatment
- Determine the optimal length of an OBVAT program that results in maximal improvement
- Determine what aspects of the CITT accommodative/vergence therapy protocol or what specific procedures are the most effective, and whether the protocol can be modified to increase its effectiveness, shorten the duration, or be provided in a home-based manner
- Objectively determine how vergence/accommodative therapy for CI alters the visual system
- Determine the potential underlying mechanism of CI and how the remediation of CI alters the vergence system
- Conduct large-scale effectiveness trials evaluating different modes of treatment in young and older adults with symptomatic CI
- Investigate the underlying mechanism of concussion-related CI and whether the vergence system responds similarly to treatment with OBVAT

DOES SYMPTOMATIC CI AFFECT READING & ATTENTION?

Divergent opinions exist regarding the relationship between CI and reading and academic performance. Some feel that there is no relationship whatsoever, while others expect improvements in reading when a patient with symptomatic CI is treated successfully. There is a clinical impression that symptoms associated with CI can interfere with the ability to sustain attention on near visual tasks, which subsequently could negatively impact reading performance. A reduced ability to sustain attention could result in reduced practice time in developing automaticity with the reading task in the early grades and reduce the intake of information in later grades. Because the information flow in cognition has a limited capacity, factors that result in divided attention reduce the flow of cognitive information in the reading process and could contribute to reading difficulties. If this is true, then it is possible that a decrease in CI-related symptoms could lead to better attention and concentration, thereby enabling the child to read more comfortably and for longer periods of time.

The NEI-funded CITT-ART,[12] a multicenter randomized trial, recently met its recruitment goal of enrolling 324 children 9 to <14 years of age with symptomatic CI who were randomized to OBVAT or a placebo comparison group. The primary outcome measure is reading comprehension; secondary outcome measures include tests of attention, tests of reading comprehension, and other reading domains. Children are followed for 1 year post-treatment to evaluate any long-term effects.

CME ANSWERS

1. b
2. e
3. a

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CONVERGENCE INSUFFICIENCY: PRACTICAL PEARLS FOR DIAGNOSIS AND TREATMENT

Susan Cotter, OD, MS

Southern California College of Optometry, Marshall B Ketchum University
Fullerton, CA

LEARNING OBJECTIVES

1. Recognize that the purpose of vergence/accommodative vision therapy is to treat binocular vision conditions (such as CI) that are diagnosed based on a sensorimotor evaluation, and that vision therapy is not used to treat a learning disability, dyslexia, or ADHD.
2. Explain the purpose of the CI Symptom Survey (CISS) and how it can be used in clinical practice.
3. Compare how pencil push-ups and office-based vergence-accommodative therapy procedures differ in terms of their ability to manipulate the stimulus such that fusional vergence can be isolated.

CME QUESTIONS

1. Which of the following was NOT a diagnostic criterion for convergence insufficiency in the CITT trials for children?
    a. Near point of convergence (NPC) receded ≥ 10cm
    b. Blur point for positive fusional vergence (PFV) (convergence amplitudes) at near that fail Sheard's criterion or are <15Δ BO
    c. Exodeviation at near at least 4Δ greater than with far fixation
2. Which of the following symptoms was most commonly reported as happening "fairly often or always" when reading and doing close work by the children with symptomatic CI enrolled into the large-scale CITT trial?
    a. Eyes hurt
    b. Diplopia
    c. Headaches
    d. Loses place when reading
    e. Reads slowly
3. Which of the following is true in regard to the Convergence Insufficiency Symptom Survey (CISS) used in the CITT studies?
    a. A score of ≥ 16 is diagnostic for convergence insufficiency.
    b. It was developed for the purpose of quantifying symptoms pre- and post-treatment.
    c. A CISS score of ≥ 21 is considered "symptomatic" for children with convergence insufficiency.
    d. The patient only need respond yes or no whether she is affected by each of the 15 symptoms when reading or doing near work.

KEYWORDS

1. Convergence insufficiency
2. Symptoms
3. Convergence Insufficiency Symptom Survey (CISS)
4. Vergence/accommodative therapy
5. Vision therapy

INTRODUCTION

Patients with convergence insufficiency (CI) often complain of symptoms while engaged in reading and other near work. Commonly reported eye-related symptoms are diplopia, blur, eyestrain, headaches, and words moving on the page. Diplopia can present as either two separate horizontal images or overlapping images, the latter sometimes interpreted as blur. Blurred vision may also result if excess accommodation is used in an effort to increase convergence through the accommodative system to maintain fusion at near. Asthenopic symptoms are commonly described as strained or tired eyes. Headaches are often periocular or in the frontal area. Words that move, jump, or swim on the page during reading and close work are presumably associated with difficulties maintaining fusion. These eye-related symptoms have long been recognized by clinicians to be associated with CI, and many have presumed these to be the predominant symptoms. However, in 221 children participating in a clinical trial for symptomatic CI, these eye-related symptoms were reported to occur less frequently than

the performance-related symptoms of poor concentration, trouble remembering what is read, losing one's place, having to reread the same line of words, reading slowly, or feeling sleepy when reading or doing close work.[1] (Figure 1)

Thus, a targeted history that includes both performance- and eye-related symptoms or using the Convergence Insufficiency Symptom Survey (CISS)[2-4] (Figure 2, see below) is recommended when children have clinical signs of CI.

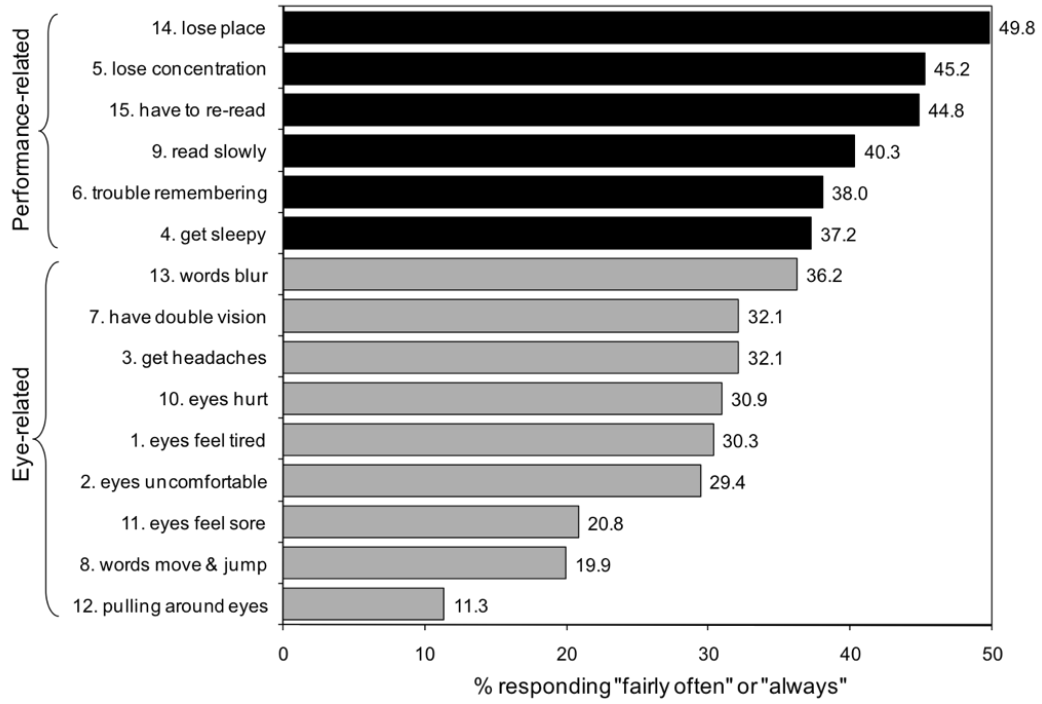

Figure 1. Percentage of 9 to17-year-old children with symptomatic CI who responded 'fairly often' or 'always' to each item on the CISS before treatment in the CITT Study. Black color indicates performance-related symptoms and gray color indicates eye-related symptoms.[1]

Figure 2. Convergence Insufficiency Symptom Survey

Name _____

Clinician instructions: Read the following subject instructions and then each item exactly as written. If subject responds with "yes" - please qualify with frequency choices. **Do not give examples; only repeat the item**. Place an "X" in the appropriate box.

Subject instructions Please answer the following questions about how your eyes feel when reading or doing close work. First think about whether or not you have the symptom. If you do, please tell me whether the problem occurs: Infrequently (not very often), Sometimes, Fairly Often, or Always.

		Never	Infrequently	Sometimes	Fairly often	Always
1.	Do your eyes feel tired when reading or doing close work?					
2.	Do your eyes feel uncomfortable when reading or doing close work?					
3.	Do you have headaches when reading or doing close work?					
4.	Do you feel sleepy when reading or doing close work?					
5.	Do you lose concentration when reading or doing close work?					
6.	Do you have trouble remembering what you have read?					
7.	Do you have double vision when reading or doing close work?					
8.	Do you see the words move, jump, swim or appear to float on the page when reading or doing close work?					
9.	Do you feel like you read slowly?					
10.	Do your eyes ever hurt when reading or doing close work?					
11.	Do your eyes ever feel sore when reading or doing close work?					
12.	Do you feel a "pulling" feeling around your eyes when reading or doing close work?					
13.	Do you notice the words blurring or coming in and out of focus when reading or doing close work?					
14.	Do you lose your place while reading or doing close work?					
15.	Do you have to re-read the same line of words when reading?					
Total the number of "X"s in each column						
Multiply by the column value (0-4)		x0	x1	x2	x3	x4
Sum 5 values						

SCORE _____

CONVERGENCE INSUFFICIENCY SYMPTOM SURVEY (CISS)

The CISS, as shown in Figure 2, is a symptom questionnaire that was designed to quantify the severity of symptoms associated with CI.[2-4] It was developed by the CITT study group to assess changes in symptoms associated with treatments for CI so that it could be used as the primary outcome measure for studies on CI. A revised version improved upon the original version and subsequent evaluations of the survey confirmed its validity and reliability.[2-4] The revised version was used for all of the CITT studies.[5-9] The CISS is comprised of 15 items that query the patient in regard to symptoms experienced when reading and doing close work. The items are read aloud verbatim and in sequential order to the patient who views a card containing a Likert-type scale of 5 possible response options (never, infrequently, sometimes, fairly often, or always). The patient responds verbally as the examiner documents the patient's response for each question. If the patient does not understand or asks for further explanation, the examiner repeats the question verbatim without clarification and asks the patient to select one of the response options. When administration is completed, the examiner scores each item as 0 (never) to 4 points (always) and then sums the scores to obtain the total CISS score. The lowest possible score (least symptoms; a 'never" response for all items) is 0 and highest possible score is 60 (most symptomatic; an "always" response for all items). In children, a score of ≥16 is considered 'symptomatic' and can be used to differentiate normal from abnormal levels of symptoms associated with CI. For young adults, a score of ≥ 21 is used. In addition to its usefulness in quantifying symptoms in research studies, the CISS can be used in clinical practice. If CI is identified during the clinical examination, then the CISS can be administered to determine the severity of symptoms and to serve as a baseline measure if treatment is to be undertaken. Alternatively, the CISS can be administered at initial intake, and for patients whose scores indicate symptoms in excess of normal (≥16 and ≥ 21 in children and young adults, respectively), testing to rule out CI or other binocular vision disorders can be administered.

DIAGNOSTIC CONSIDERATIONS

CI is diagnosed when a patient has a larger exodeviation at near than at far, combined with a remote near point of convergence (NPC) and/or decreased positive fusional vergence at near (PFV) (i.e., convergence amplitudes). The exodeviation can be phoric or tropic, and when tropic the exotropia is typically intermittent. Individuals with symptomatic CI do not always have both a remote NPC and decreased PFV; however, for clinical studies it is prudent that both criteria be present to prevent doubts regarding the validity of the diagnosis of CI. The CITT study definition of CI[7] is used clinically by many pediatric eye care providers:

1. Exophoria at near at least 4r greater than at distance
2. A receded NPC of ≥ 6cm break.[10]
3. Insufficient PFV – i.e., failing Sheard's criterion[11] (less than twice the magnitude of the deviation) or ≤ 15r base-out blur point (break point if no blur)

Patients in need of an optical correction should be tested with their correction in place. The NPC is easily measured using the accommodative/convergence rule (Bernell, Mishawaka, IN). After gently placing the centimeter-marked rod against the patient's forehead and securing a small card with a vertical column of 20/30 letters at the 40cm mark on the rod, the examiner slowly moves the target closer to the patient's eyes until diplopia is reported or the examiner observes loss of fusion. PFV is measured with a horizontal prism bar while the patient views a vertical column of 20/30 print at 40cm. As larger increments of prism are slowly introduced before one eye, the patient is asked to report when the line of letters becomes blurry or breaks into two. The PFV component used for diagnosis is the blur point (break point if the patient does not report blur). Some clinicians like to repeat the NPC and PFV measures, for example, performing 3 sequential measurements to determine if there is a fatigue effect.

WHAT IS VISION THERAPY (VT)?

The term vision therapy (VT) has negative connotations for some optometrists and ophthalmologists, presumably because it has been used as an umbrella term and been erroneously assumed or purported to treat a wide range of disorders, including non-visual conditions. First and foremost, vision therapy is prescribed to treat diagnosed conditions of the visual system. It is not a treatment for learning disabilities, dyslexia, ADHD, and the like. That said, children with learning, reading, or attention issues can also have disorders of visual function (such as CI), causing them to divide their attention between the reading/near task and any symptoms (e.g., diplopia, blur, loss of place) caused by the visual disorders – presumably, this could negatively impact efficient reading and near work. In these instances, among children with learning, reading, or attention problems who also have a diagnosed accommodative or vergence disorder, the intent of vision therapy is to treat the vision disorder with the goal of eliminating it as a potential obstacle to efficient reading or learning.

VISION THERAPY FOR OCULOMOTOR DISORDERS – INCLUDING CI

Vision therapy for oculomotor disorders, also referred to as vergence/accommodative therapy,[7] has its origins in the orthoptics field, with many of the techniques and instrumentation having evolved from those described and

popularized by ophthalmologists such as Javal, Worth, and Maddox in the late 19th and early 20th centuries. Vision therapy and orthoptics share a considerable number of clinical treatment techniques, with orthoptists providing orthoptic treatment prescribed by and executed under the supervision of an ophthalmologist, and vision therapists administering vision therapy prescribed by and implemented under the supervision of an optometrist. Currently, there appear to be two main differences: 1) therapy for the accommodative system and its interaction with the vergence system is emphasized much more in vision therapy programs, and 2) fewer orthoptists are providing therapeutic orthoptics nowadays, and those who do, are mainly prescribing home-based treatment because increased patient volume and decreased reimbursement have made office therapy impractical.[12]

Vision therapy for CI and other binocular vision anomalies consists of a sequence of activities that incorporate purposeful, controlled manipulation of target blur, disparity, and proximity, with the aim of normalizing the accommodative and convergence systems and their mutual interactions.[13] It is individually prescribed based on the results of a sensorimotor evaluation and monitored by the eye care professional. Lenses, prisms, filters, specialized instruments such as stereoscopes, and computer programs play an integral role in vision therapy. Vision therapy can be home-based or office-based, the latter usually administered by a trained therapist with oversight by the doctor. Therapy activities that parallel in-office techniques are typically taught to the patient to be practiced at home. The number of office visits depends on the severity of the diagnosed condition as well as the patient's adherence with home therapy; the length of the program for an uncomplicated CI case typically ranges from 2 to 4 months. The ultimate goal of vergence/accommodative therapy is not only to impact positively the oculomotor system per se, but for the patient to attain consistently clear and comfortable binocular vision.

GENERAL PRINCIPLES OF ACCOMMODATIVE/VERGENCE THERAPY FOR CI

One of the primary goals of therapy for CI is to increase fusional convergence amplitudes. To achieve this, therapy procedures are designed to maintain accommodation at the plane of regard while the vergence stimulus is altered, or to maintain vergence at the plane of regard while the stimulus to accommodation is altered.[14,15] Generally, the vergence demand is increased while the patient maintains clarity of the target. For example, let's assume that we want to train fusional convergence using polarized vectogram targets. The 2 targets (one seen by the right eye and the other by the left eye) would be placed approximately 40cm from the patient, and the patient instructed to keep the targets clear (thus holding accommodation constant). To train convergence, the plane of vergence is moved closer to the patient by laterally separating the targets such that the target seen by the right eye is moved to the left and the target seen by the left eye is moved to the to the right. As the targets are laterally separated, the plane of vergence is separated from the plane of accommodation, creating an increase in the fusional convergence demand. With accommodation held constant, accommodative convergence is inhibited, and thus the only way to generate more convergence to meet this new increase in vergence demand is to use fusional convergence. Another way to alter vergence demand is to maintain vergence at the plane of regard while changing the accommodative demand. This can be accomplished by placing a pair of plus lenses in front of the patient's eyes - thus creating an increase in convergence demand from the relaxation of accommodation. If one uses flipper lenses, with one side having a pair of plus lenses and the other side a pair of minus lenses, not only will there be a change in the accommodative demand, but a subsequent change in vergence demand will occur each time the patient alternately views through the plus and minus lenses. There are numerous therapy instruments and procedures that can be used for the purpose of creating various accommodative or vergence demands.

Home-based therapy procedures that parallel the in-office techniques are typically taught to the patient to be practiced at home, often for 15 to 20 minutes per day. Proponents of office-based therapy believe that the combination of office-based treatment supplemented by home-based therapy is more likely to be successful than therapy performed solely at home. First, there is the impression that patients are more likely to comply with prescribed treatment when they know they have to report back the following week. In addition, office-based therapy presents more opportunities for the patient to benefit from motor learning. Defined as a set of internal processes that are associated with practice or experience leading to relatively permanent changes in responding,[16] motor learning is an essential form of learning that appears to share common mechanisms across different motor systems.[17] With motor learning, the learner acquires a new skill (accurate and appropriate motor response) through practice and assimilation, with the skill becoming more permanent, and ultimately transferring outside of the therapy setting. Of motor learning determinants (e.g., feedback, modeling and demonstration, variability in practice, positive reinforcement, and transfer of training) practice and feedback are thought to be the most potent. Because these motor learning determinants are more consistently present when working one-on-one with a therapist, some feel that including office-based therapy is more likely than home-based therapy to result in a permanent change in the dynamics of fusional vergence and accommodation.[18]

CITT THERAPY PROTOCOLS

The office-based vergence/accommodative therapy (OBVAT) protocols for CITT and the on-going CITT-Attention & Reading Trial (ART) study[9] are shown in Figure 3, see page 500, and Table 2, see page 500, respectively. The overall treatment sequence for these studies is a well-accepted approach for the treatment of CI[14,15] and consists of both vergence and accommodative therapy procedures. Because many children with CI have associated accommodative disorders[14,19] and because the stimulation of one system affects the other, the protocols include both vergence and accommodative therapy procedures.

The therapy techniques are designed such that stimulus parameters can be manipulated with resultant changes in the patient's accommodative or vergence demand. Retinal blur and retinal disparity are the primary stimuli for the accommodative and vergence systems, respectively. Thus, in vision therapy, lenses and target distance from the patient are used to manipulate accommodation, whereas disparity and hence vergence is manipulated via prisms, mirrors, and target separation. The goal of therapy is not only to improve convergence amplitudes but also to improve the dynamics (speed of response) of the fusional vergence and accommodative systems.

One of the main differences among the 3 CITT therapy modalities (home-based pencil push-ups, OBVAT, and home-based computerized therapy combined with pencil push-ups) is their ability to allow manipulation of stimulus parameters. For example, when performing pencil push-ups, a combination of proximal, accommodative, and fusional vergence is used, with accommodation and convergence synchronized; fusional vergence cannot be isolated. In contrast, the OBVAT program is comprised mainly of procedures that require steady accommodation while the vergence demand is increased. Accordingly, because proximal and accommodative vergence are minimized, the increased vergence demand must be furnished by fusional vergence. Thus, fusional vergence is trained separately and directly, using numerous procedures with varied stimulus parameters. Home-based computer exercises provide an intermediate level of manipulation of the accommodative-convergence relationship, but lack the variety of procedures that an OBVAT program offers as well as therapist feedback. It is possible that these factors may have contributed to the poorer success rates of the pencil push-up and home-based computer therapy groups in the CITT studies.[5,7,20]

ARE THE RESULTS OF TREATMENT FOR CI STABLE IN THE LONG TERM?'

The long-term stability of improvements in symptoms and clinical signs after completing treatment for symptomatic CI were evaluated 1-year post treatment among the CITT participants who were classified as asymptomatic (CISS score <16).[21] Of the 79 subjects classified as asymptomatic at the primary outcome examination, 70 (89%) of these returned for their 1-year follow-up. Improvements in all groups were generally sustained, although the placebo group and 2 home-based groups were quite small in size (n=10) (Table 1). Long-term comparison data from other trials are not available.

Table 1. CITT 1-Year Results for Those Classified as Asymptomatic at Outcome

Therapy Group	n	% Asymptomatic	% Successful or Improved
OBVAT	32	84% (27/32)	88% (28/32)
HB Computer & PPU	10	80% (8/10)	80% (8/10)
OB Placebo VT	10	77% (10/13)	69% (9/13)
HB Pencil-Push-ups	10	67% (10/15)	67% (10/15)

% successful = CISS <16, normal NPC, & normal PFV; improved = CISS <16 or ≥10-point decrease from baseline & at the least 1 of following: normal NPC, improved NPC of > 4 cm, normal PFV, or increase of ≥10Δ in PFV.

NEURAL MECHANISM BY WHICH VERGENCE TRAINING LEADS TO A REDUCTION IN VISUAL SYMPTOMS

The mechanism by which vergence training leads to a reduction in symptoms is currently unknown. However, promising studies are in the works. In a recent fMRI study of vergence therapy on 4 adult patients with CI, Tara Alvarez and colleagues found that at baseline the CI subjects had significantly reduced convergence peak velocity to 4° symmetrical convergence steps and BOLD percent signal change within the frontal eye fields, posterior parietal cortex, and cerebellar vermis compared to subjects with normal binocular vision.[22] After undergoing repetitive vergence therapy, an increase in the functional activity of the frontal eye fields, posterior parietal cortex, and the cerebellar vermis was evident, which could in part, lead to the increase in convergence peak velocity to symmetrical step stimuli.

In another recent study, which used an objective assessment of disparity vergence before and after completing OBVAT for concussion-related CI, Scheiman et al.[23] found a statistically significant increase in peak velocity, response accuracy to 4° symmetrical convergence and divergence step stimuli, and the main sequence ratio for convergence step stimuli. These studies and others will provide information in regard to the underlying physiological mechanisms that lead to changes in clinical findings and symptoms in patients with CI.

Table 2. CITT-ART OBVAT Protocol

	Phase 1		Phase 2		Phase 3	
	O	H	O	H	O	H
Gross Convergence						
Brock String	✓	✓				
Barrel Card	✓	✓				
Fusional Vergence*						
Clown & Quoits Vectograms	C		R		J	
Computer Orthoptics (RDS)	C	C	R	R	J	J
Life Saver Cards	C	C				
Aperture Rule			R		J	
Eccentric Circles			R	R	J	J
Random Dot Card				R		J
Loose Prism Vergence Facility					J	J
Accommodative						
Monocular Loose Lens Facility	✓	✓	✓	✓		
Monocular Letter Chart Facility	✓	✓	✓	✓		
Binocular ± 2.00 D flipper Facility					✓	✓

RDS = random dot stereograms: O = office therapy; H = home therapy; C = techniques emphasize convergence amplitudes (positive fusional vergence) only; R = ramp/smooth positive & negative fusional vergence procedures; J = jump vergence procedures, some with added prism; mainly change from convergence to divergence demand; some from no vergence demand to a moderate convergence or divergence demand

CME ANSWERS

1. a
2. d
3. b

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North American Neuro-Ophthalmology Society

43rd Annual Meeting

April 1 – April 6, 2017
Washington Marriott Wardman Park • Washington, DC

Program Schedule

THURSDAY, APRIL 6

6:30 am - 12:00 pm	**Registration/Help Desk**	**Thurgood Marshall Foyer**
6:30 am - 7:30 am	**Breakfast**	**Exhibit Hall C**
7:30 am - 9:30 am	**Neuro-Ophthalmologic Side Effects of More Recently Used Medications in Treating Cancer, Rheumatologic Disorders, and Multiple Sclerosis [2 CME]** *Moderators: Rod Foroozan, MD and Judith E. A. Warner, MD*	**Thurgood Marshall Ballroom**

This symposium includes a brief case-based overview of Neuro-Ophthalmic complications limited to new or more recently used systemic medications (including an update from a NANOS platform symposium of 2010 which discussed side effects of chemotherapeutic agents). Participants will recognize relevant potential side effects of systemic medications they may encounter in clinical practice, directed to ophthalmic and Neuro-Ophthalmic issues. The symposium will focus on medications developed more recently in the treatment of epilepsy, cancer, rheumatologic disorders, and multiple sclerosis.

Upon completion of this course, participants will be able to: 1) Learn the frequency of visual deficits in patients with refractory epilepsy; 2) List the newer agents used to treat multiple sclerosis, cancer, and rheumatologic disease; and 3) Link the side effects of each agent to the expected Neuro-Ophthalmic finding.

		PAGE
7:30 am - 7:50 am	**Introduction and Lessons from Vigabatrin,** *Rod Foroozan, MD*	**505**
7:50 am - 7:55 am	**Q & A**	
7:55 am - 8:25 am	**Neuro-Ophthalmic Side Effects of New Cancer Drugs,** *M. Tariq Bhatti, MD*	**509**
8:25 am - 8:35 am	**Q & A**	
8:35 am - 8:55 am	**Side Effects of New Immuno-Modulators**, *Ore-ofe Oluwaseun Adesina, MD*	**527**
8:55 am - 9:00 am	**Q & A**	
9:00 am - 9:20 am	**Neuro-Ophthalmic Consequences of Medications for Multiple Sclerosis: The Good, The Bad, The Ugly and The Unknown,** *Heather E. Moss, MD, PhD*	**533**
9:20 am - 9:25 am	**Q & A**	
9:25 am - 9:30 am	**Closing Remarks**, *Rod Foroozan, MD and Judith E. A. Warner, MD*	

9:30 am - 10:00 am	**Coffee Break**	**Thurgood Marshall Foyer**
10:00 am - 12:00 pm	**Eye Movement Challenge: The Advanced Level [2 CME]** *Moderators: Jason S. Barton, MD, PhD, FRCPC and William A. Fletcher, MD, FRCPC* *Panelists: David S. Zee, MD, Caroline Tilikete, MD, PhD, and Michael C. Brodsky, MD*	**541** **Thurgood Marshall Ballroom**

This symposium will use a case-based format rather than didactic lectures. There will be two 50-minute sessions, each comprising several brief case presentations of unusual eye movements. For each case, a panelist will present a short history and video, followed by questions for the audience. The other panelists may comment briefly on the salient clinical features. The presenting panelist will conclude with the diagnosis and a brief summary of the condition. At the end of each session there will be a 10-minute question period.

Upon completion of this course, participants should be able to: 1) Recognize and diagnose uncommon ocular motor disorders; 2) Localize uncommon oculomotor disorders; and 3) Describe the pathophysiology of uncommon oculomotor disorders.

INTRODUCTION AND LESSONS LEARNED FROM VIGABATRIN

Rod Foroozan, MD

Baylor College of Medicine
Houston, TX

LEARNING OBJECTIVES

1. Describe the mechanism of action of vigabatrin and the relationship to retinopathy
2. Explain the frequency of visual deficits in the vigabatrin registry and phase IV vision study
3. Estimate the frequency of visual deficits in patients with refractory complex partial seizures treated with vigabatrin

CME QUESTIONS

1. What percentage of patients had baseline deficits involving the visual pathways in the vigabatrin registry and phase IV vision study?

   a. 5%
   b. 33%
   c. 65%
   d. 90%

2. The mechanism of action of vigabatrin is best characterized as:

   a. Increasing sodium channel activity
   b. Increasing gamma-aminobutyric acid activity
   c. Increasing potassium channel activity
   d. Increasing calcium channel activity

3. The vigabatrin phase IV vision study is best characterized as:

   a. A retrospective, case control study
   b. A retrospective, cross-sectional study
   c. A prospective, longitudinal open-label study
   d. A prospective, randomized study

KEYWORDS

1. Vigabatrin
2. Visual field defect
3. Refractory complex partial seizures
4. Infantile spasms
5. Retinopathy

ABSTRACT

Vigabatrin was introduced as an anti-seizure medication in the United Kingdom in 1989 and was extensively used until 1997 when concerns for peripheral visual field defects emerged. When the drug was approved in the United States in 2009 it carried a black box warning for the risk of permanent visual loss and the pharmaceutical company was mandated to create a drug registry to assess for visual deficits. The vigabatrin drug registry has documented a relatively large percentage (37%) of pre-existing, baseline visual deficits involving the visual system and a paucity (2%) of potential new visual findings. The vigabatrin vision study, a prospective, longitudinal, single-arm, open-label study, confirmed that adult patients with refractory complex partial seizures had a large number (around 33%) of visual deficits at baseline, and a single patient who developed bilateral peripheral field constriction about one year after therapy. An unexpected finding during this first year of therapy with vigabatrin was an increase in retinal thickness on optical coherence tomography. The experience from vigabatrin in the United States emphasizes the importance of baseline eye findings when considering the potential for drug toxicity involving the visual pathways.

INTRODUCTION

It is often difficult to determine the validity of reported toxicity attributed to a drug and a neuro-ophthalmic abnormality. In some cases, the patient has received combination therapy, such as surgical resection and medical therapy, and in other cases, the complications are not the focus of the report. Some manuscripts consist of individual anecdotal case reports; in others, the evaluation or at least the description of findings is incomplete. Furthermore, the source of the reports in these patients may be varied, including from literature focused on genetics, neurosurgery, neurology, and ophthalmology.

A cause and effect relationship based on the scientific method is often not achievable based on the available literature. This is in part because the precise mechanisms which result in neuro-ophthalmic toxicity are not clear for many agents. In many instances the reader would be advised to review the literature and decide for themselves whether the evidence supports a cause and effect relationship or even an association between a therapeutic agent and side effect.

HISTORY OF VIGABATRIN DEVELOPMENT AND USE

Vigabatrin, an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), was one of the first "designer drugs" used to treat seizures.[1] It was felt that by increasing GABA levels most seizures could be eliminated.

Vigabatrin was approved in the United Kingdom in 1989 for monotherapy in the treatment of infantile spasms (IS) and as adjunctive therapy for refractory complex partial seizures (CPS).[1] From 1989 to 1997 around 140,000 prescriptions were written.[2]

Effective treatment for IS early in the clinical course is critical to permit the best possible intellectual development; IS has a high mortality rate and frequently is a precursor of other forms of epilepsy and developmental delay. Treatment with vigabatrin can result in rapid cessation of seizures (often within 24 hours) and has been reported to induce complete absence of spasms by age 14 months in 76% of infants.[3-5]

Given that about one third of patients with epilepsy fail to achieve complete seizure control with approved antiepileptic drugs (AEDs), refractory CPS represents another area of significant unmet need for treatment. Without adequate seizure control, these patients suffer from the debilitating effects of uncontrolled epilepsy, which include a 4- to 7-fold increase in mortality (including from **SUDEP** - the sudden, unexpected death of someone with epilepsy), an increased rate of depression, the inability to drive, and a significant negative effect on quality of life.[6] In more than 50% of adults with refractory CPS, the addition of vigabatrin (3 g/day) resulted in a significant decrease in the frequency and severity of seizures and in complete seizure freedom in around 10%.[7,8]

Vigabatrin was known to cause retinopathy in animal models documented by electrophysiologic studies and by histopathology. GABA is used in the retina as a neurotransmitter. Evidence has suggested that vigabatrin-induced increases of GABA within the retina[9] may cause retinal atrophy through an excitotoxic mechanism.[10]

Despite its proven efficacy, the use of vigabatrin was limited by the associated risk of developing retinopathy characterized by irreversible, bilateral, concentric peripheral visual field constriction (usually more pronounced in the nasal visual field), an adverse reaction to the drug first reported in 1997.[11] Based on reports from European investigators of a vigabatrin-induced peripheral visual field defect (pVFD), the FDA rescinded its approvable letter for vigabatrin until further data were provided to substantiate a favourable benefit-risk assessment.

PRIOR LITERATURE ON THE EXPERIENCE OF VIGABATRIN-RELATED VISUAL DEFICITS

Subsequently, several reports have described this pVFD in vigabatrin-treated patients and have suggested it may occur in a variable number of treated patients (reported range, 14%–92%).[12-16] This broad range of occurrence is due to the variability in criteria and visual field test used to define a pVFD, as well as the dose and duration of treatment evaluated. The risk of developing a pVFD was most commonly correlated with the duration and dose of vigabatrin therapy.[17]

The chief problem with prior studies assessing the frequency and severity of visual deficits related to vigabatrin is that they are cross-sectional and without baseline assessments of visual function. Furthermore, detailed assessments of patients with epilepsy had not focused on visual function and evidence has suggested there may be an impact of epilepsy on the visual pathways.[18]

Ancillary testing using electrophysiology and imaging techniques (including optical coherence tomography) of the retina and optic disc has also shown abnormalities in patients who took vigabatrin.[19,20]

Final data analysis assessed by the FDA suggested that vigabatrin causes permanent, bilateral, concentric visual field constriction in 30% or more of patients that ranged from mild to severe. While there was very limited information to suggest that visual deficits develop rapidly after initiation of therapy, the approval of vigabatrin in the United States in 2009 was contingent on the inclusion of a black box warning for permanent visual loss.[21]

The FDA approval of vigabatrin was accompanied by a Risk Evaluation and Mitigation Strategy (REMS), a comprehensive program designed to reduce the risk of vigabatrin-induced vision loss, while providing risk–benefit analyses for appropriate patient populations, which included baseline eye examinations.[22]

FDA MANDATED VIGABATRIN REMS IN THE UNITED STATES FROM 2009 TO 2016

Nearly 9500 patients were enrolled in the vigabatrin drug registry from 2009 to 2016.[2,23] All prescribers were required to have a signed ophthalmologic assessment form (OAF) which recorded ophthalmologic assessments or the reason why a patient was exempted from testing (e.g., the patient's general neurologic conditions that precluded the need for vision assessment, patient blindness, co-morbid condition(s) preventing vision evaluation, or "other" reasons). The OAF forms, while reviewed by the pharmaceutical company, did not undergo independent neuro-ophthalmologic review. Nearly 30% of patients enrolled in the vigabatrin drug registry were exempted from ophthalmologic testing.

Detailed ophthalmologic testing results were sent to the drug registry on 1509 patients. Of these, 565 (37%) of all patients reviewed showed existing clinically significant pathology that was assessed as not related to vigabatrin. Most commonly, patients' testing showed visual field loss, optic disc pallor, abnormal retinal imaging, or abnormal electrophysiology, all a reflection of the effects of their underlying condition and prior therapy (such as neurosurgery) on vision. Ophthalmologic data review identified 30 patients (2.0%) with a potential vigabatrin associated effect on vision.

PHASE IV VIGABATRIN VISION STUDY

The vigabatrin vision study 13098A (NCT01278173) was a prospective, longitudinal, single-arm, open-label study of adult patients 18 years and older.[24] Ophthalmologic assessments were conducted at baseline, prior to vigabatrin administration, 26 days after receiving vigabatrin, 2-28 days after the second visit, and at months 3, 6, 9 and 12 after staring therapy. Assessment included Humphrey automated perimetry (30-2 Swedish Interactive Threshold Algorithm [SITA: Standard of FAST programs]), horizontal meridian test (middle peripheral fields), tangent corner test (far peripheral fields) spectral-domain optical coherence tomography (SD OCT) of the retinal nerve fiber layer (RNFL), visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) measures.

Primary endpoints included perimetry: mean change from reference value in mean deviation (dB) and SD OCT: mean change from reference value in average RNFL thickness (μm). Exploratory endpoints included:

- Change in visual acuity from baseline
- Percentage of patients meeting any of the following criteria for potentially clinically significant vision change in at least one eye at 2 or more consecutive visits:

Perimetry

A) Change in mean deviation > 3.0 dB as measured by automated static perimetry central 30 degree fields

B) Change in binocular visual field along the horizontal meridian (middle of the peripheral fields) based on the central readers' interpretation of the test results

C) ≥ 20 degree constriction of the mean linear measurement of the tangent corner test

SD OCT

A) Decrease in average RNFL thickness (μm) > 20%

B) Decrease of any of the measured sectors of the macula (μm) 20%

C) Decrease in total macular volume (cubic mm) > 10%

65 patients were enrolled and 38 completed the study. Twenty-one (32%) had abnormally thinned RNFL on SD OCT, 13 (20%) had abnormal perimetry, and 10 (15%) had reduced visual acuity at baseline.

There were no statistically significant mean changes in central 30 degree visual field measurements compared to reference values. Compared to reference values the average RNFL thickness increased significantly. No patient had a confirmed 3 line or more decrease in visual acuity at two or more consecutive visits. One patient developed asymptomatic bilateral visual field constriction at month 12.

CONCLUSION

The experience with vigabatrin in the United States has shown a relative paucity of new visual deficits compared to what was anticipated when the drug received approval by the FDA in 2009. Neither the drug registry nor the phase IV vision study has revealed patients with symptomatic visual loss attributed to vigabatrin. It is likely that this experience contributed to the FDA decision to alter the vigabatrin REMS. As of July 21, 2016 the language in the package insert regarding eye examinations to monitor for drug toxicity was changed from "required"[21] to "recommended."[25] The clinical experience emphasizes the difficulties inherent in studying drug toxicity using cross-sectional studies without baseline eye examinations.

CME ANSWERS

1. b
2. b
3. c

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NEURO-OPHTHALMIC SIDE EFFECTS OF NEW CANCER DRUGS

M. Tariq Bhatti, MD

Duke Eye Center and Duke University Medical Center
Durham, NC

LEARNING OBJECTIVES

1. List the currently FDA approved molecularly targeted and immune checkpoint inhibitor cancer drugs and understand their mechanism of actions
2. Identify the neuro-ophthalmic toxicity profile of the molecularly targeted and immune checkpoint inhibitor cancer drugs
3. Incorporate the material presented to work in concert with the prescribing oncologist to formulate a management strategy to mitigate neuro-ophthalmic toxicity and optimize cancer treatment

CME QUESTIONS

1. Which of the following ophthalmic disorders has been associated with aromatase inhibitors?

    a. Orbital inflammation
    b. Optic neuritis
    c. Papilledema
    d. Retinal hemorrhage

2. Which of the following cancer agents targets CTLA-4?

    a. Ipilimumab
    b. Rituximab
    c. Alemtuzumab
    d. Trastuzumab

3. Immune-related adverse events are commonly associated with which one of the following cancer drug inhibitors?

    a. Checkpoint
    b. Aromatase
    c. Janus kinase
    d. Mitogen-activated protein kinase kinase

KEYWORDS

1. Cancer drugs
2. Immune checkpoint inhibitors
3. Molecularly targeted therapy
4. Toxicity
5. Immune-related adverse events

ABSTRACT

"Cancer can take away all my physical abilities. It cannot touch my mind, it cannot touch my heart and it cannot touch my soul." *-Jim Valvano May 4, 1993*

War is a recurrent and unfortunate record in the history of human civilization that has culminated in indescribable violence and unspeakable death. However, amazingly within the confines of war have risen some of the greatest advancements in medicine (such as the intraocular lens by Sir Harold Ridley). It is within this context—in particular World War II with the study of mustard gas—that the annals of cancer chemotherapy began touching the lives of millions of people. It is estimated that in 2016, over 1.5 million people in the United States (US) will be diagnosed with cancer and of those nearly half a million will die. The amount of money being spent on research and development of new cancer therapies is staggering with a record $43 billion dollars spent in 2014. Nearly 30% of all registered clinical trials on the clinicaltrials.gov website pertain to cancer drugs. Such large numbers emphasize the urgency of finding a cure for cancer.

From over a century ago, Ehrlich's concept of a "magic bullet" to cure human disease seems to be far closer to reality than fantasy, due to our improved understanding of the cellular, molecular and genetic processes involved in human pathology. The past 2 decades has been an amazing time in the advancement of cancer treatment. Molecularly targeted therapy is a concept in which specific cellular molecules (overexpressed, mutationally activated or selectively expressed proteins) are manipulated in an advantageous manner to decrease the transformation, proliferation and/or survival of cancer cells. In addition to molecularly targeted therapy, advancements in our knowledge of the role of the immune system have led to the development of immune checkpoint inhibitors to restore and enhance cellular-mediated antitumor immunity. The US Food and Drug Administration (FDA) approval of the monoclonal antibody (mAb) rituximab in 1997 for the treatment of B cell non-Hodgkin lymphoma heralded the era of targeted therapy for cancer. A year later, trastuzumab, an anti-Her2 (Epidermal Growth Factor Receptor 2) mAb, was approved for patients with metastatic breast cancer. In 2001, imatinib was the first small molecule kinase inhibitor approved by the FDA followed in 2011 by ipilimumab, the first approved immune checkpoint inhibitor. Anastrozole, the first of three 3rd generation aromatase inhibitors (AIs), was approved in 2002.

Despite the notion that increased tumor specificity results in decreased complications, toxicity remains a major hurdle in the development and implementation of many of the targeted cancer drugs. Not only can there be a large financial burden on the healthcare system from these toxicities, but the impact on the individual patient can range from a self-limited and benign condition to a relentless and malignant process. This presentation will provide an overview of the current cellular and immunological understanding of cancer pathogenesis—the foundation upon which molecularly targeted therapies were developed—and a description of the neuro-ophthalmic toxicity profile of selected mAbs, immune checkpoint inhibitors, small molecule kinase inhibitors, and 3rd generation AIs.

INTRODUCTION

Within the context of co-morbid systemic diseases and expectations of the patient, the oncologist has a wide variety of treatment options to choose from based on the histological type, molecular marker and clinical stage of cancer (Table 1).

Table 1: CATEGORY OF CANCER THERAPIES
Bolded categories represent therapy modalities discussed in text.

I. Radiotherapy

II. Surgery

III. Standard (traditional) cytotoxic chemotherapy

IV. Molecular targeted therapy

- **Monoclonal antibody**
  - Unconjugated (naked)
  - Conjugated (antibody-drug conjugate)
  - Bispecific
- **Small molecule kinase inhibitor**
- **Hormonal therapy (3rd generation aromatase inhibitor)**
- Antisense oligodeoxynucleotide
- Recombinant peptide
- Recombinant IgG immunotoxin

V. Immunotherapy

- **Immune checkpoint inhibitors**
- Biologics-Cytokines (i.e. interferon, interleukin)
- Cell based therapies
- Vaccines
- Adoptive cellular transfer
- Oncolytic virus

Since its first clinical application in the early 1940s, cytotoxic chemotherapy has been the mainstay of medical treatment for cancer. However, in the past 2 decades a molecularly targeted approach has become the new cancer treatment paradigm and it appears that in the not too distant future the implementation of personalized treatment will be the standard of care.[1] Much has been learned about normal cell development, differentiation, survival, proliferation and ultimate death; which has in turn increased the knowledge and understanding of carcinogenesis. However, there is still much that is not understood about the epigenetic mechanisms in cellular transformation to cancer and the complicated interplay between the immune system and cellular regulation. It should be kept in mind that the financial impact of targeted cancer therapies has been enormous both in terms of sales (profit) and health care cost.[2]

Efficacy is a major goal in cancer drug development. However, safety and toxicity often lead to either limited use of a drug or prevent the utilization of a drug in clinical practice. Despite a very arduous, comprehensive and costly process of drug research and development culminating in approval by the United States Food and Drug Administration (FDA),[3] the reporting of adverse events (AEs) from clinical trials and other databases remains inconsistent and often difficult to interpret.[4,5] In a study that reviewed the results of randomized control trials (RCTs) and updated package inserts (drug label) of targeted cancer drugs, nearly 40% of serious AEs were not published in the initial RCT paper and approximately 50% of the serious AEs were not included in the initial package insert.[6] The financial and medical burden of cancer drug toxicity and AEs is enormous.[7,8] In many cases it can be difficult to ascertain the true cause and effect of an AE because of its rarity and the fact that there may be confounding factors—such as the combination of medical therapy or radiation therapy—in the treatment regimen of patients.

Dr. Rod Foroozan reviewed the neuro-ophthalmic complications of chemotherapy at the 2010 36th annual NANOS meeting in Tucson, AZ. This review aims to add to that excellent presentation by providing an overview of the current cellular and immunological understanding of carcinogenesis— the foundation upon which molecularly targeted therapies were developed—within the framework of discussing the neuro-ophthalmic toxicity profile of selected monoclonal antibodies (mAbs), immune checkpoint inhibitors, small molecule kinase inhibitors and 3rd generation aromatase inhibitors (AIs).

Multiple resources were enlisted to gather the necessary the information and data for this presentation. A detailed PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) was performed as well as a Google search (https://www.google.com/) using the terms cancer treatment, monoclonal antibodies, immune checkpoint inhibitors, immunotherapy, chemotherapy, aromatase inhibitors, and small molecule kinase inhibitors. Additional searches

were done depending on the initial results retrieved. Case reports, case series and published RCTs were also reviewed when necessary. Additional information on individual cancer drugs was collected from the package insert, FDA Adverse Event Reporting System (FAERS; http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/) and Medwatch (http://www.fda.gov/Safety/MedWatch/default.htm).

MOLECULARLY TARGETED THERAPY

The approval of the first targeted mAb rituxamb in 1997 was the clinical starting point for molecularly targeted therapy in cancer.[9] Aside from surface receptors, other targets for this novel approach include intracellular signal proteins and metabolic molecules. Targeted therapy not only affects tumor cells but also immune cells (i.e. T and B cells) and vascular-stromal cells.[1,10]

MONOCLONAL ANTIBODIES

The clinical development of mAbs began in earnest in 1972 when Kohler and Meilstein published their ground breaking technique of producing murine mAbs.[11] This was followed in 1987 with the generation of a chimeric mAb.[12] With the use of XenoMouse technology, panitumumab was the first fully human mAb approved for use in 2006 (Figure 1, see page 518).[13] A variety of mAbs exist including uncongugated (naked), conjugated (attached to effector molecules such as cytotoxic drug, bacterial or plant toxin or radiopharmaceutical agents)[14] and bispecific.[15] Other antibody products include antibody-ligand fusion proteins 16 and immunoliposomes.[14] The nomenclature of mAbs follows a very specific characterization scheme (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies.page?). The elements that make up an antibody name are prefix + target/disease class infix + source infix + stem. Some commonly used target/disease class infixs include –tu/-t for tumors, -li/-l for immunomodulatory, and -ba/-b for bacterial. The source infix can be –zu for humanized, -o for mouse, -u for fully human, or -xi for chimeric. The stem is either –mab for monoclonal or –pab for polyclonal.

The use of mAbs has become one of the cornerstone treatments in the fight against cancer. There are currently 18 FDA approved mAbs on the market (Table 2).[17] It has been estimated that by the year 2020 the world-wide sales of mAbs will be approximately 125 billion dollars.[18]

Table 2: FDA APPROVED MOLECULARLY TARGETED CANCER THERAPIES

Monoclonal Antibodies: unconjugated (naked)

Generic Name	Trade Name/Company	Target molecule	FDA approval year
Alemtuzumab	Campath®, Genzyme	CD52	2001
Bevacizumab	Avastin®, Genetech/Roche	VEGF	2004
Cetuximab	Erbitux®, Bristol-Meyers Squibb	EGFR	2004
Elotuzumab*	Empliciti®, Bristol-Meyers Squibb	SLAMF7 (cell-surface glycoprotein CD2 subset 1)	2015
Obinutuzumab	Gazyva®, Genetech/Roche	CD20	2013
Ofatumumab	Arzerra®, Genmab	CD20	2016
Panitumumab	Vectibix®, Amgen	EGFR	2006
Pertuzumab	Perjecta®, Genetech	Her2	2012
Rituximab	Rituxan®, Genetech Mabthera®, Roche	CD20	1997
Trastuzumab	Herceptin®, Genetech	Her2	1998

* First in class humanized immunoglobulin G1 immunostimulatory monoclonal antibody

Monoclonal Antibodies: conjugated

Generic Name	Trade Name/Company	Target molecule	FDA approval year
Ado-trastuzumab	Kadcyla®, Genetch	HER2	2013
Brentuximab vedotin	Adcetris®, SeatleGenetics	CD30	2011
Ibritumomab tiuxetan	Zevalin®, Spectrum pharmaceuticals	CD20	2002

Table 2: FDA APPROVED MOLECULARLY TARGETED CANCER THERAPIES CONTINUED

Monoclonal antibodies: bispecific

Generic Name	Trade Name/Company	Type of kinase/Target molecule	FDA approval year
Blinatumomab	Blincyto®, Amgen	CD3 and CD19	2014

Immune Checkpoint Inhibitors

Generic Name	Trade Name/Company	Target molecule	FDA approval year
Atezolizumab	Tecentriq®, Roche	PD-L1	2016
Ipilimumab	Yervoy®, Bristol-Meyers Squibb	CTLA-4	2011
Nivolumab	Opdivo®, Bristol-Meyers Squibb	PD-1	2014
Pembrolizumab	Keytruda®, Merck	PD-1	2014

Small Molecule Kinase Inhibitors**

Type of kinase	Generic Name	Trade Name/Company	Target molecule	FDA approval year
Reversible non-receptor tyrosine				
	Bosutinib	Bosulif®, Wyeth	Bcr-abl	2012
	Dasatinib	Sprycel®, Bristol-Meyers Squibb	Bcr-abl	2007
	Imantinib	Gleevac®, Novartis	Bcr-abl	2001
	Nilotinib	Tasgina®, Novartis	Bcr-abl	2010
	Ponatinib	Iclusig®, Ariad Pharmaceuticals	Bcr-abl	2012
	Ruxolitinib	Jakafi®, Incyte Corporation	JAK	2011
Irreversible non-receptor tyrosine				
	Ibrutinib	Imbruvica®, Pharmacyclics Inc	BTK	2015
Reversible receptor tyrosine				
	Afatnib	Gilotrif®, Boehringer Ingelheim	EGFR, Her2	2013
	Axitinib	Inlyta®, Pfizer	VEGFR	2012
	Cabozantinib	Cometriq®, Exelixis	MET, VEGFR2	2012
	Ceritinib	Zykadia®, Novartis	ALK	2014
	Crizotinib	Xalkori®, Pfizer	ALK	2011
	Erlotinib	Tarceva®, OSI pharmaceuticals	EGFR, Her2	2013
	Gefitinib	Iressa®, AstraZeneca	EGFR, Her2	2015
	Laptinib	Tykerb®, GlaxoSmithKline	EGFR, Her2	2007
	Lenvatinib	Lenvima®, Eisai Inc	VEGFR	2015
	Nintedanib	Ofev®, Boehringer Ingleheim	VEGFR	2014 (idiopathic pulmonary fibrosis)
	Pazopanib	Votrient®, GlaxoSmithKline	VEGFR	2012
	Regorafenib	Stivarga®, Bayer	VEGFR	2012
	Sorafenib	Nexavar®, Bayer	VEGFR	2013

Table 2: FDA APPROVED MOLECULARLY TARGETED CANCER THERAPIES CONTINUED

	Sunitinib	Sutent®, Pfizer	VEGFR	2006
	Vandetanib	Caprelsa®, AstraZeneca	EGFR, VEGFR, RET	2011
Serine/threonine				
	Dabrafenib	Tafinlar®, GlaxoSmithKline	B-Raf	2013
	Palbociclib	Ibrane®, Pfizer	CDK	2015
	Trametinib	Mekinitst®, GlaxoSmithKline	MEK	2013
	Vemurafenib	Zelboraf®, Genetech	B-Raf	2011
Lipid				
	Idelalisib	Zydelig®, Gilead Sciences	PI3K	2014

**** Based on groupings from Wu P, Nielsen TE, Clausen MH. FDA-approved small-molecule kinase inhibitors. Trends Pharmacol Sci. 2015 Jul;36(7):422-39.**

Third Generation Aromatase Inhibitors

Generic Name	Trade Name/Company	Target Enzyme	FDA approval year
Anastrozole	Arimidex®, AstraZeneca	Aromatase (Estrogen synthetase)	2002
Exemestane	Aromasin®, Pfizer	Aromatase (Estrogen synthetase)	2005
Letrozole	Femara®, Novartis	Aromatase (Estrogen synthetase)	2004

Abbreviations:
ALK- Anaplastic lymphoma kinase
Bcr-abl- Breakpoint Cluster Region-Abelson
BTK- Bruton's Tyrosine Kinase
CD- Cluster of Differentiation
CDK- Cyclin-Dependent Kinase
CTLA-4- Cytotoxic T-Lymphocyte-Associated Protein 4
EGFR- Epidermal Growth Factor Receptor
EpCAM- Epithelial Cell Adhesion Molecule
Her2- Epidermal Growth Factor Receptor 2
JAK- Janus Kinase
MEK- Mitogen-activated Protein Kinase Kinase
MET- Hepatocyte Growth Factor Receptor
mTOR- Mammalian Target of Rapamycin
PD-1- Programmed Cell Death Protein **1**
PD-L1- Programmed Death Ligand 1
PI3K- Phosphoinositide 3-Kinase
RET- Rearranged During Transfection
SLAMF7- Signaling Lymphocytic Activation Molecule F7
VEGF- Vascular Endothelial Growth Factor
VEGFR- Vascular Endothelial Growth Factor Receptor

The mechanism of action (MOA) by which mAbs exert their anti-cancer effects is varied and includes apoptosis, activation or inhibition of a surface cell receptor, antibody-dependant cellular cytotoxicity (ADCC), and complement-dependant cytotoxicity (CDC). In addition mAbs can target tumor cells, immune cells (i.e. T cell or B cell) or vascular/stromal cells (Figure 2).[16,19,20]

The toxicity or AEs of a particular mAb is primarily related to its MOA and/or the unintended targeting of a cell or organ system.[21] Toxicity can be limited if the mAb is directed at a specific target on the neoplastic cell without affecting normal or healthy cells. The 4 general categories of mAb associated AEs are immune reaction (infusion reaction), excessive cytokine release or storm, immunosuppression and autoimmunity.[21,22]

In general terms, the ocular toxicity profile of mAbs is good. Several review papers have summarized the ocular AEs reported with mAbs.[23-27] Neurological side effects due to demyelination from mAbs have been associated with anti-tumor necrosis factor agents, none of which are approved for cancer therapy.[28] The following is a focused discussion of the neuro-ophthalmic complications associated with several selected mAbs.

Ado-trastuzumab
The conjugated mAb Ado-trastuzumab has been reported to cause dry eye, blurred vision, cataract formation, conjunctivitis, photophobia and lacrimal duct edema.[29]

Alemtuzumab
Alemtuzumab is a humanized IgG1 mAb that targets a variety of immune cells including B cells, T cells, and macrophages that express the cluster of differentiation (CD) 52 antigen. No specific ocular toxicities have been associated with alemtuzumab.

A unique AE associated with alemtuzumab is the increase in autoimmunity. The black box of the package insert indicates the fatal risks of pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia.[30] Post-marketing experience has identified several autoimmune disorders including Goodpasture syndrome, Graves disease, aplastic anemia, Guillain Barré syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy. The risk of Graves disease in cancer patients receiving alemtuzumab is not known but in multiple sclerosis patients it has been estimated to be approximately 20%.[31] Progressive multifocal leukoencephalopathy (PML) has been reported to occur in the setting of alemtuzumab therapy (see section on ritixumab).[32,33]

Bevacizumab
Bevacizumab, a humanized IgG1 mAb, targets vascular endothelial growth factor (VEGF) thereby preventing binding to the VEGF receptor (VEGFR), resulting in the inhibition and regression of the tumor vasculature.[34] Sherman et al, reported 5 patients who developed an optic neuropathy while recieving bevacizumab in addition to fractionated radiation therapy and temozolomide for glioblastoma.[35] In a meta-analysis, bevacizumab was found to be associated with a 3 fold higher risk of cerebral stroke and haemorrhage.[36] Posterior reversible encephalopathy syndrome (PRES), a disorder of cerebral vascular autoregulation resulting in vasogenic edema, has been reported with bevacizumab.[37]

Brentuximab vedotin
Brentuximab vedotin is a conjugated mAb against the cell surface protein CD30, used in Hodgkin lymphoma and anaplastic lymphoma, that has been associated with peripheral sensory neuropathy and PML.[38] There are no known ocular toxicities.

Cetuximab
Cetuximab is a chimeric IgG1 mAb that is an epidermal growth factor receptor (EGFR) inhibitor. EGFR is found in corneal epithelial cells and hair follicles, therefore the ocular side effects of cetuximab are related to the function of the inhibition of the receptor thereby causing keratitis, conjunctivitis, blepharitis and eyelash trichomegaly.[24,25,27]

Rituximab
Rituximab is a chimeric IgG1 mAb directed against CD 20, which is predominately found on B cells. Its MOA is not entirely known but is thought to work by ADC, ADCC and apoptosis. The package insert carries a black box warning regarding fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions and PML.[39] PML is an infectious demyelinating disease of the central nervous system caused by the polyomavirus John Cunningham (JC) virus associated with significant morbidity and mortality.[40] The exact pathophysiology is not known but it is believed to be due to the re-population of immature B cells that contain the JC virus.[41] Nearly a decade after receiving approval, in 2006 the FDA disseminated an alert to physicians regarding 2 patients with systemic lupus erythematosus (SLE) who developed PML following rituximab treatment (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126519.htm). The manufacturer of rituximab sent out 2 letters to physicians in 2008 describing the association of rituximab with PML.[41] Subsequently the package insert was modified with the addition of the risk of PML and the institution of a risk evaluation and mitigation strategy (REMS) plan.[42] The package insert indicates that the majority of patients developed PML within 12 months from the last infusion and that many of the patients were concomitantly treated with chemotherapy or a hematopoietic stem cell transplant.[39] The exact risk of developing PML in the setting of cancer treatment is not known, but the overall frequency has been estimated to be 1:30,000.[33]

Aside from rituximab, alemtuzumab and brentuximab vedotin the other mAbs associated with PML include bevacizumab, cetuximab, and ibritumomab tiuxetan.[43,44]

Trastuzumab
Trastuzumab is a humanized IgG1 mAb that targets the epidermal growth factor receptor 2 (Her2).[45] Dry eye, tearing, conjunctivitis and blurred vision have been reported with trastuzumab.[24] Saleh et al described a unique case of bilateral macular ischemia and edema in the setting of trastuzumab. However, the patient also received radiation and docetaxel therapy.[46] In the review by Huillard et al, papilledema, retinal hemorrhage, retinal artery occlusion and retinal vein occlusion have been reported with trastuzumab.[25]

IMMUNE CHECKPOINT INHIBITORS

Cancer immunotherapy relies on the strategy of actively manipulating one of the 3 basic steps in the generation and regulation of anti-tumor immunity (Figure 3, see page 520).[47] Immune checkpoint inhibitors are fundamentally different because of their unique MOA. Instead of a passive or an immunomodulatory role, immune checkpoint inhibitors activate the immune system by blocking the immune inhibitory pathways activated by cancer cells.[47-49]

There are currently four FDA approved immune checkpoint inhibitors (Table 2, see page 511-513). Ipilimumab is a fully humanized mAb against the cytotoxic T lymphocyte antigen 4 (CTLA4) found on T cells preventing it from binding to CD 80 and CD 86 ligands on dendritic cells (Figure 4A, see page 521) thereby allowing for T cell proliferation. In comparison, nivolumab and pembrolizumab target the programmed death-1 (PD-1) ligand found on the surface of T cells disrupting its interaction with the protein programmed death-ligand 1 (PD-L1) of cancer or dendritic cells, releasing the inhibitory blockade of T cell activation (Figure 4B, see page 521). Atezolizumab targets PD-L1 resulting in a similar immune activation (removal of inhibition) effect as nivolumab and pembrolizumab (Figure 4B, see page 541).

Immune checkpoint inhibitors have a unique safety profile because the immune system is activated, with subsequent dys-immune toxicity termed immune-related adverse events (IRAEs).[50,51] IRAEs are common, occurring in 70-90% of patients and affect multiple organ systems including the skin, gastrointestinal tract, lung, kidney, blood, adrenal gland and thyroid.[50,52] In addition, immune checkpoint inhibitors have been associated with autoimmune diseases such as SLE, rheumatoid arthritis, Graves disease, Vogt-Koyanagi-Harada (VKH) syndrome, myasthenia gravis and giant cell arteritis.[26,50,53,54]

Ipilimumab
As the first approved immune checkpoint inhibitor, with the largest amount of published data, the neuro-ophthalmic side effects of ipilimumab will be emphasized in this section.

The incidence of ocular IRAEs is less than 1%.[55] Several ophthalmic toxicities have been associated with the use of ipilimumab including blepharitis, conjunctivitis, keratitis, episcleritis, scleritis, uveitis, and choroidal neovascularization.[23,25,27,55]

Yeh and Francis reported bilateral optic nerve edema, subretinal fluid and anterior uveitis in a 67-year-old man treated with ipilimumab for metastatic melanoma. Cranial magnetic resonance imaging (MRI) revealed small vessel ischemic changes and a lumbar puncture documented a slightly elevated intracranial pressure (23.5 cmH_2O). Only topical steroids were given and by four months the optic nerve edema resolved but was replaced with pallor associated with persistent bilateral visual field defects.[56] Papillitis in the setting of VKH and thyroid eye disease due to Graves disease have been described with ipilimumab.[26,27,55] Hahn and Pepple reported a patient with bilateral iritis and bilateral optic nerve edema associated with macular edema, which they termed neuroretinitis.[57] Several case reports and case series have documented the occurrence of orbital inflammation.[27,58,59] Johnson et al described a 69-year-old woman with ptosis and external ophthalmoparesis due to myasthenia gravis after receiving ipilimumab infusions.[54]

Neurological IRAEs associated with ipilimumab are diverse including both the central and peripheral nervous system. Hypophysitis, PRES, peripheral neuritis (Guillain-Barré syndrome), meningitis, encephalitis, myelitis and facial neuritis have been reported with ipilimumab treatment.[27,50-52]

SMALL MOLECULE KINASE INHIBITORS

It is beyond the scope of this presentation to discuss the intricacies and complexities of the various intracellular signal molecules and their relationship to one another in maintaining normal cell development, differentiation, survival and proliferation. Suffice it to say that dysfunction of these signal pathways results in an abnormal cell cycle and development of neoplasia. A basic knowledge of signal transduction dysregulation of cancer cells is important in the context of understanding the efficacy and toxicity of small molecule kinase inhibitors.[60] Although incompletely understood, it is apparent that there are a number of complex, independent, parallel and interconnected signal transduction pathways involving the extracellular, cell surface and intracellular compartments (Figure 5, see page 522).

Small molecule kinase inhibitors are a group of anti-cancer drugs that affect the intracellular signal pathways that are dysfunctional in cancer cells.[61,62] Small molecule kinase inhibitors are adenosine triphosphate (ATP) mimetics or analogues that can target the extracellular or intracellular components of a cell surface receptor as well as intracellular protein kinases.[63] As a result of this inhibition of ATP transfer there is no post-translational phosphorylation, causing inactivity of the receptor or molecule leading to inactivity or paradoxical hyperactivity of downstream signal pathways.[64]

Small molecule kinase inhibitors are distinct from mAbs because they are smaller in size, shorter in half-life, administered orally, metabolized by the cytochrome

p450 enzymes and have a different MOA (Figure 6, see page 523).[1] As is the case for mAbs, the nomenclature for identifying a small molecule kinase inhibitor follows a specific scheme,. All small molecule kinase inhibitors end with the suffix –ib, and the stem -tin indicates a tyrosine kinase inhibitor.[65] FDA approval of the first small molecule kinase inhibitor—imantinib—occurred 15 years ago.[66] Since then there has been a steady increase in the number of drugs that have reached the market, totalling 27 as of 2016 (Table 2, see page 511-513).[67] Some of the kinase inhibitors target a single protein while others target multiple proteins.[63] It is not within the scope of this presentation to discuss each small molecule kinase inhibitor but rather they will be discussed as a group based on their target molecule with special emphasis on a particular kinase inhibitor if it has been associated with a unique or noteworthy toxicity.

Epidermal Growth Factor Receptor Inhibitors
There are currently five epidermal growth factor receptor (EGFR) inhibitors on the market: afatinib, erlotinib, gefitinib, laptinib and vandetanib. The EGFR, with its downstream effect on epithelial growth factor (EGF), is important in corneal healing and proliferation of Meibomian gland epithelial cells. In addition the EGFR controls hair follicle differentiation.[27] As a result the EGFR inhibitors can cause keratitis, dry eye, conjunctivitis, episcleritis, blepharitis, ectropion, entropion and trichomegaly.[26,68 69] There are also reports of uveitis associated with EGFR kinase inhibitors.[25]

Vascular Endothelial Growth Factor Receptor Inhibitors
The seven vascular endothelial growth factor receptor (VEGFR) inhibitors are axitinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib and sunitinib. Neuro-ophthalmic toxicity seems to be infrequent with these agents as demonstrated by the few reports of neurosensory retinal detachment and PRES.[24,70,71]

Breakpoint Cluster Region-Abelson Inhibitors
As mentioned above, the first FDA approved small molecule kinase inhibitor was the breakpoint cluster region-abelson (Bcr-abl) inhibitor imantinib. Currently there are 4 other Bcr-abl inhibitors: bosutinib, dasatinib, nilotinib and ponatinib. Thirty to 70% of patients taking imantinib develop periorbital edema.[26,27] In some cases the periorbital edema can cause visual impairment requiring surgical intervention.[72] Other complications include epiphora, keratitis, and conjunctival hemorrhage.[24,27] Retinal hemorrhage and macular edema have also been associated with imantinib.[24,73,74]

Two cases of optic neuritis in the setting of imantinib have been reported.[75,76] Details are provided for one of the cases, which involved bilateral visual loss with normal neuroimaging and cerebrospinal fluid results. Discontinuation of imantinib and institution of oral steroids was associated with an improvement of vision to "normal" from counting fingers.[75] Optic disc edema has been reported with imantinib.[77,78] In the case reported by Kwon et al, the patient had bilateral disc edema (with normal visual function) that resolved with discontinuation of imantinib. When the medication was restarted the disc edema did not recur. The intracranial pressure of the patient was not measured when the optic nerves were edematous.[77]

Mitogen-Activated Protein Kinase Kinase Inhibitors
To date trametinib is the only mitogen-activated protein kinase kinase (MEK) inhibitor in clinical use but there are many molecules that are in various phases of clinical development.[79] MEK is one of a series of protein kinases within the mitogen-activated protein kinase (MAPK) pathway (RAS-RAF-MEK-ERK).[80] The package insert lists retinal vein occlusion (incidence 0.2%) and retinal pigment epithelial detachment as ocular toxicities associated with trametinib.[81] One case report documented cystoid macular edema with trametinib.[82] Draganova et al described a 55-year-old woman who developed bilateral panuveitis, chorioretinal folds and serous retinal detachments during trametinib and dabrafenib (see below) therapy.[83]

Of those MEK inhibitors still being investigated in clinical trials a multitude of AEs have been identified including keratitis, epiphora, eyelid edema, blurred vision, double vision, visual disturbances (colored spots, halos), retinopathy (macular edema, central serous retinopathy, serous retinal detachment), and optic neuropathy.[24,26,69,82,84,85] The combination of trametinib and dabrafenib appears to be associated with an increased risk of intracranial hemorrhage.[81,86]

B-Raf Inhibitors
Dabrafenib and vemurafenib are the only two B-Raf inhibitors available on the market. Similar to MEK, B-Raf is part of the MAPK cascade. There are many similar molecules that are being investigated in clinical trials and as of yet have not received FDA approval.[87,88]

The package inserts for both dabrafenib and vemurafenib list uveitis in the warning and precautions sections.[89,90] There are also reports of retinal vein occlusion occurring in patients taking B-Raf inhibitors.[25]

As mentioned above, the combination use of dabrafenib and tramentinib seems to increase the risk of AEs.[83,84]

Bruton's Tyrosine Kinase Inhibitors
Ibrutinib is the only Bruton's tyrosine kinase (BTK) inhibitor currently on the market. To date there has been no ocular toxicity associated with ibrutinib. However, the package insert cautions the possibility of fatal intracranial hemorrhage.[91] A fatal case of PML was described in a 75-year-old man treated with ibrutinib; however, he was also treated with rituximab and other chemotherapeutic drugs several years prior to presentation.[92]

Anaplastic Lymphoma Kinase Inhibitors
Crizotinib and ceritinib are the two anaplastic lymphoma kinase (ALK) inhibitors being used in clinical practice. In two open-label, randomized, active-controlled trials reported in the package insert, 60-70% of patients experienced

a "vision disorder" defined as diplopia, photophobia, photopsia, blurred vision, reduced visual acuity, visual impairment and vitreous floaters.[93] Light to dark visual adjustment difficulties have been described by patients taking crizotinib.[23,27] In the warning and precautions section of the package insert, the incidence of severe visual loss is estimated at 0.2% with a particular mention of optic nerve disorders.[93] Chun et al reported a 69-year-old woman treated with crizotinib for metastatic lung adenocarcinoma who developed no light perception vision in the left eye and a visual field defect in the right eye. There was no mention of the appearance of the optic nerves on clinical examination but MRI demonstrated bilateral optic nerve enhancement.[94] The following statement is taken directly from the package insert: discontinue XALKORI in patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss. There is insufficient information to characterize the risks of resumption of XALKORI in patients.[93]

Based on the package insert approximately 19-21% of patients experience gait disturbance, hypoesthesia, muscular weakness, neuralgia, peripheral neuropathy, paresthesia, peripheral sensory neuropathy, polyneuropathy, sensory disturbance.[93]

Janus Kinase Inhibitors

Ruxolitinib is the only Janus kinase (JAK) inhibitor on the market. No significant ocular toxicities have been associated with ruxolitinib. However, a case of bilateral retinitis due to toxoplasmosis was reported in a patient being treated with ruxolitinib.[95] PML has been associated with ruxolitinib and is mentioned in the package insert.[96,97]

3RD GENERATION AROMATASE INHIBITORS

Third generation AIs are indicated for the treatment of breast cancer in postmenopausal women. Currently there are three FDA approved 3rd generation AIs (Table 2, see page 511-513). Unlike tamoxifen, which blocks estrogen from binding to the estrogen receptor, 3rd generation AIs inactivate the cytochrome P-450 enzyme aromatase thereby reducing the production of estrogen from androgens (Figure 7, see page 523).[98] Aromatase activity is high in fat and muscle cells of postmenopausal woman as well as breast cancer cells.[99] Although all three of the 3rd generation AIs reduce estrogen levels, there is a pharmacological difference between them. Letrozole and anastrozole are type 2 or nonsteroidal inhibitors and exemestane is a type 1 steroidal inactivator.

In general the AIs are well tolerated.[98] Compared to tamoxifen, which is associated with an increased risk of thromboembolism, the AIs have not been associated with increased frequency of deep venous thrombosis and pulmonary embolism.[99] The cardiovascular effects of AIs are not known and the data is limited.[100]

Anastrozole-Letrozole-Exemestane

There is no special mention of ocular AEs in the package insert of any of the three currently approved 3rd generation AIs.[101-103] Eisner et al observed an 11.4% frequency of retinal hemorrhage in patients taking anastrozole. All the patients had only one hemorrhage. The authors hypothesized that either a decrease in estrogen level compromised the vascular system or resulted in vitreoretinal traction.[104] In a follow-up study, Eisner et al found increase vitreous traction on the fovea in patients taking anastrozole.[105] Chatziralli et al studied 80 patients taking AIs and found a significant proportion of patients had ocular surface manifestations (75% blepharitis, 42.5% Meibomian gland dysfunction, 30% superficial punctate keratitis, 47% blurred vision and 30% foreign body sensation).[106] Moschos et al performed an optical coherence tomography and electrophysiology study on patients taking AIs and found reduced retinal nerve fiber layer thickness, delayed visual evoked potential recordings and abnormal multifocal electoretinogram tracings.[107] Case reports have described retinal artery occlusion and macular edema with AIs.[108,109]

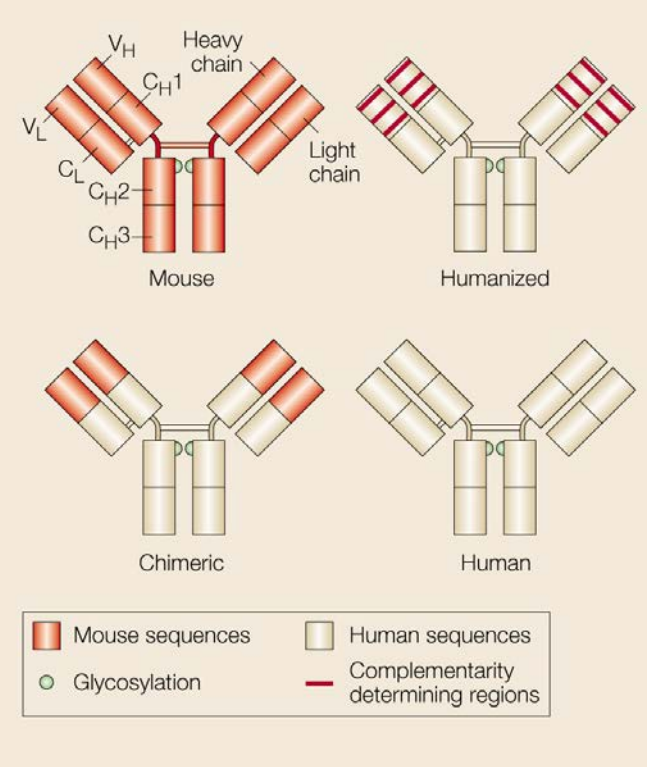
Cognitive dysfunction has been associated with AIs, however it is not clear based on the available data whether there is a causative relationship.[98,100] A single case report described a 55-year-old woman who developed PRES while on anastrozole therapy. As is the case with so many of such reports, the patient was receiving other medications that may have contributed to the findings; paclitaxel and bevacizumab in the past and fluoxymesterone with the anastrozole.[110] Parathesias occur more frequently with AI compared to tamoxifen.[111]

CONCLUSION

There has been a tremendous advancement in the medical treatment of cancer in the past 2 decades. Molecularly targeted therapy holds the promise of more personalized and selective treatment with the added benefit of less toxicity compared to traditional cytotoxic chemotherapy. However, with the introduction of new cancer therapies and unique MOAs that carry the capability to interfere with critical intracellular signal pathways, modulate the immune system and in some cases activate the immune system; novel AEs have become a clinical challenge that physicians involved in the care of cancer patients should recognize. In addition, physicians should be prepared to institute a management plan to minimize the possibility of any permanent neuro-ophthalmic complications.

FIGURE LEGENDS

Figure 1: Key therapeutic antibody technologies



Murine antibodies: Derived by hybridoma technology following immunization of mice or, less commonly, rats.

Chimeric antibodies: Obtained by joining the antigen-binding variable domains of a mouse monoclonal antibody (mAb) to human constant domains: mouse VL to human CL and mouse VH to human CH1–CH2–CH3 for light and heavy chains, respectively.

Humanized antibodies: In the simplest case, these are created by grafting the antigen-binding loops, known as complementarity-determining regions (CDRs), from a mouse mAb into a human IgG. The generation of high-affinity humanized antibodies generally requires the transfer of one or more additional residues from the so-called framework regions (FRs) of the mouse parent mAb. Several variants of the humanization technology have been developed.

Human antibodies: These have high affinity for their respective antigens and are routinely obtained from very large, single-chain variable fragments (scFvs) or Fab phage display libraries. Moreover, the difficulty in obtaining antibodies to self-antigens that are highly conserved between mouse and humans using hybridoma technology is readily overcome using phage display technology.High-affinity human antibodies have also been obtained from transgenic mice that contain some, or preferably many, human immunoglobulin genes and genetically disrupted endogenous immunoglobulin loci. Immunization elicits the production of human antibodies recoverable using standard hybridoma technology. A human anti-epidermal growth factor (EGF) receptor mAb obtained using transgenic mice eradicates large, established tumours in some preclinical xenograft models, auguring well for ongoing oncology trials.

Clinical experience: Chimeric, humanized and human antibody evidence indicates that these types of antibody are less immunogenic than those of mice. Humanized antibodies contain less foreign sequence than their chimeric counterparts and are presumed to be less immunogenic. Similar arguments have been made about humanized and human antibodies, despite the lack of substantiating clinical data. Other factors that affect the immunogenicity of antibodies include the method and frequency of administration, dose, patients'disease and immune status, antigen specificity of the antibody and immune complex formation with antigen.

Choice of antibody technology: Humanization and human antibodies are now the preferred technologies for developing antibodies as therapeutics. Humanization is a clinically well-validated technology that might be favoured if a well-characterized mouse mAb is available. By contrast, direct routes to human antibodies offer faster preclinical development in cases with no existing mouse mAbs. The choice of different human antibody technologies will depend on their availability, local expertise and commercial considerations.

Reproduced with permission: Carter P. Improving the efficacy of antibody-based cancer therapies. Nat Rev Cancer. 2001 Nov;1(2):118-29.

Figure 2: Mechanisms of tumour cell killing by antibodies.

a. Direct tumour cell killing can be elicited by receptor agonist activity, such as an antibody binding to a tumour cell surface receptor and activating it, leading to apoptosis (represented by the mitochondrion). It can also be mediated by receptor antagonist activity, such as an antibody binding to a cell surface receptor and blocking dimerization, kinase activation and downstream signalling, leading to reduced proliferation and apoptosis. An antibody binding to an enzyme can lead to neutralization, signalling abrogation and cell death, and conjugated antibodies can be used to deliver a payload (such as a drug, toxin, small interfering RNA or radioisotope) to a tumour cell.

b. Immune-mediated tumour cell killing can be carried out by the induction of phagocytosis; complement activation; antibody-dependent cellular cytotoxicity (ADCC); genetically modified T cells being targeted to the tumour by single-chain variable fragment (scFv); T cells being activated by antibody-mediated cross-presentation of antigen to dendritic cells; and inhibition of T cell inhibitory receptors, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4).

c. Vascular and stromal cell ablation can be induced by vasculature receptor antagonism or ligand trapping (not shown); stromal cell inhibition; delivery of a toxin to stromal cells; and delivery of a toxin to the vasculature. MAC, membrane attack complex; MHC, major histocompatibility complex; NK, natural killer.

Reproduced with permission: Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. Nat Rev Cancer. 2012 Mar 22;12(4):278-87.

Figure 2: Mechanisms of tumour cell killing by antibodies.

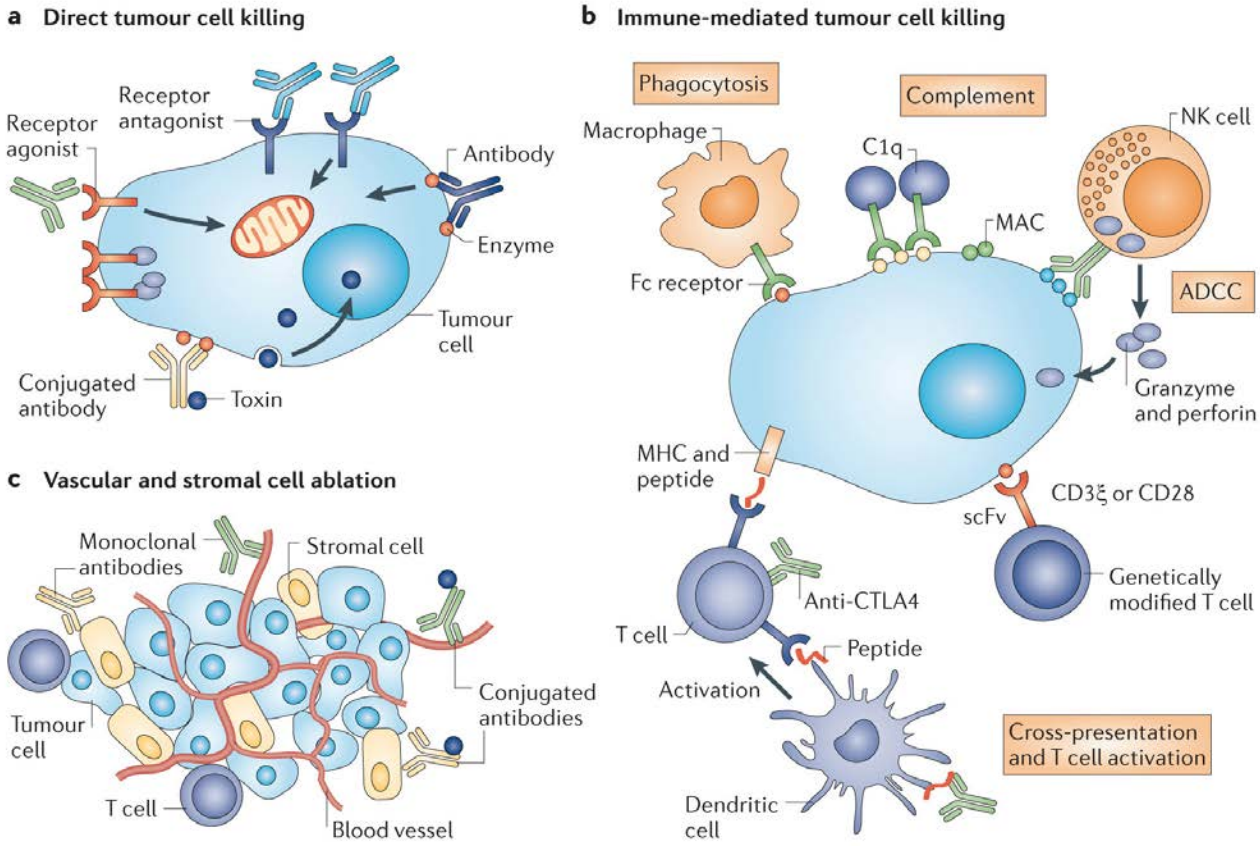
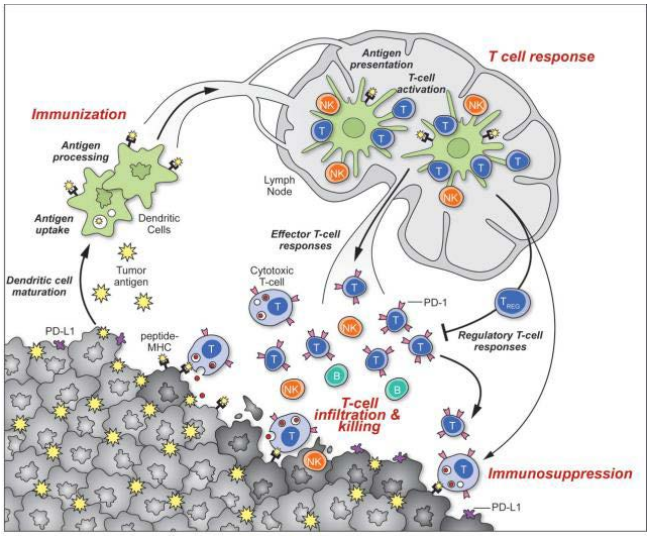


Figure 3: Generation and regulation of antitumour immunity.



Understanding the events in generating and regulating antitumour immunity suggests at least three sites for therapeutic intervention: promoting the antigen presentation functions of dendritic cells, promoting the production of protective T-cell responses and overcoming immunosuppression in the tumour bed. Antitumour immune responses must begin with the capture of tumour associated antigens by dendritic cells, either delivered exogenously or captured from dead or dying tumour cells. The dendritic cells process the captured antigen for presentation or cross-presentation on MHC class II and class I molecules, respectively, and migrate to draining lymph nodes. If capture and presentation occurred in the presence of an immunogenic maturation stimulus, dendritic cells will elicit anticancer effector T-cell responses in the lymph node; if no such stimulus was received, dendritic cells will instead induce tolerance leading to T-cell deletion, anergy or the production of Treg cells. In the lymph node, antigen presentation to T cells will elicit a response depending on the type of dendritic cell maturation stimulus received and on the interaction of T-cell co-stimulatory molecules with their surface receptors on dendritic cells. Thus, interaction of CD28 or OC40 with CD80/86 or OX40L will promote potentially protective T-cell responses, while interaction of CTLA4 with CD80/86 or PD-1 with PD-L1/PD-L2 will suppress T-cell responses, and possibly promote Treg formation. Antigen-educated T cells (along with B cells and NK cells) will exit the lymph node and enter the tumour bed, where a host of immunosuppressive defense mechanisms can be produced by tumours (or infiltrating myeloid cells) that oppose effector T-cell function. These include the upregulation of PD-L1/L2 on the cancer cell surface, release of PGE2, arginase and IDO (all T-cell suppressors), and the release of VEGF (triggered in part by intratumoral hypoxia), which inhibits T-cell diapedesis from the vasculature, and thus infiltration into the tumour bed.

Reprinted with permission: Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011 Dec 21;480(7378):480-9.

Figure 4: The use of antibodies in active and passive immunotherapy of cancer.

a. Checkpoint blockade by anti-CTLA4. CD80 and CD86 are ligands expressed on the surface of activated dendritic cells during the presentation of MHC [human lymphocyte antigen (HLA)]–peptide complexes to T cell receptors. CD80/86 binds to the costimulatory molecule CD28 to help activate T cell proliferation and then to the checkpoint inhibitor CTLA4 to attenuate T cell proliferation. The antibody ipilimumab blocks the interaction of CTLA4 with its ligands, thereby releasing the checkpoint inhibitor and favoring T cell proliferation.

b. Checkpoint blockade and inhibiting immune suppression by anti-PD1 or anti–PDL1. (Left) T cell influx into tumors results in the release of IFN-g, which up-regulates PD-L1 expression by tumor cells. PD-L1 binds to PD-1, which is expressed by activated T cells, generating a negative signal that causes T cell exhaustion (inhibiting the ability of T cells to recognize and kill their targets). (Right) During antigen presentation by dendritic cells, PD1 can also act as a checkpoint inhibitor where a negative signal can be sent by its binding to either PD-L1 or the closely related (and dendritic cell–specific) negative regulatory ligand PD-L2. Generally, inhibition of both PD-L1 and PD-L2 (e.g., by anti–PD-1) is required to block negative regulation by dendritic cells, whereas only PD-L1 inhibition (by anti- PD-1 or anti–PD-L1) should relieve immunosuppression (immune rheostat) activity in the tumor bed. Note that, for clarity, only the primary interactions of PD-1, PD-L1, and PD-L2 are illustrated.

c. Bispecific antibodies against CD3 passively recruit cytotoxic T cells to tumor cells. Blinatumomab is a single-chain bispecific antibody that is composed of an anti-CD3 arm that recognizes the T cell receptor and an anti-CD19 arm that recognizes a surface antigen on the surface of B cell lymphoma cells; diagrammed is a conventional bispecific IgG for clarity. Recruitment of the T cells to the tumor cells in this way results in efficient tumor cell killing, as if the T cell had recognized its cognate peptide-MHC on the tumor cell target.

Reprinted with permission: Sliwkowski MX, Mellman I. Antibody therapeutics in cancer. Science. 2013 Sep 13;341(6151):1192-8.

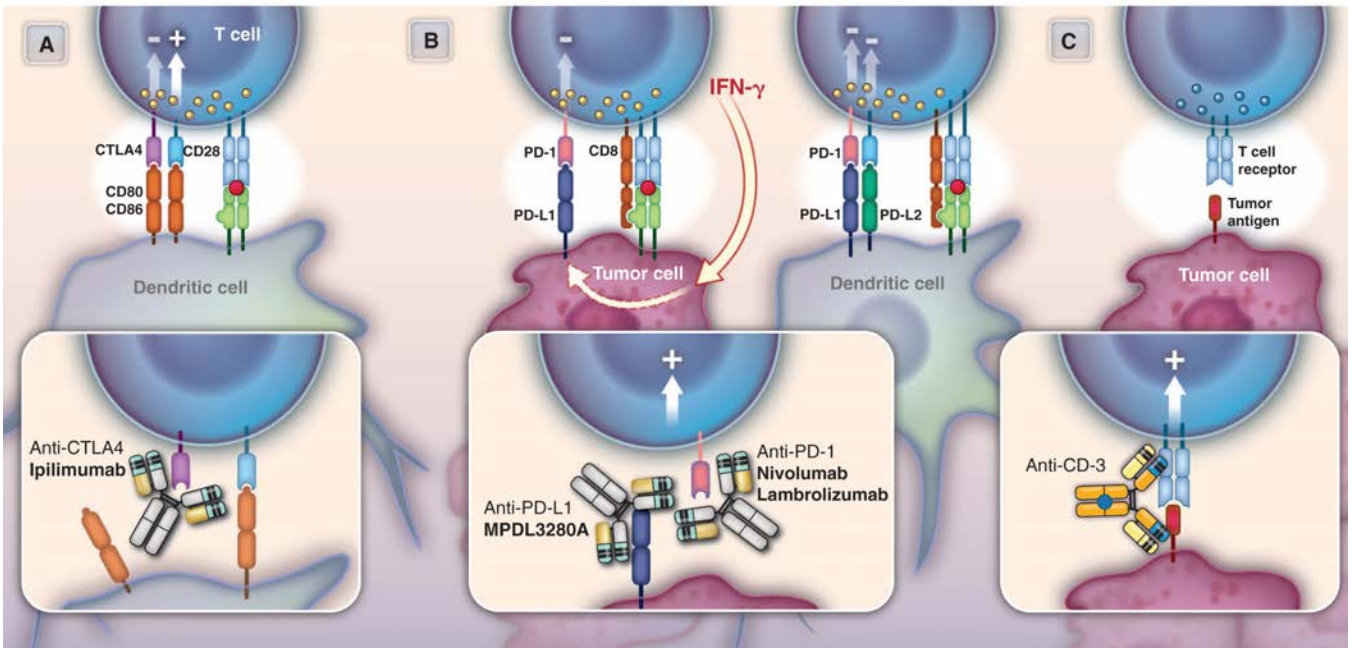


Figure 5: Rationale for Targeting Both the Ras/Raf/MEK/ERK and Ras/PI3K/PTEN/Akt/mTOR Pathways for Suppressing Cancer Growth.

a. The Ras/Raf/MEK/ERK and Ras/PI3K/PTEN/Akt/mTOR pathways are both activated by upstream receptor ligation and frequently co-regulate many downstream targets in parallel. Thus for effective elimination of many cancers or prevention of aging, it may be necessary to target both signaling pathways. Activation of these pathways could also result in increased transcription of many genes that promote cellular growth and malignant transformation.

b. Inhibition of mTOR can result in the induction of autophagy, which is a very important mechanism of cell death, especially in solid tumors.

c. As described previously, both the Ras/Raf/MEK/ERK and Ras/PI3K/ PTEN/Akt/mTOR pathways regulate the activity of apoptotic proteins by post-translational mechanisms. Targeting this pathway may also contribute to the induction of apoptosis. Signaling molecules promoting phosphorylation events are indicated in green. Stimulatory signaling events are indicted in green lines with a green arrow before the target of the phophorylation. Small molecule inhibitors are indicated in red. Inhibitory phosphorylation events are indicated in red lines with a block on the end before the target of the inhibition. Inhibitory signaling or proapoptotic molecules or inactivated molecules are indicated in yellow. A growth factor and a growth factor receptor are indicated in purple. Active transcription factors are indicated in purple diamonds. Inactivated transcription factors are indicated in yellow diamonds.

Please refer to original manuscript for colour-marked figure.

Reproduced with permission: Chappell WH, Steelman LS, Long JM, et al. Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR inhibitors: rationale and importance to inhibiting these pathways in human health. Oncotarget. 2011 Mar;2(3):135-64.

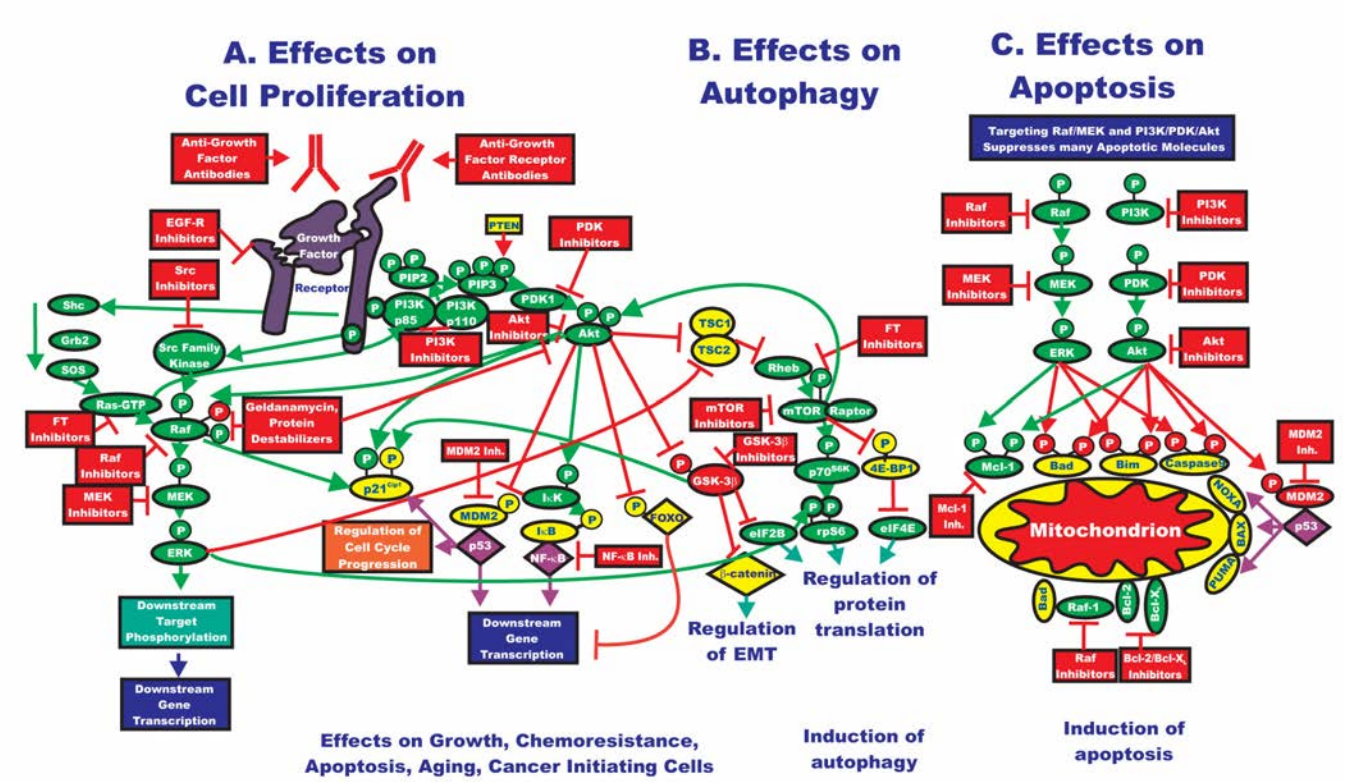
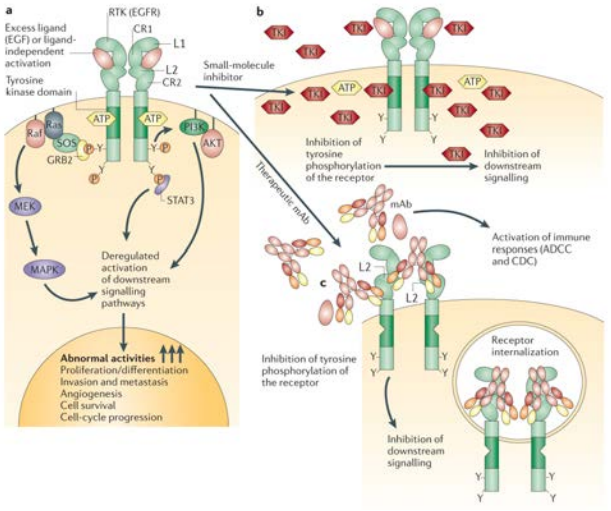


Figure 6: Distinct mechanisms of small-molecule inhibitors and monoclonal antibodies for targeting receptor tyrosine kinases in cancer cells.



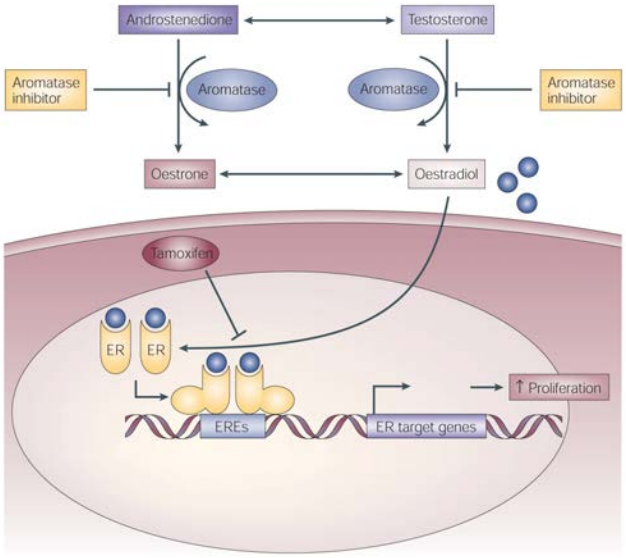
a. Epidermal growth factor receptor (EGFR) and receptor tyrosine kinase (RTK)- dependent growth signalling in cancer cells. The extracellular region of EGFR consists of four domains, the ligand-binding domains (L1 and L2) and the cysteine-rich domains (CR1 and CR2), and the C-terminal domain of EGFR contains six tyrosine residues (Y; only two are depicted here for simplicity). Following the activation of EGFR by ligand binding or ligand-independent dimerization, the Ras–Raf–MEK–MAPK pathway is activated through the growth factor receptor bound protein 2 (GRB2)–SOS complex. EGFR-mediated signalling also activates the phosphatidylinositol 3-kinase (PI3K)– AKT pathway, which contributes to anti-apoptotic effects of EGFR activation. Additionally, signal transducer and activator of transcription (Stat) proteins (STAT1, STAT3 and STAT5) are also activated. The coordinated effects of these EGFR downstream signaling pathways lead to the induction of cellular responses including proliferation, differentiation, cell motility, adhesion and angiogenesis. The deregulation of EGFR-mediated signalling in some cancer cells leads to aberrant proliferation, invasion, metastasis and neovascularization.

b. Small-molecule tyrosine kinase inhibitors (TKIs) such as gefitinib function as ATP analogues and inhibit EGFR signalling by competing with ATP binding within the catalytic kinase domain of RTKs. As a result, the activation of various downstream signalling pathways is blocked. Each TKI has a different selectivity for RTKs, and some are dual- or multi-selective, which might provide a therapeutic advantage.

c. By contrast, therapeutic monoclonal antibodies (mAbs) bind to the ectodomain of the RTK with high specificity (for example, cetuximab binds to the L2 domain of EGFR), and thereby inhibit the downstream signalling by triggering receptor internalization and hindering ligand–receptor interaction. Unlike small-molecule inhibitors, mAbs also activate Fcγ- receptor-dependent phagocytosis or cytolysis by immune-effector cells such as neutrophils, macrophages and natural killer cells by inducing complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC). MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase.

Reproduced with permission: Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer. 2006 Sep;6(9):714-27.

Figure 7: Mechanism of action of aromatase inhibitors and tamoxifen.



Oestradiol binds to the oestrogen receptor (ER), leading to dimerization, conformational change and binding to oestrogen response elements (EREs) upstream of oestrogen-responsive genes including those responsible for proliferation. Tamoxifen competes with oestradiol for ER binding whereas aromatase inhibitors reduce the synthesis of oestrogens from their androgenic precursors.

Reproduced with permission: Johnston SR, Dowsett M. Aromatase inhibitors for breast cancer: lessons from the laboratory. Nat Rev Cancer. 2003 Nov;3(11):821-31.

CME ANSWERS

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SIDE EFFECTS OF NEW IMMUNO-MODULATORS

Ore-ofe Oluwaseun Adesina, MD

Ruiz Department of Ophthalmology and Visual Schience at the McGovern Medical School Houston
Houston, TX

LEARNING OBJECTIVES

1. Explain indications for and mechanisms of action of some of the most commonly used biologic rheumatologic drugs
2. Explain the neurologic side effects of the more recently developed biologic drugs and how these may affect the visual system
3. Coordinate care with the primary treating physician in the case that neuro-ophthalmic side effects develop in patients taking these drugs

CME QUESTIONS

1. There is thought to be a causal relationship between use of anti-TNF-α drugs and the development of neurologic symptoms because

    a. the onset of symptoms occurs after the initiation of treatment or treatment re-challenge.
    b. partial or complete resolution of symptoms occurs in the majority of patients upon discontinuation of the anti-TNF-α agents.
    c. the drugs are unmasking disease in patients already predisposed to developing autoimmune disease.
    d. there is a preponderance of evidence that a direct causal relationship exists.

2. The optic neuropathy associated with the use of anti-TNF-α agents

    a. can have features similar to demyelinating optic neuritis or ischemic optic neuropathy.
    b. is always identical to demyelinating optic neuritis in presentation.
    c. is associated with discontinuation of the anti-TNF-α agent.
    d. always improves once the offending drug is discontinued.

3. If a patient develops neurologic symptoms while on anti-TNF-α therapy, one should

    a. continue the drug at a lower dose.
    b. stop the drug and begin a neurologic workup.
    c. continue the drug and begin a neurologic workup.
    d. stop the drug without further workup.

4. It is recommended that patients with a history of CNS demyelinating disease

    a. take anti-TNF-α drugs without reservation.
    b. take anti-TNF-α drugs with careful monitoring.
    c. avoid the use of anti-TNF-α drugs completely.
    d. use a lower dose of anti-TNF-α drugs.

5. The majority of progressive multifocal leukoencephalopathy cases seen in association with the listed biologics have been associated with

    a. adalimumab.
    b. etanercept.
    c. rituximab.
    d. certolizumab pegol.
    e. abatacept.

KEYWORDS

1. Rheumatologic drugs
2. Biologics
3. Demyelination
4. Visual loss

INTRODUCTION

Medications used in the management of rheumatologic disorders include therapeutic agents with varying mechanisms of action. The older well known drugs include glucocorticoids, non-steroidal anti-inflammatory drugs and the antimetabolites and cytotoxic medications such as cyclophosphamide, mycophenolate mofetil, methotrexate and azathioprine (disease modifying anti-rheumatic drugs – DMARDs). Of particular interest, however, are the drugs known as biologics. These drugs are not derived from compounds with predictable chemical structures; rather they are complex molecules or mixtures of molecules that are produced by the cells of living microorganisms, plants or animals, often using recombinant DNA.

Recombinant DNA is an important process for producing biologics and requires isolating DNA from human cells. This DNA segment is generally modified (often combined with other mammalian DNA) and then inserted into bacterial or mammalian cells, which then express the desired protein.[1] While not necessarily new to medicine (insulin, growth hormone, and erythropoietin have been around for

decades), with the exponential increase in the discovery and understanding of molecular targets for disease therapy, biologics are now being developed with more varied cellular, genomic, and immunologic targets to effect therapeutic responses. Drugs developed this way can often produce dramatic clinical responses and improvements in quality of life; however, as biologic agents, they all have the ability to incite an antibody-mediated immunologic response in ways that are unpredictable and sometimes with deleterious side effects.

Side effects of biologic drugs include severe infections, induction of systemic lupus erythematosus, malignant lymphoma, congestive heart failure, and demyelinating diseases.[2] The purpose of this discussion is to highlight the known neurologic and neuro-ophthalmic manifestations of some of these therapeutic agents. The biologic drugs associated with neuro-ophthalmic and neurologic side effects are the tumor necrosis factor alpha (TNF- α) inhibitors, rituximab and natalizumab. The TNF- α inhibitors have been directly linked to neurologic side effects while rituximab and natalizumab are associated with the development of progressive multifocal leukoencephalopathy (PML). The older conventional drugs do not incite an immune response and have not been associated with direct neurologic or neuro-ophthalmic side effects, but have been associated with the development of PML.

Multiple resources were used to gather the information and data utilized for this presentation. A PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) was performed as well as a Google search (https://www.google.com/) using the terms biologics, neurologic side effects, treatment, rheumatologic disease, immunotherapy, TNF- α inhibitors, demyelination, and vision loss. Additional searches were done depending on the initial results retrieved. Case reports, case series and published randomized controlled trials were also reviewed when necessary. Information on the FDA-approved indications for the use of many drugs was obtained from the website: http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/19/rheumatology

For treatment of PML: https://www.uptodate.com/contents/progressive-multifocal-leukoencephalopathy-treatment-and-prognosis

THE BIOLOGIC DRUGS

Table 1. List of biologic drugs and their FDA-approved indications for use.

Drugs	Date of FDA Approval	FDA-approved Use
TNF-α inhibitors		
Infliximab (Remicade, Janssen Biotech, Inc., Horsham, PA)	2002	RA
Adalimumab (Humira, AbbVie, Inc., North Chicago, IL)	2002	Moderate to severe RA
Etanercept (Enbrel, Immunex Corporation/Amgen, Inc., Thousand Oaks, CA)	2002	Psoriatic arthritis
Golimumab (Simponi, Janssen Biotech, Inc., Horsham, PA)	2009	RA, Psoriatic arthritis, ankylosing spondylitis
Certolizumab pegol (Cimizia, UCB, Inc., Smyrna, GA)	2009	RA
Others		
Rituximab (Rituxan, Genentech, Inc., South San Francisco, CA)	2006	Moderate to severe RA
Tocilizumab (Actemra, Genentech, Inc., South San Francisco, CA)	2010, 2011	RA, systemic JIA
Abatacept (Orencia, Bristol-Myers Squibb Company, Princeton, NJ)	2008	JIA
Anakinra (Kineret, Swedish Orphan Biovitrum AB, Stockholm, Sweden)	2011	RA
Canakinumab (Ilaris, Novartis Pharmaceuticals Corporation, East Hanover, NJ)	2013	Systemic JIA
Apremilast (Otezla, Celgene Corporation, Summit, NJ)	2014	Psoriatic arthritis
Ocilizumab (Actemra, Genentech, Inc., South San Francisco, CA)	2013	Pauciarticular JIA
Vedolizumab (Entyvio, Takeda Pharmaceuticals America, Inc., Deerfield, IL)	2014	UC and Crohn's disease
Tofacitinib (Xeljanz, Pfizer, Inc., New York, NY)	2012	RA
Natalizumab (Tysabri, Biogen, Inc., Cambridge, MA)	2007	Crohn's disease

RA=rheumatoid arthritis; JIA=juvenile idiopathic arthritis; UC=ulcerative colitis

TNF- α INHIBITORS

TNF-α is a pro-inflammatory cytokine that is often elevated along with other cytokines in autoimmune diseases. It is secreted by microglia and macrophages in the CNS in 2 forms: a transmembrane protein (tmTNF) and a soluble form (sTNF).[2] Both interact with the 2 TNF receptors, TNFR1 and TNFR2. The TNF-α inhibitors are monoclonal antibodies (mab) that work by binding TNF-α and inhibiting its interaction with its receptor. These agents include infliximab (Remicade, Janssen Biotech, Inc., Horsham, PA), adalimumab (Humira, AbbVie, Inc., North Chicago, IL), etanercept (Enbrel, Immunex Corporation/Amgen, Inc., Thousand Oaks, CA), golimumab (Simponi, Janssen Biotech, Inc., Horsham, PA), and certolizumab pegol (Cimzia, UCB, Inc., Smyrna, GA). Infliximab is a chimeric monoclonal antibody composed of the constant region of human immunoglobulin and 2 murine variable regions and is administered as an intravenous (IV) infusion. Etanercept is a fully human dimeric fusion protein composed of a TNF-α type II receptor and the Fc portion of IgG-1. It is administered as a subcutaneous injection. Adalimumab and golimumab are fully human monoclonal antibodies identical to human IgG1, composed of the constant and variable regions of human immunoglobulin targeted toward TNF-α. Both are administered as subcutaneous injections. Certolizumab pegol is an antigen-binding fragment portion of an IgG antibody attached to a polyethylene glycol moiety and is administered as a subcutaneous injection or IV infusion. All 5 agents neutralize soluble TNF-α and bind to and neutralize transmembrane TNF-α.

NEUROLOGIC EFFECTS OF TNF- α DRUGS

To date more than 500 cases of neurological complications have been associated with the use of anti-TNF-α agents including optic neuritis (ON), multiple sclerosis (MS), Guillain-barré syndrome (GBS) and Miller Fisher syndrome (MFS), transverse myelitis, peripheral neuropathies and leukoencephalopathy.[3-6] All TNF-α inhibitors have been associated with neurologic side effects. A Pubmed search produced one case of uveitis associated with certolizumab pegol[7]; however, another study suggested a reduced rate of uveitis in patients with ankylosing spondylitis on certolizumab versus those not treated with the drug.[8]

MULTIPLE SCLEROSIS-LIKE DISEASE

TNF-α inhibitors have been associated with the development of demyelinating disease (DD), including ON and MS in patients being treated for inflammatory bowel disease, inflammatory skin disorders, and inflammatory arthritis. TNF-α levels have been found to be elevated in the CSF and serum of patients with progressive MS, and TNF-α levels are shown to correlate with disease severity.[2] TNF-α has also been implicated in myelin and oligodendrocyte damage in MS. Based on these observations, a murine model was developed to determine the efficacy of TNF-α inhibitors for the treatment of MS with promising results. This, however, did not translate to efficacy in human clinical trials, as infliximab- and lenercept-treated patients with progressive MS developed an increase in relapse rates and MRI lesion burden.[4] This indicated that TNF-α agents are inappropriate for treating MS and may, in fact, initiate or unmask an underlying DD.

The form of DD seen in association with TNF-α inhibitors is often similar to MS clinically and radiographically. In Winthrop et al.'s 2013 retrospective review[9] analyzing the characteristics of anti-TNF-α associated demyelination, 22 patients were found to have CNS involvement. Of those patients 16 (72.7%) had brain involvement, 8 (36.4%) had transverse myelitis, including 4 with brain involvement, and 5 (22.7%) had retrobulbar ON, including 2 patients with associated brain involvement and 1 patient with associated transverse myelitis. CSF analysis was normal in 6 patients, revealed raised protein level in 4, immunoglobulin oligoclonal bands in 11 and CSF pleocytosis in 4. MRI showed multiple subcortical white matter lesions in all but 2 patients with isolated ON. Anti-TNF-α treatment was discontinued in all patients, and 15 patients received steroids for neurological involvement. Neurological symptoms completely resolved in 12 patients, partly in 8 and remained stable in 2. After a mean follow-up of 19.7 months, 5 patients met McDonald criteria for the diagnosis of MS. In other reports, patients have developed MS-like demyelination anywhere from 4 weeks to 6 years after initiation of therapy with etanercept, adalimumab and infliximab.[3, 6]

OPTIC NEUROPATHY

While the clinical presentations of demyelinating and TNF-α-associated ON are often similar, there are some differences that may indicate a non-demyelinating i.e. ischemic or toxic etiology of optic neuropathy in at least some anti-TNF-α associated cases. In a review of 18 cases (23 affected eyes) of isolated TNF-α associated ON, the majority of cases occurred in females and between the ages of 36 and 65 years.[5] Infliximab was the anti-TNF-α agent reported in 11/17 (65%) cases, and symptom onset occurred within the first 12 months of anti-TNF-α therapy in 15/17 (88%) cases reported. ON was unilateral in 12/17 (71%) cases. As with MS-related ON, afferent pupillary defects, visual field abnormalities, and color vision abnormalities were present in the majority of cases. Visual impairments of worse than 20/40 were reported in 12/17 (71%) cases, and optic nerve enhancement was seen on MRI in 5/10 (50%) reported cases. Anti-TNF-α therapy was discontinued in almost all cases reported, and corticosteroids were given to the majority of patients. Resolution of symptoms occurred in 6/17 (35%) cases while partial improvement or stabilization without change occurred in 11/17 (65%) cases. Atypically, however, disc edema was seen in a majority of cases, and this and other series do not report pain as a prominent symptom associated with vision loss.[4,5,10] Simsek et al. reported a

series of 15 patients, 3 of whom had what was described as bilateral anterior optic neuropathy. These patients did not experience significant visual recovery after cessation of the anti-TNF-α agent and had capillary dilation and vascular leakage as well as swelling in both optic nerve heads, which were felt to be more suggestive of an ischemic or toxic form of optic neuropathy. Also supporting the concept of a non-demyelinating anti-TNF-α-associated optic neuropathy is Chang and Miller's case of bilateral optic neuropathy in a 62-year-old man who developed bilateral painless vision loss with bilateral optic disc swelling shortly after receiving his third dose of golimumab for psoriatic arthritis.[11] He had no optic nerve enhancement on MRI, and extensive CSF and serum evaluation for secondary causes was negative. His vision improved and disc swelling resolved after stopping the golimumab and receiving treatment with systemic corticosteroids. This may be more consistent with a toxic optic neuropathy than acute inflammatory demyelination.

There are reports of patients receiving anti-TNF-α drugs who develop unilateral or bilateral ON with transverse myelitis.[5] To date, there are no seropositive neuromyelitis optica (NMO) or myelin oligodendrocyte glycoprotein antibody (MOG-ab) positive cases of ON associated with transverse myelitis with anti-TNF-α agents. A prospective investigation of NMO and MOG-ab in patients developing concurrent ON and transverse myelitis while taking anti-TNF-α drugs could shed more light on the spectrum of transverse myelitis in these patients.

GUILLAIN-BARRÉ/MILLER FISHER-LIKE DISEASE

As with MS, TNF-α has also been implicated in the pathogenesis of GBS and its variants. Levels of TNF-α and other cytokines are elevated in the serum of affected patients and have been correlated in many studies with disease severity.[3, 12] TNF-α levels have also been seen to normalize in parallel with the clinical recovery of patients. As with central DD, peripheral demyelination presents similarly to classic GBS and MFS clinically and biochemically. Shin et al. reported 16 patients with anti-TNF-α-associated acute inflammatory demyelinating polyneuropathy (AIDP) associated with infliximab therapy in 10 patients, with etanercept therapy in 5 patients, and adalimumab in 1 patient.[13] Six patients had a preceding upper respiratory tract infection, flu-like illness, or low-grade fever, and one patient received influenza vaccine 6 days before the onset of ataxia; all had a temporal association of their disease presentation with the initiation of anti-TNF-α therapy. The patient who received influenza vaccine presented with cerebellar ataxia and nystagmus and ultimately experienced an areflexic flaccid quadriplegia and bilateral bulbar palsies after initiation of anti-TNF-α therapy. Anti-GQ1b antibodies were found at a titer less than 1:100, consistent with progression of MFS to a generalized form of GBS syndrome. Among the 13 patients for whom follow-up data were available and anti-TNF-α therapy was discontinued, 1 experienced no resolution, 9 had partial resolution, and 3 had complete resolution. These patients all received intravenous immunoglobulin (IVIG) or plasmapheresis. Another series included several cases of chronic inflammatory demyelinating polyneuropathy. Histopathological findings of a demyelination/remyelination process were seen in several cases, and positive antiganglioside antibodies were found to be present in the sera of others.[10] Several cases of myasthenia gravis have been reported in association with anti-TNF-α use; however, specific biochemical and electrophysiological data are not available for those cases.[5]

DO ANTI-TNF-α DRUGS CAUSE CNS DISEASE?

A causal relationship is suspected in the cases of anti-TNF-α-associated neurologic disease due to the onset of demyelination after the initiation of treatment or treatment re-challenge and partial or complete resolution of symptoms in the majority of patients upon discontinuation of the anti-TNF-α agents and/or treatment with glucocorticoids. It is not clear if the drugs are unmasking disease in patients already predisposed to developing an autoimmune disorder or initiating demyelination in patients who otherwise would not have developed a CNS diathesis. A 2015 Mayo study reviewed the incidence of idiopathic inflammatory DD (IIDD) in 9905 patients with inflammatory bowel disease (IBD) treated with anti-TNF-α agents. While many anecdotal relationships were described, overall, anti-TNF-α biologics were not felt to impact the risk of developing clinical IIDD in patients with IBD. In the case of ON, a 2013 retrospective, population-based cohort study identified 61,227 eligible inflammatory disease patients with either new anti-TNF-α or new non-biologic DMARD use.[9] Among this cohort, 3 ON cases occurred in anti-TNF-α users a median of 123 days after starting the anti-TNF-α drug. The authors concluded that ON is rare among those who initiate anti-TNF-α therapy and occurs with similar frequency among those with non-biologic DMARD exposure. There is no way to know from the study, however, if therapy exacerbates already existing subclinical DD or incites new-onset disease.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Although the neurologic side effects associated with TNF-α inhibitors are well documented, there is far less evidence for a direct or indirect relationship between any of the other biologic or chemical drugs with neurologic events. All of the immunomodulatory drugs suppress the immune system, predisposing patients to opportunistic infections and their complications. Of these infectious diseases, PML is of particular importance because it primarily affects the CNS and has the potential to produce a myriad of neuro-ophthalmic manifestations.[14]

PML is a DD affecting the CNS caused by a reactivation of the ubiquitous human polyoma John Cunningham (JC) virus. The virus induces a lytic infection of oligodendrocytes, [15] producing a subacute progressive disorder with multifocal white matter involvement of almost any part of the brain. It is almost exclusively seen in the setting of immune compromise, most commonly in patients with HIV/AIDS, but also in patients with blood dyscrasias and in iatrogenic immune compromise in post-transplant states and the treatment of autoimmune disease. The disease is associated with a high mortality rate as there is no specific treatment for JC virus. Common findings include behavioral and cognitive abnormalities as well as motor weakness, gait abnormalities, language problems and incoordination. Neuro-ophthalmic manifestations include visual field defects, cortical blindness, visual blurring and distortion from cortical involvement, and diplopia and nystagmus from brainstem involvement. There are no descriptions of a primary optic neuropathy or peripheral nervous system involvement.[14]

In a large review of drug-induced PML, approximately 20% of all cases were found in association with the treatment of autoimmune disorders.[16] The DMARDs associated with PML infection are listed in Table 2, below, and include almost all of the commonly used immunomodulatory drugs.

Table 2. List of disease modifying anti-rheumatic drugs associated with progressive multifocal leukoencephalopathy

Drug Class	Therapeutic Agent
Biologics	Rituximab (Rituxan) Natalizumab (Tysabri)
Conventional DMARDs	Cyclophosphamide Prednisone Tacrolimus Cyclosporine Mycophenolic acid Azathioprine Interferon β-1a Methotrexate Peginterferon α-2a Prednisolone Interferon α/β

DMARDs=disease modifying anti-rheumatic drugs

Of these drugs, only rituximab and natalizumab are from the class of rheumatologic biologics while the rest are conventional immunosuppressive drugs. Molloy and Calabrese reviewed the association between DMARD use and development of PML and also found rituximab to be the biologic with the most common association with the disease. A direct causal relationship could not be established, however, as the majority of patients taking rituximab were also concurrently receiving conventional immune suppression or glucocorticoids.[17] The estimated risk of PML in rheumatoid arthritis patients taking rituximab is 1:25,000 according to a review by Clifford et al.[18] There are case reports of the anti-TNF-α drug infliximab and belatacept (a derivative of abatacept; Nulojix, Bristol-Myers Squibb Company, Princeton, NJ) are associated with PML, but these are very rare and do not support a causal relationship.[19, 20] The reason for a stronger association between rituximab and PML may be related to its mechanism of action as an antibody to CD20, causing direct suppression of B-cell and plasmablast function as opposed to immunomodulation and suppression of cytokines as secondary immune modulators. The association between natalizumab and PML is well known; however, as it is primarily used in the treatment of MS its association with the disease will not be discussed in detail here. Although there is no specific treatment for JC virus, restoration of the host adaptive immune response appears to prolong survival.[21, 22] This includes discontinuing the drug as quickly as possible, and in the case of natalizumab-associated PML, starting plasma exchange to eliminate circulating drug that might delay immune reconstitution.[23]

THERAPEUTIC IMPLICATIONS

Despite the lack of a definitive causal relationship between the use of biologics with the induction of neurologic disease, current recommendations are that a baseline neurological examination should be performed prior to the initiation of anti-TNF-α or other biologic therapy for any rheumatologic indication.[6] Use of anti-TNF-α therapies is not recommended in patients with a personal history of DD and should be approached cautiously in patients with a family history of DD. For patients who develop neurologic symptoms, anti-TNF-α therapy should be immediately withheld pending workup, including comprehensive neurological and neuro-ophthalmic examinations and MRI of the brain or spinal cord depending on the patient's symptoms. If the patient's neurologic symptoms do not improve after stopping therapy, treatment with steroids, plasma exchange or IVIG should be considered as indicated.[24] If there is no concrete evidence of an active demyelinating illness, consideration can be given for resuming anti-TNF-α therapy only when all symptoms have completely resolved.[25] These patients should be carefully monitored by a neurologist for recurrence of symptoms. For patients who do have clinical, radiographic or biochemical evidence of CNS inflammatory disease, the offending anti-TNF-α agent should not be re-initiated if it is felt to be the cause of the patient's findings.

CONCLUSION

Biologic drugs are complex proteins produced by the cells of living microorganisms, developed with specific cellular, genomic, and immunologic targets to effect therapeutic responses. They often produce dramatic clinical responses and quality of life improvements in patients afflicted with rheumatologic disorders; however, they may also produce neurologic side effects related to the induction of an

untoward immune response. The most commonly reported neurologic side effects of neuro-ophthalmic import include MS, ON, and Guillain-Barré/Miller Fisher variants of AIDP associated with anti-TNF-α use. The development of PML has also been associated with the use of DMARDs and can cause neurologic and neuro-ophthalmic symptoms. While a definitive causal relationship has not been established in most cases, physicians treating patients taking these drugs must be aware of the potential for the development of these adverse effects. Current recommendations advocate cessation of the biologic agents if symptoms develop. An appropriate neurologic workup should be performed including referral for neuro-ophthalmic evaluation if indicated.

CME ANSWERS

1. d
2. a
3. b
4. c
5. c

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NEURO-OPHTHALMIC CONSEQUENCES OF MEDICATIONS FOR MULTIPLE SCLEROSIS: THE GOOD, THE BAD, THE UGLY AND THE UNKNOWN

Heather E. Moss, MD, PhD

Stanford University
Palo Alto, CA

LEARNING OBJECTIVES

1. Recognize the expanding spectrum of medications prescribed for treatment of multiple sclerosis
2. Identify specific neuro-ophthalmic consequences of fingolimod (macular edema) and alemtuzumab (thyroid eye disease)
3. Explain current and future treatment options for patients with optic neuritis

CME QUESTIONS

1. A patient with MS presents for screening eye exam prior to starting fingolimod therapy. She has a normal funduscopic exam with no macular edema. Assuming that she does not develop visual symptoms, an appropriate follow up plan is:

    a. No follow up is needed.
    b. Follow up 3-4 months after starting the medication regardless of past medical history.
    c. Follow up every 3-4 months if the patient has a history of diabetes or uveitis.

2. A woman with no history of multiple sclerosis presents with acute optic neuritis. A current treatment option for this acute illness is:

    a. IV methylprednisolone
    b. Anti-Lingo 1
    c. Dalfampridine (Ampyra)
    d. Teriflunamide (Aubagio)
    e. Phenytoin

3. A patient presents with proptosis and right hypotropia with limited supraduction. She has a history of multiple sclerosis and received treatment for this with intravenous infusions 6 months ago. Which of the following is most likely to be the medication associated with diplopia:

    a. Daclizumab
    b. Dimethylfumarate
    c. Alemtuzumab

KEYWORDS

1. Multiple Sclerosis
2. Medication complications
3. Macular Edema
4. Thyroid eye disease
5. Infection

INTRODUCTION

The landscape of therapies for multiple sclerosis (MS) is constantly shifting. Currently, there are 11 FDA approved agents for chronic disease treatment, multiple drugs in clinical trials for acute and chronic disease management and numerous compounds used for symptom control. Beyond treating patients who may be on these medications and in some cases prescribing these medications, neuro-ophthalmologists may be the evaluating physician for specific complications with neuro-ophthalmic symptoms and signs. Thus it is critically important that neuro-ophthalmologists stay abreast of new and emerging MS medications.

The focus of this syllabus and the accompanying talk is consequences of MS medications, both benefits and harms, as they pertain to the afferent and efferent visual pathways. The intent is neither to comprehensively review pharmacology and efficacy of MS medications, nor to provide an update on MS. The interested reader is referred to excellent reviews by Dr. Green in the NANOS 2015 annual meeting syllabus (available through NOVEL)[1] and by Dr.'s Eckstein & Bhatti in the recent literature[2] for further information on these topics.

MEDICATIONS

DISEASE MODIFYING AGENTS APPROVED FOR TREATMENT OF MULTIPLE SCLEROSIS

Table 1 lists agents currently approved by the United States Food and Drug Administration (FDA) for treatment of multiple sclerosis. The dosing route and frequency are listed to emphasize the range of dosing schedules and routes – from daily oral formulations to yearly infusions. Of

particular note is alemtuzumab, which is administered in two brief cycles 12 months apart. The FDA approval dates for MS indications and non-MS indications are provided to give a sense of the combined experience with each agent. The interested reader is referred to the FDA website,[3] the source of the information in Table 1, for more specific labelling information including approved indications.

Table 1: Disease modifying medications for multiple sclerosis approved by the US FDA (as of September, 2016)

Medication name (brand name)	Route of administration	FDA approval for MS	Prior FDA approval for other indications
Interferon B1a (Avonex) (Rebif)	IM weekly SC TIW	1996 2002	
Peginterferon B1a (Plegridy)	SC QOW	2014	
INTERFERON B1B (Betaseron) (Extavia)	SC QOD	1993 2009	
Glatiramer acetate (Copaxone) (Glatopa - generic)	SC daily SC TIW SC daily	1996 2014 2015	
Daclizumab (Zinbytra)	SC monthly	May, 2016	1997 as Zenapax for anti-organ transplant rejection
Mitoxantrone (Novantrone)	IV q3mo	2000	1987 for acute non-lymphcytic leukemia 1996 for prostate cancer
Natalizumab (Tysabri)	IV q28d	2004	
Alemtuzumab (Lemtrada)	IV daily x 5d @12mo IVd x 3s	2014	2001 as Campath for B cell chronic lymphocytic leukemia
Fingolimod (Gilenya)	PO daily	2010	Studied in renal transplant 2006
Teriflunomide (Aubagio)	PO daily	2012	Active metabolite of leflunomide, approved in 1998 as Arava for rheumatoid arthritis
Dimethyl fumarate (Tecfidera)	PO BID	2013	

DISEASE MODIFYING AGENTS ON THE HORIZON (SELECTED)

Siponimod (BAF312) is a novel oral medication for which phase 2 trial results were recently published.[4] Multiple clinical trials in MS, and one in polymyositis are ongoing. A clinical trial in dermatomyositis was recently completed, though has not yet been published.[5]

Ozanimod (RPC1063) is being studied in Crohn disease, ulcerative colitis and multiple sclerosis. Results of a phase 2 study in MS have been published.[6]

ACUTE THERAPEUTIC AGENTS ON THE HORIZON (SELECTED)

Anti-lingo-1 (BIIB033) is an IV infusion that has been studied in acute optic neuritis and MS. Safety & tolerability data in 72 healthy individuals and 47 MS patients were published in 2014.[7] Results of a trial of acute optic neuritis have been presented at conferences, including NANOS, and the publication is in press.

SYMPTOMATIC THERAPY (SELECTED)

Dalfampridine (Ampyra), received FDA approval in 2010 for an indication of improving walking speed in patients with MS. An older version, 4-aminopyridine, has been used off label through compounding pharmacies in the past, but did not have FDA approval for any indication.

Table 2: Levels of likely best evidence for evaluation of harms of therapies (modified from Center for Evidence Based Medicine[8])

Level	Likely best evidence
Level 1	Systematic review of randomized trials, nested case-control studies, or observational study with dramatic effect N of 1 trial with patient you are concerned about
Level 2	Randomized trial or observational study with dramatic effect
Level 3	Non-randomized controlled cohort/follow up study (post-marketing surveillance)
Level 4	Case series, case control, or historically controlled studies
Level 5	Mechanism based reasoning

EVALUATING BENEFITS AND HARMS OF THERAPIES

Evaluating evidence for therapeutic harms requires a similar strategy to evaluation of evidence with regards to therapeutic benefits. The Center for Evidence Based Medicine (CEBM.net) has compiled a hierarchy of likely best evidence that serves as an excellent starting point (Table 2).[8]

As with evaluation of any evidence, attention must be paid to the power of the study to detect harms, duration of the study (i.e. duration of drug exposure and follow up) and study population. Current clinical trial designs often fail to identify rare long-term risks.

A particular challenge is identifying the resources to provide the evidence regarding harms of medications. Literature reviews using databases such as Google Scholar or PubMed offer excellent access to the published literature. Clinicaltrials.gov is an excellent database with which to identify ongoing and completed trials, many of which post preliminary results.[5] The FDA website includes a search function for approved drugs with links to labels and evaluations which contain information from studies used to grant the approval and also has publically available documents regarding new drug applications.[3] The National Registry of Drug-induced Ocular Side Effects is an excellent resource for ophthalmic consequences of medications.[9] The staff responds promptly to electronic inquires by providing published references and a copy of any relevant chapters from their book.[10]

Beyond case reports in the literature, multiple agencies maintain reporting systems including the FDA (the FDA Adverse Event Reporting System)[11] and the National Registry of Drug-induced Ocular Side Effects.[9] FDA data files of safety reports are publically available but require an advanced level of database savviness to process and interpret. A freedom of information request can be submitted to obtain individual safety reports. The National Registry of Drug-induced ocular side effects offers to make case-level data available, given time and funds. Both of these systems are limited by reporting bias.

NEGATIVE CONSEQUENCES OF MS MEDICATIONS (RELEVANT TO NEURO-OPHTHALMOLOGISTS)

MACULAR EDEMA (FINGOLIMOD)

Fingolimod is a non-selective sphingosine 1 phosphate (S1P) receptor modulator that limits egress of lymphocytes from lymph nodes. There are multiple subtypes of the S1P receptor, and modulation of these is thought to be responsible for both the beneficial effects and common adverse effects such as bradycardia (S1P receptors on atrial cells) and macular edema (ME) (S1P receptors on retinal endothelial cells altering vascular permeability). Macular effects were studied prospectively in pivotal trials

of fingolimod in MS due to prior evidence of ME as a dose dependent adverse event in renal transplant recipients treated with Fingolimod in clinical trials.[12,13]

In pooled safety data from phase 2 and 3 trials of fingolimod for MS and their extension studies (2615 total patients exposed) 26 cases of macular edema were reported and 19 of these were confirmed. One of these cases was ultimately judged to be due to non-drug associated BRAO. 74% were unilateral and 68% were symptomatic. 68% developed ME within 4 months, while 11% developed it after 12 months (mean 207d, median 99d). In the clinical dose group (0.5mg), there were 5 cases (0.3% cumulative incidence). In the higher dose group there were 14 cases (1.5% cumulative incidence). 5/26 patients (19%) with a history of uveitis developed ME – all were in the higher dose group.[14-16] Reports of atypical cases include severe bilateral macular edema (ME) occurring 10 days after medication initiation in a patient with diabetes[17] and single report of macular hemorrhage associated with Fingolimod use.[18] The clinical trials provide minimal information regarding type of macular edema, though most case reports describe and show images of intra-retinal cysts.

In addition to risk associations of dose and uveitis history, diabetes is likely associated with increased risk of fingolimod-associated macular edema based on observations made during study of fingolimod for renal transplant. In these trials ME was 7 times more common in diabetics, occurring in 28% of diabetics receiving fingolimod vs. 15% of diabetics not receiving fingolimod.[14] It is important to note that fingolimod doses were higher in these trials than in MS trials. Studies of fingolimod in MS excluded diabetics, and the risk of ME associated with MS dosing of fingolimod in diabetics has not been determined.

There may also be more subtle effects of Fingolimod on the macula. In a study of 30 patients taking fingolimod with two groups of 30 matched MS patients not taking the drug, a small increase in macular volume ($0.025mm^3$) was seen in fingolimod treated patients, but not seen in either of the two control groups.[19]

The FDA package insert suggests ophthalmic evaluation prior to or shortly after starting therapy and 3-4 months after starting therapy. The North American Neuro-Ophthalmology Society (NANOS) and the AAO Ophthalmic News and Education (ONE) Network Neuro-Ophthalmology Committee propose considering a screening evaluation for uveitis or pre-existing macular disease prior to starting or within a few weeks of starting medication. They recommend an evaluation following 3-4 months of therapy and advise educating patients that the risk of ME is low, but may be increased if there is a history of uveitis or diabetes.[20]

Resolution typically occurs within 6 months following cessation of fingolimod, with 84% of patients in the pooled safety cohort having complete resolution.[13,14] Control of ME with continued fingolimod administration has been reported with frequent (q2hr) topical ketorolac and dexamethasone.[21] Subtenon triamcinolone was associated with resolution of ME in a single case and allowed the patient to continue on fingolimod without recurrence for 7 months.[22] Intravitreal triamcinolone has been used to treat ME and allow continuation of fingolimod for at least 12 months.[23]

In theory, selective S1P receptor modulators should have fewer adverse effects than fingolimod, which is a non-selective receptor modulator.[24] In a phase II trial of ozanimod, one such selective modulator, 170 MS patients received ozanimod for 24 weeks, and there were no cases of macular edema.[6] Siponimod is another selective S1P receptor modulator. In a 2 year extension study of a randomized trial with 184 patients receiving drug, none experienced macular edema.[4] However, the duration of these trials and number of patients treated are not sufficient to exclude ME as a rare adverse reaction at this time.

THYROID EYE DISEASE (ALEMTUZUMAB)

Alemtuzumab is an anti-CD52 monocolonal antibody that has been approved for treatment of B-cell chronic lymphocytic leukemia since 2001, and was approved for treatment of multiple sclerosis in 2014. It acts through depletion of T and B lymphocytes. The dosing regimen is unique, consisting of 5 daily infusions, followed by 3 daily infusions after a 12 month interval. In clinical studies it has been associated with autoimmune thyroid disease and thyroid ophthalmopathy. Alemtuzumab is also associated with other autoimmune conditions including immune mediated thrombocytopenia and anti-glomerular basement membrane disease. Though incompletely understood, it has been proposed that these associations are due to immune reconstitution in the months following treatment.[25]

Cumulative prevalence of alemtuzumab associated thyroid dysfunction in a phase 2 trial for RRMS was 34% with 73/216 patients experiencing 102 episodes. Onset was as early as 6 months and as late as 7 years following treatment, with peak incidence in year 3. 79.5% of affected patients developed Graves' hyperthyroidism or thyroiditis with the balance developing hypothyroidism. The majority of Graves' patients were anti-TSH (thyroid stimulating hormone) receptor antibody positive at the time of diagnosis with thyroid dysfunction and a minority were anti-TPO (thyroid peroxidase) antibody positive. Younger, female patients were more likely to have thyroid dysfunction. There were no associations between development of thyroid dysfunction and baseline characteristics of MS, MS treatment response, immune status or immune reconstitution rates.[26] Monitoring of thyroid function prior to treatment initiation and every three months until 48 months after last treatment course is recommended.[25]

In the phase II trial for RRMS, 3/39 patients within an initial episode of thyroid dysfunction consistent with Graves' and 1/4 with second episode of thyroid dysfunction consistent with Graves' (following a first episode of hypothyroidism)

developed significant ophthalmopathy, one of which was treated with orbital decompression.[26] A case series of 5 patients in phase III studies of alemtuzumab for RRMS includes two that had associated ophthalmopathy. In one, clinical assessment score (CAS)[27] 2 ophthalmopathy developed 38 months after initiation of alemtuzumab and progressed to CAS 5 ophthalmopathy which was managed with IV methylprednisolone. In the other CAS 1 ophthalmopathy was managed with artificial tears.[28] A separate case report describes Graves' ophthalmopathy developing 1 year after Graves' thyroid disease was diagnosed and 3 years after alemtuzumab treatment. This patient had persistent lid retraction following thyroidectomy.[29]

Daclizumab is also associated with autoimmune conditions including severe autoimmune hepatitis. There are no reported cases of ophthalmic autoimmune conditions in the literature, though experience with the drug is limited as it was approved in May, 2016.[30]

OPPORTUNISTIC INFECTIONS

Given the immune system modulation that is the basis of many MS therapies it is not surprising that many are associated with opportunistic infections including progressive multifocal leukoencephalopathy (PML) due to John Cunningham (JC) virus infection[31] and herpes virus infections. Disseminated viral infections, some of which have been fatal, have occurred in patients treated with natalizumab[32], alemtuzumab[25] and fingolimod.[33] Severe infections have also occurred in daclizumab treated patients.[30]

PML is a life threatening infection due to JC virus that presents with focal neurological deficits and often seizures. Typical MRI appearance is T2 hyperintense, T1 hypointense lesions affecting the white matter including subcortical U-fibers, though posterior fossa involvement is not uncommon. Enhancement is variable. Though there are no proven treatments, several approaches have been associated with improved outcomes at the case series level including plasma exchange and mirtazapine in natalizumab associated PML.[34] A challenge in PML management is that some therapies such as cessation of and removal of immunomodulatory therapy can provoke immune reconstitution inflammatory syndrome, which can also cause central nervous system injury.[35] This has been managed with gluococorticoids in case series. PML in MS patients has been most recognized in association with natalizumab, leading to its withdrawal from the market and subsequent reintroduction with refined administration guidelines. Though not seen in the clinical trials leading to its approval, PML has subsequently been reported in association with fingolimod. It has also occurred in association with dimethyl fumarate, both in association with drug-induced lymphopenia and without.[36] PML has not yet been reported in association with daclizumab treatment, though duration of experience is minimal at this time.

Teriflunomide has not been associated with an increased risk of infection (serious or otherwise) compared with placebo based on a pooled safety analysis of 6400 patients on drug for a median of 670 days.[37] This is a unique amongst the newer MS disease modifying agents.

POSITIVE CONSEQUENCES OF MS MEDICATIONS (RELEVANT TO NEURO-OPHTHALMOLOGISTS)

VISUAL FUNCTION IMPROVEMENT (NATALIZUMAB, ALEMTUZUMAB, ANTI-LINGO-1, 4-AMINOPYRIDINE)

Two phase III trials of natalizumab included low contrast visual acuity as a tertiary endpoint.[38] 100%, 2.5% and 1.25% binocular contrast acuities were performed at each of 10 study visits, which occurred every 12 weeks. Z-scores for change from baseline demonstrated decline in 2.5% and 1.25% low contrast visual acuity in 315 patients receiving placebo and stability of vision in 627 natalizumab treated patients with statistical difference between the two groups seen at the 12 week visit and increasing in magnitude at future visits. There were no differences between groups in 100% contrast visual acuity. Prevalence of sustained worsening of 100% contrast VA was low and similar between treatment groups. However, there was lower cumulative probability of sustained 1.25% contrast VA worsening in natalizumab treated patients over 120 months.

In a phase II trial of alemtuzumab vs. interferon β-1a (IFNB-1a) for treatment naïve patients with relapsing remitting MS, contrast sensitivity was evaluated as an exploratory efficacy outcome in 273/324 patients. This was performed in each eye using Pelli-Robson charts. Sustained improvement was more likely to occur and sustained worsening less likely to occur in alemtuzumab versus IFNB-1a treated patients with both groups showing small, though statistically significant improvements in contrast sensitivity over 36 months.[39]

Anti-LINGO-1 has been studied for treatment of acute optic neuritis. Psychophysical visual function measures were not affected, though VEP latency was shorter in treated patients, suggesting a neuro-protective effect. The data has been presented at multiple conferences and is publically available at clinicaltrials.gov.[5] However, the manuscript had not been published at the time this syllabus was finalized.

Neuroprotective strategies are being actively investigated to decrease axonal loss during optic neuritis episodes. A recently completed phase II trial of 86 patients suggested that phenytoin administered for 3 months following optic neuritis was associated with less RNFL loss in comparison with placebo treated patients.[40] An open label trial of high dose biotin in patients with primary or secondary progressive multiple sclerosis included four with prominent optic nerve involvement, all of whom had visual acuity

improvement over 3 months.[41] Two of the patients had VEPs recorded and demonstrated improvement. A recent trial of amiloride in acute optic neuritis[42] did not show benefit (Presented at European Committee for Treatment and Research in Multiple Sclerosis Meeting; M. Craner, personal communication).

4-aminopyridine, the immediate release form of dalfampridine, is a potassium channel blocker that improves conduction in demyelinated neurons. Based on this, dalfampridine was studied for treatment of slow gait in MS and has FDA approval for treatment of this. 4-aminopyridine was studied in a randomized study of 22 patients with chronic optic neuropathy defined by OCT RNFL thinning. Low contrast VA, OCT and VEP were studied as outcome measures with 14 patients included in the final analysis (after exclusion for MS relapses during the study and non-adherence). 8/28 eyes treated with 4-AP showed improvement in LCVA compared with 3/28 placebo eyes, though there was no group difference. VEP latency improved in the 4-AP group but declined in the placebo group. This beneficial effect was more pronounced in eyes with less RNFL thinning.[43] 4-aminopyridine has also shown beneficial effects on nystagmus,[44] as have other agents. Dalfampridine, the commercially available formulation, has not been formally studied for vision or nystagmus outcomes.

DELAY OF PROGRESSION TO MS (I.E. AFTER CLINICALLY ISOLATED SYNDROME)

Multiple trials in the current century have evaluated IFNB-1b, glatiramer acetate, and cladrabine in patients with clinically isolated syndromes, including optic neuritis, and brain lesions on MRI (typically 2 or more). All showed a modest benefit of treatment in comparison with placebo on cumulative incidence of second clinical demyelinating event and development of new MRI lesions. Revision of MS diagnostic criteria in 2010, to allow diagnosis of MS following clinically isolated syndrome with concurrent radiographic demonstration of dissemination in time and space, has complicated interpretation of some of these studies since some included patients with enhancing brain lesions.[45] Due to the length of the trials, generally 2-3 years, long-term benefits including effects on disability have not been studied. Practice regarding treatment of optic neuritis patients with non-enhancing brain lesions on MRI varies throughout the world.[46]

Only one of the new MS therapies, teriflunomide, has been studied with regards to delaying onset of clinically definite MS in patients with clinically isolated syndrome and 2 or more T2 lesions on brain MRI. Similar to other agents studied, subjects receiving teriflunomide had both decreased progression to clinically definite MS and fewer new T2 lesions on MRI over 2 years. However, development of disability was no different between groups.[47]

CONCLUSION

The good: In trials of disease modifying MS medications that have included visual outcomes, treatment benefit has been demonstrated. There are candidates in the pipeline and on the market to improve visual outcomes following acute optic neuritis and to improve optic nerve function in patients with established optic neuropathy.

The bad: Two recently approved disease modifying MS drugs have specific neuro-ophthalmic risks. Fingolimod is associated with a low risk of macular edema that responds well to treatment discontinuation. Alemtuzumab is associated with autoimmune thyroid dysfunction and thyroid orbitopathy in a proportion of those affected.

The ugly: Many of the newer disease modifying MS drugs have powerful immune effects and are associated with potentially life threatening infections including PML and herpes virus infections.

The unknown:

- Absence of evidence is not evidence of absence with regards to both benefit & harm. Clinical experience in terms of numbers of patients treated and longer durations of treatment are necessary to determine the extent of many harmful consequences.
- Will there be macular edema associated with more specific S1P receptor modulators?
- Do other agents improve visual outcomes?

CME ANSWERS

1. b
2. a
3. c

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EYE MOVEMENT CHALLENGE: THE ADVANCED LEVEL

Jason S. Barton, MD, PhD, FRCPC

University of British Columbia
Vancouver, Canada

Michael C. Brodsky, MD

Mayo Clinic
Rochester, MD

William A. Fletcher, MD, FRCPC

University of Calgary
Calgary, Canada

Caroline Tilikete, MD, PhD

Hospices Civils de Lyon, University Lyon I, Lyon
Lyon, France

David S. Zee, MD

Johns Hopkins University School of Medicine
Baltimore, MD

I. CASES

SESSION 1.

Case 1 (CT). The negative consequences of being fit
A 55 year-old man complained of longstanding recurrent brief episodes of right monocular blurring of vision, oscillopsia and vertical diplopia.

The episodes became more frequent with stress and physical exercise. Neurological and ophthalmologic findings were normal except for hypertropia of the right eye, which increased during adduction and depression, suggestive of right superior oblique palsy. The right eye also showed irregular oscillations.

Case 2 (CT) Don't make me mad
A 35-year-old exhausted mother complained of spells of rotatory vertigo for a few months.

The symptoms lasted for a few minutes and were triggered when she was stressed, angry or shouting at her four kids. Examination showed normal saccades, smooth pursuit, horizontal oculocephalic reflex and VOR suppression. There was no spontaneous nystagmus in central or eccentric gaze, including when fixation was removed. Repeated head-shaking, however, triggered right-beating nystagmus, and hyperventilation for 30 sec triggered left-beating nystagmus and vertigo. Weber's test was normal and an audiogram showed normal pure-tone thresholds and speech discrimination.

Case 3 (WF) What goes up comes down too
A 61-year-old man was referred with 5 years of constant oblique diplopia.

It was slightly worse in the morning and not relieved by sleep. Orthoptic testing initially showed mildly limited right eye abduction, an incomitant esotropia and a left hypertropia. The incomitant pattern of the deviations suggested right VI and left IV nerve palsies. CT and MRI showed an arachnoid cyst in the right middle fossa. He was given prisms that improved the diplopia. The esotropia and left hypertropia worsened gradually over the next 5 years and elevation of the right eye became mildly limited, triggering a neuro-ophthalmology referral.

Examination showed an incomitant 20 prism-diopter esotropia, a 12 prism-diopter left hypertropia, and ductional limitations that again suggested right VI and left IV nerve palsies. Sustained upgaze did not show lid fatigue but on resuming primary gaze he now had a right hypertropia, which gradually reverted over a few minutes to the resting left hypertropia.

Case 4 (WF) Falling down but not looking down
A 56-year-old woman had a recently discovered eye movement abnormality and 10 years of increasing imbalance.

She had episodic falls triggered by sudden general rigidity and tremor ("my earthquakes"). Over the previous 7 years, she had seen 4 neurologists who had noted mild signs of spasticity, dysarthria, gait ataxia and, more recently, cervical dystonia. MRI of the brain was normal. In the last year, she was found to have abnormal vertical saccades, but she had no visual complaints.

Case 5 (DZ) What shifted in his overhead bin?
A 32 year old healthy man came to attention during a preflight physical.

Since childhood he had noted that objects moving past him to the left, and only to the left, would vibrate side-to-side. The only findings were a bit of gaze-evoked nystagmus on far left gaze. With attempted smooth pursuit to the left or with attempted VOR suppression with the head rotating to the left, there was abrupt left-beating nystagmus. Optokinetic stimulation produced the same findings as attempted smooth pursuit or VOR suppression.

Case 6 (DZ) Life of the (neuro-ophthalmology) party
A young woman was seen in the vestibular clinic for headaches and dizziness.

An incidental finding was gaze-evoked nystagmus on left gaze, seen under Frenzel lenses. When this was brought to her attention she noted that she could make her eyes wiggle as a party trick.

Case 7 (MB) A divergent point of view
A 6-year-old boy was referred for intermittent exotropia and frequent squinting of the left eye.

Development had been normal, with no family history of strabismus. Examination showed 20 prism-diopters of intermittent exotropia with bilateral ptosis and fixed downgaze. He frequently squinted the left eye during attempted fixation. On gaze to either side, both eyes simultaneously abducted.

Case 8 (JB) Tilting at windmills
This 64-year-old woman had fluctuating diplopia for 11 years, after resection of a thalamic lesion.

After the surgery she had intermittent diplopia three or four times a day, lasting a few minutes, often aborted by squeezing her eyes tight. She was not sure about the direction of diplopia.

Examination showed 3 prism-diopters of left hypertropia in downgaze.Otherwise she was orthotropic and had full ductions, normal smooth pursuit and saccades. She had a right head tilt at rest.

Case 9 (JB) The distracting dinner date
A 29 year-old man had 6 months of odd dinner-time behaviour.

Initially he noted mild blurring of the superior field and a brief flash of light when he opened his mouth, chewed, or clenched his teeth. After a while, he noted right periorbital discomfort and sometimes slight oblique diplopia when chewing. His wife noted strange movements of his right eye as he ate. He had been well otherwise.

Visual function and eye movements were normal. Pupils and lids were symmetric. Hertle measures at rest were 19mm od and 18mm os. The neurological exam was normal. A CT scan of his head with contrast had been reported as normal.

SESSION 2

Case 10 (MB): Look this way, no, that way
A 6-month-old boy was seen for suspected delayed visual maturation with poor visual tracking. Since birth, he had "looked out of the side of his eyes." Within the last month, he had begun turning his head to either side. He had a history of hypotonia and a "skin tag on his left pinkie."

Examination showed cyclic episodes of alternating conjugate gaze deviation necessitating a contraversive head turn to view objects of interest. On subsequent examinations, horizontal head thrusts became more prominent and he showed developmental delay in motor and speech development.

Case 11 (MB) Bouncing babies
Two identical twin girls from Indonesia presented with repetitive bursts of rapid vertical saccadic oscillations. These oscillations began at 3 months of age. They occurred only in supine position and disappeared when a cheek was tapped. There were no associated limb movements. Both infants were born full term and were otherwise developmentally normal. They had no antecedent illnesses and showed no signs of acute infection or other systemic abnormalities.

Both children underwent negative investigations to rule out neuroblastoma that included urinary VMA, abdominal ultrasound, and chest x-ray. MR imaging detected no structural abnormalities within the brain. Results of EEG were also normal. In both twins, the abnormal eye movements resolved by 6 months of age. The children are now 4 years of age and attaining normal developmental milestones.

Case 12 (DZ) The back-row kid
A young child was evaluated by her local ophthalmologist for difficulty seeing the board at school.

The ophthalmologist noticed something "funny" about her eye movements and referred her to us for an evaluation.

Case 13 (DZ) Is this on the consent form?
A patient had an MRI scan in a high strength machine (7T) and complained of vertigo when moved into the machine.

Case 14 (CT) Driving with the top down
A 50-year old woman with bipolar disorder, controlled by lithium for 7 years, presented with vertical oscillopsia.

It started a year earlier while she was driving in the Alps and had persisted. Oscillopsia increased with physical activity and was synchronous with her heart beat. She had no complaints of vertigo, tinnitus or imbalance.

Neurological and ophthalmologic findings were normal apart from a spontaneous vertical pendular nystagmus in primary gaze and gaze-evoked nystagmus. The nystagmus in central gaze was synchronous with her pulse. It did not change with hyperventilation, after changing head position or after horizontal or vertical head shaking. Head-thrust maneuvers in the horizontal plane and in the planes of the vertical canals showed a normal vestibulo-ocular reflex. Valsalva manoeuvre against a closed glottis induced an upbeating and counter-clockwise-beating nystagmus. Weber's test was negative. Pressure changes in the ear canal did not induce vertigo, oscillopsia or nystagmus. Audiogram revealed normal pure-tone thresholds and speech discrimination scores. Tympanogram was normal. MRI and MR angiography were normal.

Case 15 (WF) She's got rhythm
A 42-year-old woman with neurofibromatosis type 1 endorsed a constant slight oscillopsia in her right eye for many years. She could not describe the trajectory. Visual acuity was 20/30 right eye and 20/20 left eye. In central gaze, the right eye exhibited a barely visible constant biphasic vertical nystagmus with a faster downward phase and a frequency of about 1.5 Hz. There was a synchronous slight movement of the right lower lid and slight ptosis of the upper lid. The left eye did not oscillate.

Case 16 (WF) Front and center
A 20-year-old college student was referred for abnormal eye movements.

He had 14 months of progressive dysarthria, decreasing speech output and increasing apathy. He had been an A+ student but had become withdrawn and had recently stopped classes. He had become almost anarthric but could still text sentences over his phone. Verbal comprehension and reading were intact. A neurologist had noted "slow saccades and difficulty maintaining upgaze", hypomimia, a brisk jaw jerk and a positive pout reflex. Otherwise, bulbar muscles, limb muscles and reflexes were normal. MRI showed mild isolated atrophy of both frontal lobes. There was no family history of neurologic disorders. Investigations were negative for Niemann-Pick type C, Gaucher's, Wilson's, Whipple's, spinocerebellar ataxia, metachromatic leukodystrophy, intermediate filament inclusion disease, myotonic dystrophy and autoimmune encephalopathy.

Case 17 (JB) The wheels on the bus
This 20-year-old man was seen for abnormal eye movements.

As a child he had global developmental delay and did not talk until age 3 or walk until age 6. He had had epilepsy for at least 6 years, often typified by tonic posturing with eye and head deviation, followed by somnolence and fatigue.

Abnormal eye movements were noted since childhood, as well as jerking movements of his head to look around. He sat close to the television, and an optometrist documented myopia (-4.00 diopters) and astigmatism.

He was taking carbamazepine, vitamin D, calcium and erythropoietin. He had renal failure and was on dialysis. He had two brothers, one with the same syndrome.

There was no field defect and fundoscopy was normal.

Case 18 (JB) Head to toe
This 28-year-old man noted intermittent left lower lid twitching for a year.

He noted this by chance while sitting and moving his toes. It had become bothersome because it occurred constantly while walking. There was no other facial or limb twitching. There was no history of trauma, facial palsy, diplopia or ptosis.

Despite his lack of diplopia, exam showed a left IV nerve palsy with large vertical fusional amplitudes, presumably congenital.

North American Neuro-Ophthalmology Society

43rd Annual Meeting

April 1 – April 6, 2017
Washington Marriott Wardman Park • Washington, DC

NANOS ON-SITE REGISTRATION/HELP DESK HOURS:

Location:	**Thurgood Marshall Foyer**
Saturday:	**2:00 pm – 8:00 pm**
Sunday - Monday:	**6:30 am – 5:30 pm**
Tuesday:	**6:30 am – 12:30 pm**
Wednesday:	**6:30 am – 5:30 pm**
Thursday:	**6:30 am – 12:00 pm**

SATURDAY, APRIL 1

Opening Reception – Marriott Foyer

6:00 pm - 7:30 pm

Please join us for the Opening Reception at the Washington Marriott Wardman Park. All are welcome to attend the opening reception, which features complimentary cocktails and hors d 'oeuvres.

SUNDAY, APRIL 2

Members-in-Training Program and Reception – Marriott Foyer

5:30 pm - 6:30 pm

New to Neuro-Ophthalmology? All students, residents and fellows-in-training are encouraged to attend!

TUESDAY, APRIL 4

Afternoon Excursions

12:30 pm – 4:30 pm

All excursions depart from the Marriott entrance near Harry's Pub at 12:30 pm and include transportation, a boxed lunch, and admission (if applicable). Excursions return to the hotel at 4:30 pm.

VIP TOUR OF THE UNITED STATES CAPITOL BUILDING - $198/person

No building in the country exudes such an aura of power and drama as The United States Capitol! Guests will be able to enjoy a once in a lifetime opportunity when touring the building with a former member of Congress. Once inside, guests will travel the ornately painted Brumidi Corridors until they reach Statuary Hall, which served as the House of Representatives' Chamber until 1857. Following Statuary Hall, guests will pass through the Rotunda for a closer look at its magnificent architecture and stunning murals depicting early America and its growth as a democracy. When congress is not in session, guests will have the rare opportunity to visit the House of Representatives' chamber and sit in the Member's chairs on the "floor" of the House as they listen to more fascinating facts from the former member and our master tour guide.

Recommended Attire: *Casual attire. Comfortable walking shoes.*

TOUR OF MOUNT VERNON ~ GEORGE WASHINGTON'S ESTATE - $105/person

Mount Vernon was the plantation home of George Washington, first President of the United States, and his wife, Martha Dandridge Custis Washington. The historic estate includes not only the Mount Vernon Mansion, George and Martha's home, but also a host of colonial era buildings, beautiful gardens, a working distillery and gristmill, and museum and interactive education center. Guests will tour the mansion and the surrounding service buildings, the interactive education center, and the Washington family museum, where personal effects of George and Martha are on display. Located 15 miles south of Washington, DC along the scenic Potomac River, Mount Vernon is a true national treasure guests will enjoy exploring.

Recommended Attire: *Casual attire. Comfortable walking shoes that may get dirty. Umbrella or rain jacket. Sunglasses.*

SEGWAYS IN THE CITY - $170/person
The Segway is the first of its kind—a self-balancing, personal transportation device that's designed to operate in any pedestrian environment. Your private tour will begin with luxury mini coach transportation to your tour start location. Upon arrival, guests will receive a thirty minute training session on the operation and safety of the Segway and will have ample time for practice. Then, it's all aboard and off to the Smithsonian Castle along the National Mall, the U.S. Capitol Building, Washington Monument and World War II Memorial. The Vietnam Veterans Memorial (including the Three Servicemen and Nurses Memorial), the Lincoln Memorial, and the Korean War Memorial are also visited throughout the tour. Guests will enjoy this unique perspective along the National Mall!

Recommended Attire: *Comfortable/athletic attire. Closed-toe, athletic sneakers or walking shoes. Sunglasses.*

WEDNESDAY, APRIL 5

Annual NANOS Reception and Banquet
6:30 pm – 11:30 pm
Join colleagues for a fun, casual evening of socializing, dining and dancing at the NANOS Annual Banquet and Reception which will be held in the Thurgood Marshall Ballroom at the Washington Marriott Wardman Park. Event is complimentary for attendees, but guests must purchase tickets for $100 per person.

KEYWORD INDEX

SAVE THE DATE

2018

44TH ANNUAL MEETING

NANOS

Hilton Waikoloa Village-Waikoloa Village, Hawaii, The Big Island

March 3-8, 2018

NORTH AMERICAN NEURO-OPHTHALMOLOGY SOCIETY


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