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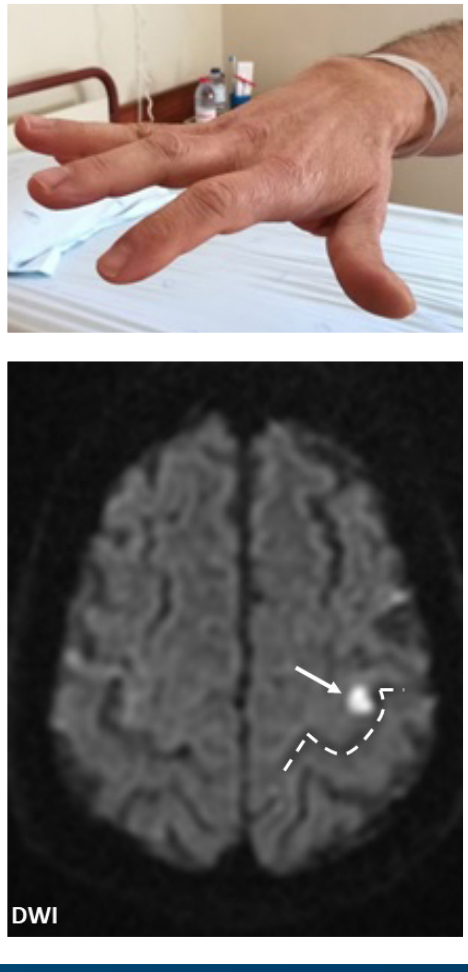

ACADEMIA BRASILEIRA DE NEUROLOGIA

Congresso Brasileiro de Neurologia
2020 2022
Fortaleza.CE

Caros Amigos,

É com muito prazer que convidamos a todos para o Neuro 2022, o XXX Congresso da Academia Brasileira de Neurologia, que será realizado aqui em Fortaleza entre os dias 21 a 24 de setembro do próximo ano.

Nós da Comissão Organizadora, atentos às condições epidemiológicas e sanitárias, planejamos um evento híbrido. Teremos o retorno de atividades presenciais para o número de participantes permitido pelas normas vigentes e faremos transmissão ao vivo para os que preferirem participar de forma virtual.

Esperamos vocês no Neuro 2022 para refletirmos a neurologia do Futuro através de estratégias inovadoras, abrindo o espaço de reconhecimento de toda a produção em neurociências de nosso país, a qual nos guiará pelos melhores caminhos futuros. Faremos isso a partir de quatro eixos principais: **Discutir, Rever, Abordar e Inovar**.

Iremos **Discutir** os dilemas éticos e os desafios como neurologistas; **Rever** temas importantes para a prática neurológica e seu ensino; **Abordar** os avanços dos últimos anos; e **Inovar** na maneira de agir, diagnosticar e tratar.

Com a participação de todos o debate em torno destes tópicos terá a consistência e a força necessária para melhorar o nosso exercício profissional e, por consequência, a neurologia em nosso País.

Além das belezas naturais de Fortaleza, queremos fazer do Neuro 2022 uma oportunidade ímpar para o tão desejado reencontro, seja de forma presencial ou virtual, e uma experiência transformadora inesquecível.

Acessem nosso site, www.neuro2022.com.br e contribuam com sugestões de temas.

Até lá.

Norberto Frota | Presidente do Congresso
Fernanda Maia | Secretária
Pedro Braga Neto | Tesoureiro
Manoel Sobreira | Coord. da Comissão Científica
João José Carvalho | Presidente de Honra

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NEURO-PSIQUIATRIA

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Apoio:

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ACADEMIA BRASILEIRA DE NEUROLOGIA

Torne-se um membro

da Academia Brasileira de Neurologia, veja as suas vantagens:

- Os sócios da ABN são reconhecidos pela World Federation of Neurology, entidade mundial da qual a ABN faz parte representando o Brasil.
- A ABN é a entidade representativa dos neurologistas no Brasil junto a Associação Médica Brasileira.
- Receber redução no valor de inscrições em congressos, cursos e simpósios realizados ou apoiados pela ABN e por outras entidades associadas à Academia.
- Receber antecipadamente a publicação online das Revistas Arquivos de Neuro-Psiquiatria e Dementia & Neuropsychologia, antes mesmo da disponibilização da mesma na Scielo.
- Acesso ao Portal RIMA – Rede de Informática de Medicina Avançada. Sistema de informação cientifica com altos níveis de evidência com mais de 2400 revistas internacionais.
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- Ter a possibilidade de realizar congressos, simpósios, cursos e jornadas eventualmente apoiados pela ABN.
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- Se inscrever para pertencer em até 3 Departamentos Científicos da Academia, além dos Departamentos Científicos de Neurologia Geral e História da Neurologia.
- Eventualmente ser convidado a participar de atividades científicas, culturais e ou das comissões da Diretoria da ABN.
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- Indicação de seu nome juntamente com os demais de sua região como recomendado ABN, quando solicitado por pacientes.
- Ter um foro de discussão de temas com relação à atividade profissional do neurologista.
- Defesa Profissional: Ações de políticas de estado; ações de competidores não-médicos.

Arquivos de Neuro-psiquiatria

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EDITORIAL

ARTICLE

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Dialysis headache

Cefaleia em diálise

Mario Fernando Prieto PERES[1]

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Headache in dialysis is the rule, not the exception[1]. Although a common and debilitating experience in patients undergoing the procedure, little is known about its mechanisms. In this edition, Melo et al.[2] is shedding some light in the understanding of this condition by studying 100 consecutive dialytic patients with structured questionnaires and transcranial doppler ultrasonography.

Although the International Classification of Headache Disorders (ICHD-3)[3] makes "Dialysis Headache" seem too simple, broad, and obvious, without any attempt of distinguishing different patterns within this context, the authors found migraine or tension-type headache in three quarters of the studied population, but headaches starting or worsening during dyalisis and/or resolving within 72 hours occurring in only half.

Two new aspects have been shown in this paper. Quality of life was significantly worse in headache patients; therefore, more attention should be given to the topic. The neurovascular mechanism was studied with transcranial doppler of the middle cerebral artery bilaterally, comparing blood flow and vascular resistance. Dialysis headache is neurovascular, due to cerebral vasodilation. It has been previously proposed that nitric oxide might be involved[4], an assumption confirmed by Melo et al.

Implications arise from these findings, in therapy and classification. Should we pretreat patients so that dialysis can be prevented? If so, what kinds of therapies could be started? Since CGRP is involved, would Anti-CGRP Monoclonal Antibodies help? Are patients responsive to triptans? Hopefully the future will tell and guide treatments by further clinical trials in this setting.

In terms of classification, if the tension-type or migraine pattern prevails, aren't we talking about a primary headache trigger? It seems more logical thinking "dialysis headache" as a trigger rather than a secondary headache, as it is currently defined in the ICHD-3. More research is welcome in the area.

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ARTICLE

Semi-automated data collection from electronic health records in a stroke unit in Brazil

Coleta de dados semiautomáticos de registros eletrônicos de saúde na unidade de acidente vascular cerebral no Brasil

Raquel Franco Zambom VALÊNCIO[1], Juli Thomaz de SOUZA[2], Fernanda Cristina WINCKLER[2], Gabriel Pinheiro MODOLO[3], Natalia Cristina FERREIRA[3], Silmeia Garcia Zanati BAZAN[2], Marcos Christiano LANGE[2,4], Carlos Clayton Macedo de FREITAS[3], Sergio Alberto Rupp de PAIVA[2], Rogério Carvalho de OLIVEIRA[2], Gustavo José LUVIZUTTO[5], Rodrigo BAZAN[3]

ABSTRACT

Background: There is a high demand for stroke patient data in the public health systems of middle and low-income countries. **Objective:** To develop a stroke databank for integrating clinical or functional data and benchmarks from stroke patients. **Methods:** This was an observational, cross-sectional, prospective study. A tool was developed to collect all clinical data during hospitalizations due to stroke, using an electronic editor of structured forms that was integrated with electronic medical records. Validation of fields in the electronic editor was programmed using a structured query language (SQL). To store the results from SQL, a virtual table was created and programmed to update daily. To develop an interface between the data and user, the Embarcadero Delphi software and the DevExpress component were used to generate the information displayed on the screen. The data were extracted from the fields of the form and also from cross-referencing of other information from the computerized system, including patients who were admitted to the stroke unit. **Results:** The database was created and integrated with the hospital electronic system, thus allowing daily data collection. Quality indicators (benchmarks) were created in the database for the system to track and perform decision-making in conjunction with healthcare service managers, which resulted in improved processes and patient care after a stroke. An intelligent portal was created, in which the information referring to the patients was accessible. **Conclusions:** Based on semi-automated data collection, it was possible to create a dynamic and optimized Brazilian stroke databank.

Keywords: Stroke; Benchmarking; Artificial Intelligence; Supervised Machine Learning; Emergency Service, Hospital.

RESUMO

Antecedentes: Há alta demanda de dados de pacientes com acidente vascular cerebral (AVC) nos sistemas de saúde de países de baixa e média renda. **Objetivo:** Desenvolver um banco de dados de AVC para integrar dados clínicos ou funcionais e indicadores de qualidade de pacientes com AVC. **Métodos:** Estudo observacional, transversal e prospectivo. Foi desenvolvida uma ferramenta para coletar dados clínicos durante as internações por AVC por meio de um editor eletrônico de formulários estruturados integrado ao prontuário eletrônico. A validação dos campos no editor eletrônico foi programada em linguagem de consulta estruturada (SQL). Para armazenar os resultados da SQL, uma tabela virtual foi criada e programada para atualização diária. Para desenvolver interface entre os dados e o usuário, foram utilizados o *software Embarcadero Delphi* e o componente *DevExpress* para gerar informações apresentadas na tela. Os dados foram extraídos dos campos do formulário e também do cruzamento de outras informações do sistema informatizado, incluindo pacientes internados na unidade de AVC. **Resultados:** O banco de dados foi criado e integrado ao sistema eletrônico do hospital, permitindo coleta diária de dados. Indicadores de qualidade foram criados no banco de dados para que o sistema acompanhasse e realizasse a tomada de decisão com os gestores dos serviços de saúde, resultando em melhoria no processo e no atendimento ao paciente após AVC. Foi criado um portal inteligente, no qual eram registradas as informações referentes aos pacientes. **Conclusões:** Com a coleta de dados semiautomática, foi possível criar um banco de dados de AVC dinâmico e otimizado em unidade de AVC no Brasil.

Palavras-chave: Acidente Vascular Cerebral; Benchmarking; Inteligência Artificial; Aprendizado de Máquina Supervisionado; Serviço Hospitalar de Emergência.

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Conflict of interest: There is no conflict of interest to declare.

Authors' contributions: GJL, CCMF, RCO, RB: conceptualization, data curation, formal analysis, writing – original draft preparation, project administration, supervision, writing – review & editing; RFZV, JTS, FCW, GPM, NCF: investigation, methodology; RB, SGZB, MCL, SARP: supervision, validation, visualization, roles/writing – original draft, writing – review.

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INTRODUCTION

Stroke is the second leading cause of death and disability worldwide. It has a significant socioeconomic impact on low- and middle-income countries, thereby affecting public health status[1-3]. In the last 40 years, databank projects have been implemented to provide information on the clinical courses and outcomes of stroke[4-8].

Implementation of a databank is important for planning and decision-making by healthcare service managers, in order to improve processes and stroke care outcomes[9]. However, integration of these databanks is limited to large centers and clinical trials, thus restricting access to low and middle-income countries[10]. In accordance with the principles of stroke care lines in developing countries, it is necessary for all quality criteria during stroke hospitalization to be registered in electronic medical records, with the aim of establishing new healthcare policies[11].

Based on these premises, implementation of a computerized database system containing the main clinical indicators of stroke patients has become a reality in developing countries[12,13]. Over recent years, the introduction of artificial intelligence has helped in development of databases that are integrated in networks, with the capacity to identify clinical data with greater agility and security[14,15].

Therefore, the aim of this study was to develop an interface for accessing stroke patient data and the main benchmarks in acute stroke care, in order to create a semi-automated databank for implementation in low and middle-income countries.

METHODS

Study design, setting and participants

This project with the aim of developing a semi-automated stroke databank was conducted at the stroke unit of Faculdade de Medicina de Botucatu, Botucatu, Brazil. This stroke unit has 10 beds, with an average of 30 patients/month, and belongs to a tertiary-level hospital with 684 beds. The hospital has a hospital information system (HIS) that includes electronic patient records containing clinical and treatment information. All patients who were admitted to the stroke unit were included in this project. The study was approved by the institution's Ethics in Human Research Committee.

Procedures

To organize the information, the tool was designed to include initial data, a clinical summary of the presentation, hospital course (including complications and infections), investigation/complementary examinations (including computed tomography [CT], electrocardiography, echocardiography, Holter data, carotid and vertebral duplex data, CT angiography, magnetic resonance imaging [MRI] angiography, control CTs or MRIs and transcranial Doppler) and discharge conditions (including etiological diagnosis, medications, discharge with therapy plan, rehabilitation and destination of the patient). The rules for each subgroup were planned so as to validate the completion of certain fields, all of which were mandatory for the service to be completed.

The database interface was developed on the HIS platform, and clinical data were collected based on the following benchmarks for stroke care: 1) prophylaxis for deep venous thrombosis, starting no later than the second day; 2) hospital discharge with antiplatelet therapy for patients with non-cardioembolic stroke; 3) hospital discharge with oral anticoagulation for patients with atrial fibrillation or atrial flutter; 4) use of antiplatelet agents when indicated, starting on the second day of hospitalization; 5) hospital discharge with statins for patients with atherothrombotic stroke; 6) hospital discharge with prophylactic therapy and rehabilitation plan; 7) percentage of patients with acute cerebrovascular disease; 8) length of hospital stay; 9) complications; 10) stroke type-specific ICD-10; 11) hospital mortality; 12) time to CT <25 min; and 13) door-to-needle time ≤60 min.

Execution, monitoring and control phase

To execute the development of the tool, an electronic editor of structured forms was used, which was integrated with the electronic medical record platform used in the institution. Parameterized fields and validation rules were created for essential fields. The rules were created in the field editor. Radio button components were used for information with only one choice and checkbox components were used when the information consisted of multiple choices. In addition, the validation of fields was programmed using a structured language, i.e. in structured query language (SQL)[16].

Mandatory fields were configured in the editor, and each field was parameterized. All patients who were admitted to the stroke unit were included in the database, as this was mandatory at the time of transfer to another ward or at the time of the patient's discharge or death.

Databank storage

To store the results from SQL, a virtual table was created and programmed to update daily at 04:00 h. The interface between the data and user was developed using the program Embarcadero Delphi, and the DevExpress component was used to generate the information displayed on the screen.

Data quality

The stored data were analyzed to check the data quality in accordance with the pre-established rules for creating the tool as mandatory fields with relationships between the fields. A rule was also created to identify patients who were admitted to the stroke unit and then transferred to another

unit, but for whom no discharge summary was filled out at any time during hospitalization. In preparing SQL and business rules for both data analysis and for out-of-base patients, the PL/SQL (Procedural Language for SQL) tool was used via Embarcadero. The data were extracted from the fields of the form and also from cross-referencing of other information from the computerized system, such as patients who were admitted to the stroke unit.

RESULTS

Once extracted, the data were stored in a database, and any type of information could be consulted at any time, thus allowing cross-referencing between the data of the tool and the patients' demographic profile. The indicators that were established according to the area and database were available in almost real time, with daily updates at 04:00 h. The database began registering patients in August 2018 and has included data from approximately 1,000 stroke patients to date.

Both qualitative and quantitative results can be obtained from the detailed data included in the database. The results can be grouped to create filters that can be applied to any column within the database. This provides an overview of the total number of patients for each parameter, thus resulting in development of appropriate public health policies.

In addition to the specific data characteristics of stroke patients, and owing to the integration with the electronic medical record, important clinical data such as hospital course, laboratory test results, imaging tests and surgeries, as well as the main scales used in the stroke unit, can be displayed on the screen (Figure 1).

The quality indicators (benchmarks) were created in the database for the system to track and perform decision-making in conjunction with healthcare service managers. This resulted in improved processes and patient care after a stroke (Figure 2).

An intelligent portal was created, in which all the information referring to patients' care was available in a single location in a dynamic and objective manner. Development of an interface with a specific database for a hospital area enabled creation of a new concept in relation to the data that were already included in the computerized system, thus allowing new ideas to emerge in order to improve and facilitate the interpretation of large volumes of data (Figure 3).

DISCUSSION

This study reports the development of a tool integrated with electronic medical records that is capable of recording clinical data on patients admitted to a stroke unit and identifying the main indicators of quality of care, using artificial intelligence to improve the quality of care and decision-making process.

Several studies using previous databases have been conducted in low and middle-income countries to identify the quality of healthcare services[17-20]. Zetola et al. observed the registration of patients in a database with identification, previous clinical history, family history, treatments, previous comorbidities, complementary laboratory tests,

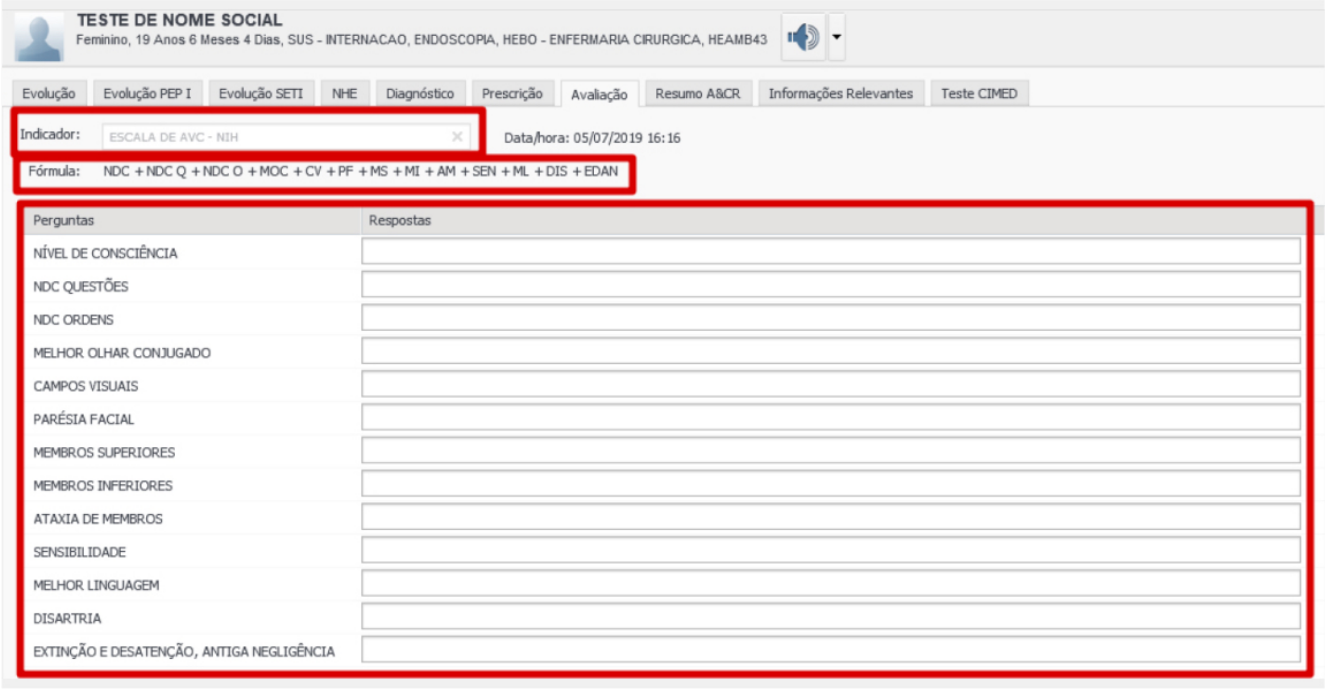

Figure 1. National Institutes of Health Stroke Scale displayed in the electronic medical record.

cardiac tests and neuroimaging tests. Using a computerized system, these data could be extracted dynamically, and their study suggested that a risk factor control program might lead to a reduction in stroke incidence[17].

In 2013, a single database for stroke patients was established in Joinville, Brazil, via a municipal law that required all public and private healthcare establishments to forward monthly information on stroke patients to the Department of Health to create an integrated database. In 2014, the Ministry of Health coordinated a simultaneous study in five cities in Brazil to assess the incidence of, mortality due to and main risk factors for stroke. The study included individuals with stroke and determined the environmental context of stroke, using a national database of stroke patients in Latin America[21,22].

The *Rede Brasil AVC* (Brazil Stroke Network), created to improve overall care for stroke patients in Brazil, is a non-governmental organization formed by professionals from various areas with the aim of providing quality care to stroke patients, from prevention to rehabilitation[23]. However, population studies to monitor clinical data on stroke patients need to be integrated into networks with shared access and periodic audits. The development of the tool in this study will help facilitate exploration of clinical data and quality indicators in low and middle-income countries.

Studies on the development of systems containing specific data on stroke patients have not been previously reported. Data collection methods were not reported in previous studies that included databases. Access to information has become increasingly faster and easier through technological advances that enable implementation of structured and standardized electronic databases that use artificial intelligence. Analysis on large datasets of patient characteristics, outcomes from treatments and their costs can help identify the most clinically effective and cost-efficient treatments for a population. Models, analytics, visualization large amounts of data and use of artificial intelligence come together to offer different perspectives on healthcare challenges within the contexts of time and geography. They provide strategic solutions to assist in management, decision-making and future clinical research[24,25].

Figure 3. Business intelligence applied to stroke databank.

INDICADORES DE SEGURANÇAS E QUALIDADE - PORTARIA 665 DO MINISTÉRIO DA SAÚDE

ANO

MES	1	2	3	4	5	6	7	8	9	10	11	12	13
⊕ ANO : 2018													
⊖ ANO : 2019													
12	23	23	3	24	7	23	67,86	10,45	7	22	5	4	1
11	21	20	4	26	6	18	86,21	6,81	6	25	3	8	1
10	25	17	1	21	6	20	100	7,97	7	20	2	7	0
09	14	12	3	14	1	15	94,74	9,05	3	16	1	5	1
08	25	22	2	25	4	27	93,55	8,28	6	24	5	11	0
07	35	34	4	37	8	42	93,48	8,75	10	35	5	10	1
06	27	16	4	23	5	20	96,43	6,43	6	23	2	4	0
05	23	20	3	21	1	22	88,46	5,25	3	20	1	3	1
04	16	14	0	18	3	8	100	6,38	4	19	2	5	1
03	18	15	0	18	2	9	100	5,27	2	14	2	7	1
02	30	20	2	28	7	24	93,33	5,78	4	26	3	6	0

1. profilaxia para trombose venosa profunda iniciada até o segundo dia
2. alta hospitalar em uso de antiagregante plaquetário em pacientes com AVC não cardioembólico
3. alta hospitalar em uso de anticoagulação oral para pacientes com Fibrilação Atrial (FA) ou "Flutter", salvo contraindicações
4. uso de antiagregantes plaquetários, quando indicado, iniciado até o segundo dia de internação
5. alta hospitalar em uso de estatina para pacientes com AVC aterotrombótico, salvo contraindicações
6. alta hospitalar com plano de terapia profilática e de reabilitação
7. porcentagem de pacientes com doença cerebrovascular aguda atendidos na Unidade de AVC
8. o tempo de permanência hospitalar do paciente acometido por AVC visando redução do mesmo
9. as seguintes complicações: trombose venosa profunda, úlcera de pressão, pneumonia, infecção do trato urinário
10. CID-10 específico do tipo de AVC à alta hospitalar
11. mortalidade hospitalar por AVC, visando redução da mesma
12. tempo porta-tomografia < 25 minutos
13. tempo porta-agulha < 60 minutos

Figure 2. Safety and quality indicators.

An integrated system significantly integrates separate sectors, and teamwork is recorded. This enables top management to fully analyze healthcare processes. Development of this database for stroke patients will optimize this search time and provide large quantities of relevant information for the area available, which can be used to support future studies[26,27].

In conclusion, through development of integration of this tool and electronic medical records, a dynamic and optimized stroke data bank was created. This database will be useful for managing quality indicators, assisting in the planning of actions at the stroke unit and supporting decision-making, and will serve as a basis for future studies and generation of new knowledge.

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ARTICLE

Epidemiological analysis of stroke patients with emphasis on access to acute-phase therapies

Análise epidemiológica de pacientes com AVC com ênfase no acesso às terapias de fase aguda

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ABSTRACT

Background: Stroke is a public health problem. For patients with ischemic stroke, venous thrombolysis and mechanical thrombectomy are effective therapeutic options. However, even after the National Stroke Treatment Guidelines were published in 2012, the number of cases treated is still lower than expected. **Objective:** To identify the determining factors for obtaining access to acute-phase therapies in the state of Espírito Santo (ES) and investigate the profile of stroke patients treated at the Central State Hospital (HEC). **Methods:** Retrospective data from the medical records of 1078 patients from May 2018 to December 2019 were analyzed. **Results:** Among the 1,078 patients, 54.9% were men and the most prevalent age group was 60 to 79 years. Systemic arterial hypertension was the main single risk factor. Regarding treatment modality among the patients who arrived at the HEC within the therapeutic window, 47% received some type of acute-phase therapy. Waking up with the deficit was the main contraindication for venous thrombolysis in these cases. **Conclusions:** Application of the flowchart established by SESA-ES seemed to be effective for enabling responsiveness of care for stroke victims. Public emergency transport services had a fundamental role in this process. In addition, the care provided by the tertiary stroke center provided excellent access to acute-phase therapies. However, despite the efficiency of the service provided at the HEC, it only reached a maximum of 50% of the ES population. This service model therefore needs to be expanded throughout the state.

Keywords: Stroke; Mechanical Thrombolysis; Health Profile; Public Health.

RESUMO

Antecedentes: O acidente vascular cerebral (AVC) é um problema de saúde pública. Nos casos de AVC isquêmico, a trombólise venosa e a trombectomia mecânica são efetivas opções terapêuticas de fase aguda. Entretanto, mesmo com a Diretriz Nacional de AVC publicada desde 2012, o número de casos tratados ainda é baixo. **Objetivo:** Apurar os fatores determinantes para o acesso às terapias de fase aguda na realidade espírito-santense e investigar o perfil dos pacientes de AVC atendidos no Hospital Estadual Central de Vitória (HEC). **Métodos:** O presente estudo analisou dados retrospectivos de prontuários de 1.078 pacientes no período de maio de 2018 a dezembro de 2019. **Resultados:** Dos 1.078 pacientes, 54,9% eram homens e a faixa etária mais prevalente foi a de 60 a 79 anos. A hipertensão arterial sistêmica foi o principal fator de risco isolado. Quanto ao tratamento, identificou-se que entre os pacientes que chegaram ao HEC na janela terapêutica 47% receberam terapia de fase aguda e que acordar com o déficit foi a principal contraindicação para trombólise venosa nesses casos. **Conclusões:** As análises demonstraram que a aplicação do fluxograma estabelecido pela Secretaria de Estado da Saúde do Espírito Santo parece ser eficaz na agilidade de atendimento das vítimas de AVC e que o Serviço de Atendimento Móvel de Urgência tem um papel fundamental nesse processo. Além disso, a assistência de um centro terciário de AVC permite acesso às terapias de fase aguda com excelência. Todavia, mesmo que o modelo de serviço prestado no HEC seja eficiente, ele atinge no máximo 50% da população do ES, sendo necessária a sua ampliação.

Palavras-chave: Acidente Vascular Cerebral; Trombólise Mecânica; Perfil de Saúde; Saúde Pública.

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INTRODUCTION

Stroke is an important public health problem and has been the second leading cause of death worldwide since the year 2000[1]. In Brazil, the prevalence of stroke is no different, since in 2017 it was the third leading cause of death. In the state of Espírito Santo, the number of occurrences is also significant, with more than 4,000 cases of hospitalization for stroke per year[2]. According to the World Health Organization, stroke is defined as the development of sudden neurological deficits, resulting from a vascular injury, with symptoms lasting 24 hours or more, which compromises cognitive, sensory or motor functions[3]. Most of the patients who survive have permanent cognitive and motor sequelae, which impacts family and social dynamics[4].

Among the therapeutic possibilities for ischemic stroke, venous thrombolysis (VT) is one of the most effective. It can increase the chances of a good clinical outcome by up to 30%[5]. VT is currently indicated for patients with evolution of up to 4.5 hours from the time of symptom onset (ictus), while respecting inclusion and exclusion criteria[6]. This form of treatment was approved in Brazil in 2001 but, despite recent advances in this treatment class, the number of patients who have access to it is still low in this country[7]. Mechanical thrombectomy (MT) is another acute-phase treatment that has been established for stroke. Its use has been correlated with a chance more than 50% of reducing functional impairment[8]. It has been indicated for patients who present arterial occlusion of proximal vessels and with up to 6 hours of ictus, while also respecting clinical and radiological criteria[9].

Given that the characteristics of stroke are severe, it is clear that urgent adequate medical assistance needs to be sought as soon as the first signs and symptoms appear. Time is a critical component for enabling access to the existing therapies[10].

In order to standardize patient care in the most diverse regions of Brazil, the Ministry of Health made stroke care guidelines available in 2013[11]. These provide instructions for professionals at all levels of healthcare. Following this same logic, in 2018 the Health Department of the State of Espírito Santo (SESA-ES) published the Clinical Guidelines for Managing Stroke Patients. Through this document, it was sought to reduce morbidity and mortality due to stroke. A more specific flow for care, referring to service units, was described[12].

The aims of this study were to investigate the profile of stroke victims treated at the Central State Hospital (HEC) in Vitória, from May 2018 to December 2019, and to examine the determinant factors for achieving access to acute-phase therapies within the realities of the state of Espírito Santo.

METHODS

This study was carried out after a consent statement had been signed by the board of HEC and approval had been obtained from the Institutional Review Boards (IRB) of the Multivix Faculty of Teaching, Research and Extension.

To develop this study, secondary data obtained retrospectively through analysis of the contents of medical records were evaluated. The study included all patients who were referred to HEC with suspected stroke, from May 2018 to December 2019, as long as they were 18 years old or older and had presented ictus within less than 6 hours. Patients with ictus up to 24 hours were also included, as long as the Glasgow Coma Scale score was greater than 10. Patients who had diagnoses of hemorrhagic stroke with surgical indication, subarachnoid hemorrhage (SAH), brain tumors, neuroinfectious or malignant middle cerebral artery (MCA) stroke with an indication for urgent surgery were excluded from the analyses.

The following data from the medical records were analyzed: sociodemographic data; patient's place of origin; time interval between ictus and hospital admission (called ictus-to-admission time); time interval between telephone contact from SAMU (public emergency transport service) to the hospital and hospital admission (called SAMU-to-admission time); presence of risk factors for stroke; number of patients undergoing acute-phase therapies (VT and/or MT); time interval between the onset of symptoms and the start of acute-phase therapy (called the therapeutic window); and time interval between hospital admission and infusion of the bolus of the thrombolytics (called door-to-needle time, DNT).

After data collection, statistical analyses were performed using the SPSS software version 24.0. Asymmetries were observed with regard to the continuous descriptive variables according to the Shapiro-Wilk test ($p<0.05$) and these were therefore taken as the median, minimum and maximum and 95% confidence interval (95%CI). Nominal variables were presented as frequencies and percentages. To check the influence of sex, age and place of origin on the therapeutic window, the chi-square test was used; and on the ictus-to-admission time, the Mann-Whitney and Kruskal-Wallis nonparametric tests were used. The significance level was taken to be 0.05. Cross-validations, Student's *t*-tests and ANOVA allowed possible correlations between the variables analyzed to be determined and conclusions to be reached.

RESULTS

Retrospective data from 1,330 patients were evaluated, as shown in the flowchart in Figure 1.

Regarding the sociodemographic profile, the patients' ages ranged from 20 to 98 years, with a median of 67 years. The data were thus divided into three age categories: young, patients aged between 20 and 59 years; middle-aged, 60 to 79 years old; and extremely aged, 80 years old or over. Middle-aged was the most prevalent category, accounting for 74.3% of the cases, followed by extremely aged with 16.5% and, lastly, the young category with only 9.2%. Regarding sex, men were

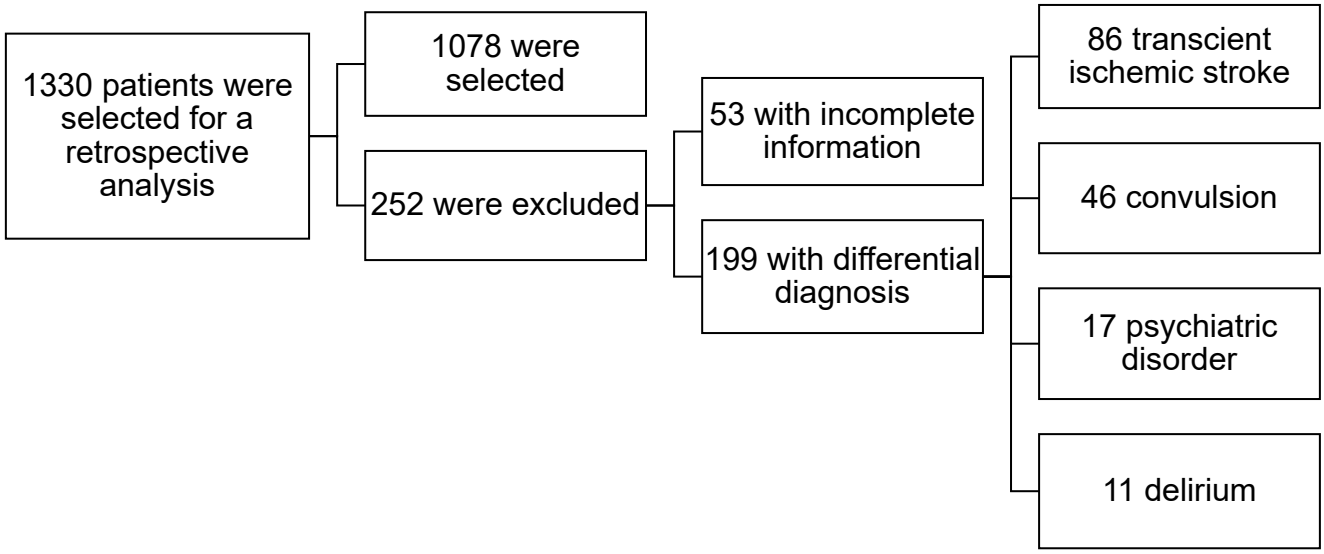


Figure 1. Patients selected for the study, according to the inclusion and exclusion criteria.

more affected by stroke, with 54.9% of the cases. Also within the sociodemographic profile, it was possible to demonstrate that the HEC received patients from 18 different cities, distributed as shown in Figure 2.

Clinically, the patients were assessed for isolated risk factors that may have been present in their clinical history. Systemic arterial hypertension was found to be present in 75% of patients and was the most prevalent factor, followed by diabetes in 31% of the cases, previous stroke in 21.5% and smoking in 21%. Less than 1% of the patients had no risk factors. The most prevalent type of stroke among the patients assisted was ischemic stroke, which was seen in 97.8% of the sample. This very high rate of stroke was expected, considering the inclusion and exclusion criteria of the study.

The profile of the healthcare provided at the HEC was also evaluated using different variables. The patients' place of origin was registered, as shown in Table 1.

Ictus-to-admission time was registered retrospectively for only a portion of our sample (n=729 patients), as these data were not available in some medical records that were evaluated. This time was divided into different categories according to the therapeutic window for acute-phase treatment, and is shown in Table 2.

Table 3 summarizes the main data relating to the temporality of the care provided. Door-to-needle time was evaluated only for patients who underwent thrombolytic treatment.

The analysis on the SAMU-to-admission time was extrapolated to ascertain any possible correlations with the distance from the city of origin to the HEC, as shown in Figure 3.

The ictus-to-admission time was also detailed with a view to searching for possible correlations with gender, age and place of origin, as shown in Table 4.

After evaluation, the patients were guided to undergo one of the therapeutic modalities thus categorized: clinical treatment, for patients who received anticoagulation, anti-aggregation and/or statin; venous thrombolysis; mechanical thrombectomy; or combined therapy for patients who underwent venous thrombolysis and mechanical thrombectomy. Clinical treatment was the most prevalent modality (68.3%) (Figure 4).

Also with regard to treatment modality, it was found that among the patients who managed to arrive at the HEC within the therapeutic window of up to 4.5 hours, 47% received acute-phase treatment. Table 5 shows the main reasons why patients who arrived within the therapeutic window did not undergo venous thrombolysis (VT) interventions. Table 5 also shows the main reasons for delays in VT procedures, in cases in which such delays occurred.

DISCUSSION

The state of Espírito Santo has more than 4,000 hospitalizations caused by stroke per year[2]. During the study period, 1,078 admissions due to this disease were registered at HEC. Considering that these data related to a period of about two years, and that in 2018 and 2019, HEC was the only public hospital in the state that had a stroke unit, it is possible to estimate that about 3,000 people who were hospitalized due to stroke in this state did not receive the ideal treatment[6]. Ordinance no. 665, of April 12, 2012, established financial incentives for stroke units to be set up within the scope of the Brazilian National Health System (*Sistema Único de Saúde* [SUS], in Portuguese). According to this document, professional training would be necessary for emergency care, and for expanding access to diagnostic tests and VT[13]. Pontes-Neto also highlighted the importance of effective changes in order to increase the availability of MT, in addition to reinforcing the pre-hospital environment through development of

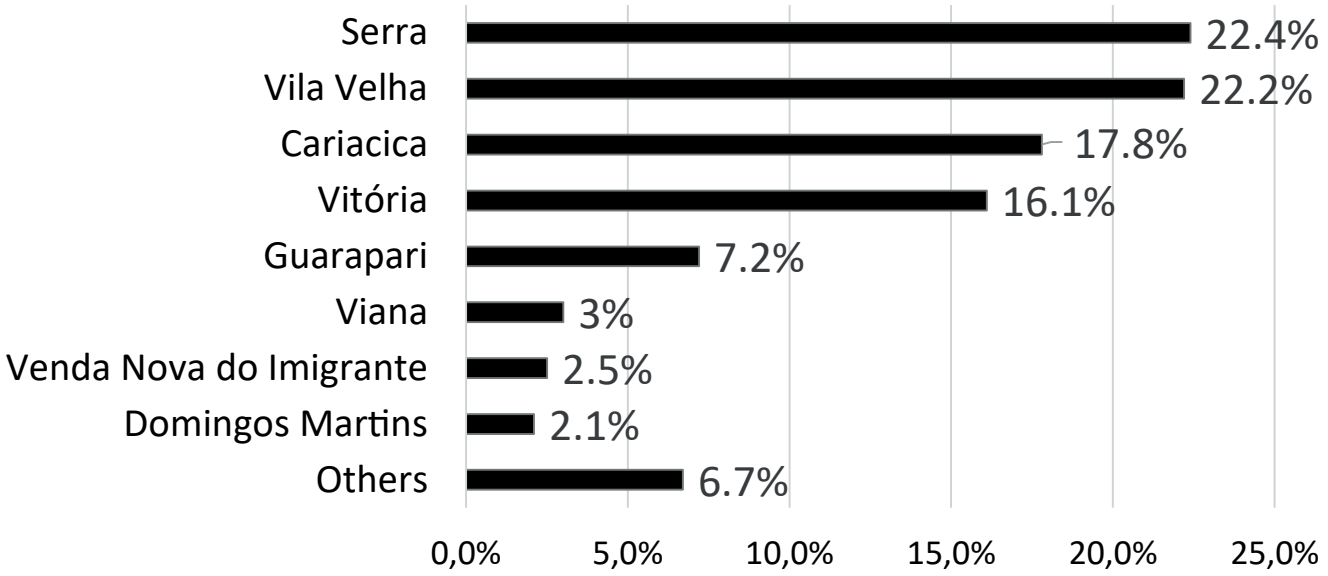


Figure 2. Municipality of origin and percentages of the total number of patients treated.

Table 1. Place of origin of patients treated at Central State Hospital, with respective percentages.

Place of origin (n=1,078)	n (%)
Emergency room	424 (39.3)
Household	355 (32.9)
GV public hospital	141 (13.1)
State inland hospital	70 (6.5)
Others	44 (4.1)
Public road*	25 (2.3)
GV private hospital	19 (1.8)

GV: Greater Vitória; *Rescued by SAMU on public roads.

Table 2. Ictus-admission time in hours (n=729).

Ictus- admission time in hours (n=729)	n (%)	Median (min-max)	(95%CI)
Up to 1 hour	20 (2.7)	212 (8–1,800)	(201.5–228)
Between 1 and 3 hours	287 (39.4)		
Between 3 and 4.5 hours	168 (23)		
Between 4.5 and 8 hours	172 (23.6)		
More than 8 hours	82 (11.2)		

95%CI: 95% confidence interval.

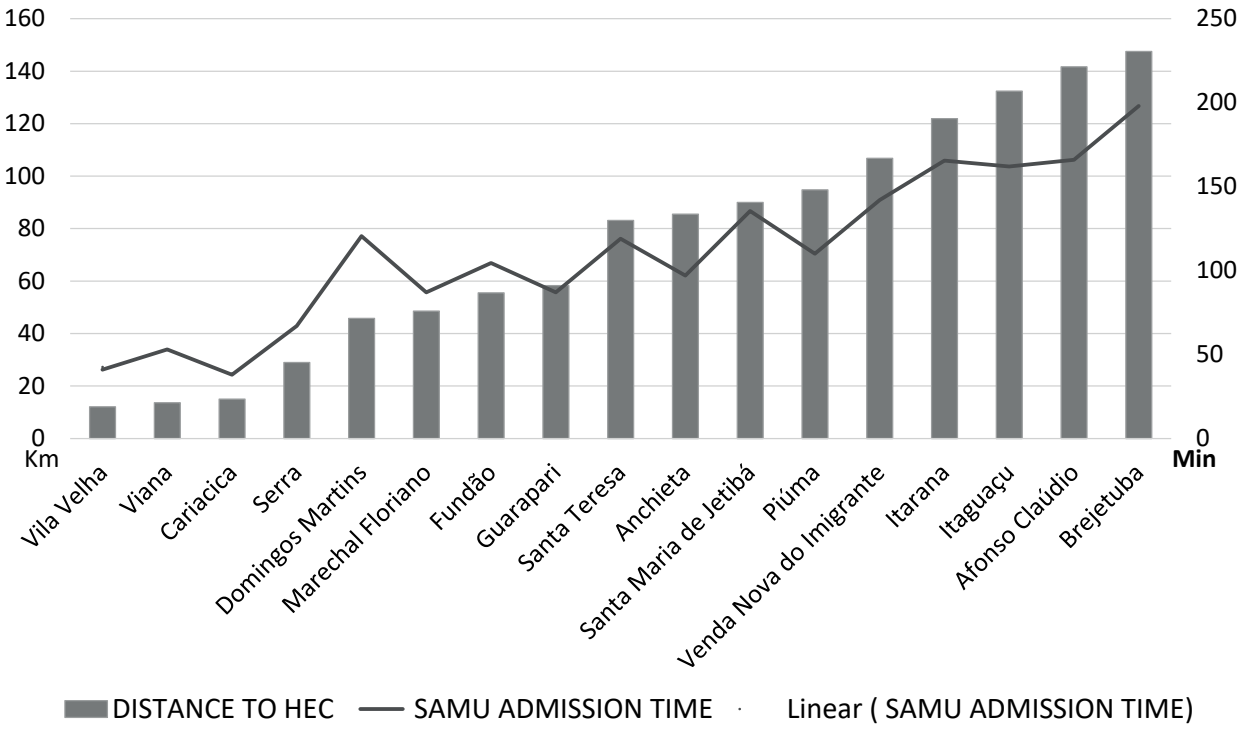
Table 3. Median (min-max) of SAMU-admission time and door-to-needle time, in minutes, among patients seen at Central State Hospital (95%CI).

Median of SAMU-admission time and door-to-needle time, in minutes, among patients seen at HEC	Median (min-max)	95%CI
SAMU-admission contact (n=1,047)	56 (5–420)	54–59
Door-to-needle in minutes (n=294)	28 (0–86)	27–31

SAMU: Public Emergency Transport Service; HEC: Central State Hospital; 95%CI: 95% confidence interval.

strategies that would improve the patient care process[14]. The data gathered in the present study demonstrated that stroke was more prevalent among men and middle-aged people, in agreement with the data of Locatelli et al., who found the same profile in their study[13]. However, it is known that there is a direct relationship between increased incidence of stroke and aging[14], and the high prevalence of middle-aged patients can be explained simply through the absolute number of people in this age group in ES, which is more than five times the number of elderly people over 80 years old[15]. The patients classified as young people with stroke accounted for 9% of the sample, and this was within the range proposed by Smajlovic, who affirmed that although the proportion of young people with stroke would vary between countries, it would lie between 5 and 20%[16].that stroke is a disease with high morbidity, it is important to note that stroke among economically active individuals directly impacts the economy of a country, which therefore emphasizes the need for research aimed at preventing stroke in this age group.

HEC received patients from 18 municipalities in ES. Serra was the city that sent the most patients, followed by Vila Velha. Together, these two cities accounted for more than 50% of the sample, which can be explained by the fact that they are the most populous cities in the state[17]. According to the IBGE (*Instituto Brasileiro de Geografia e Estatistica*, in Portuguese), ES has 78 municipalities, so our sample represented only 23% of them. The explanation for the low number of municipalities represented may be related to the areal coverage provided by SAMU during the period studied (Figure 5), since all 18 municipalities with SAMU coverage sent patients to HEC[18]. On the other hand, despite the sample only representing 23% of these municipalities, these 18 cities have more than 50% of the population across the state, reaching approximately 2 million inhabitants[17].



HEC: Central State Hospital; SAMU: Public Emergency Transport Service.

Figure 3. Relationship between SAMU-to-admission time and municipalities from which the patients treated at the Central State Hospital came.

Table 4. Relationship between ictus-admission time and the variables of gender, age and place of origin, indicating the median value for each situation (min-max) and (95%CI).

		Ictus-to-admission time (in minutes)	Median (95% CI)	p-value
Gender (n=729)	Male (n=405)	218 (12–1,440)	194–234	0.875
	Female (n=324)	210 (8–1,800)	191–225	
Age (n=729)	Young	205 (24–1,440)	159–240	0.40
	Middle-aged	219 (12–1,800)	201–231	
	Extremely elderly	204 (8–1,320)	172–245	
Place of origin (n=602)*	Residence	214 (30–1,140)	182–240	0.756[a]
	Healthcare centers	212 (8–1,140)	197.7–229.5	
	Spontaneous demand	295 (60–960)	107–540	

95%CI: 95% confidence interval; *Greater Vitória municipalities only; [a]Kruskal-Wallis test.

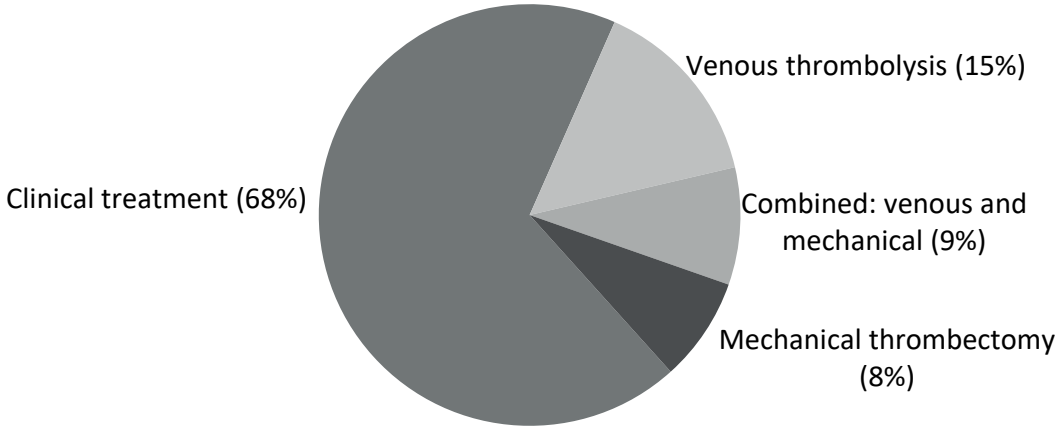


Figure 4. Percentages of treatments, according to the categories of therapeutic modalities.

Table 5. Reason for not applying venous thrombolysis and reasons for delayed venous thrombolysis procedures.

		n (%)
Contraindication for VT (n=177)	Wake up with deficit	39 (22)
	NIHSS low (<2)	26(14.7)
	Others	39 (22)
	Indeterminate ictus	24 (13.6)
	Contraindication on CT	26 (14.7)
Justification for delay in starting VT (n=53)	Difficulty in controlling blood pressure	27 (50.9)
	Others	19 (35.8)
	Difficulty in obtaining intravenous line	7 (13.2)
	Delay in laboratory	4 (7.5)
	Angiotomography	3 (5.7)
	Hemodynamic definition	2 (3.8)

VT: venous thrombolysis; NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography.

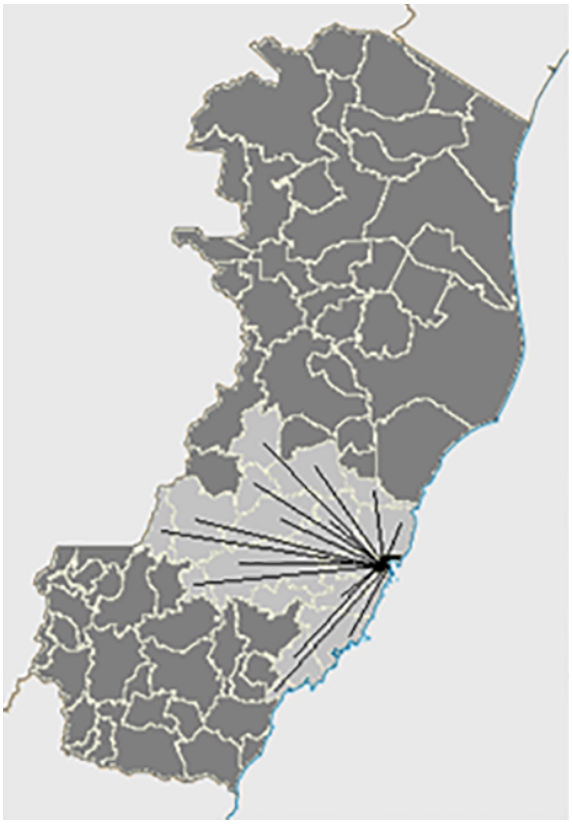


Figure 5. Map highlighting the municipality of Vitória, where the Central State Hospital is located, and the radius of coverage of Public Emergency Transport Service among the municipalities of Espírito Santo.

Hypertension (HT) is the comorbidity that most correlates with stroke[14,19]. In the present study, 75% of the patients had HT, which made it the most prevalent risk factor among HEC patients, followed by diabetes, previous stroke and smoking. The importance of knowing the risk factors is corroborated by Passos, who stated that the incidence of stroke can be reduced through public policies aimed at knowing the etiology, risk factors and the profile of patients[20].

According to data in the literature, patients who resorted to SAMU or went directly to the hospital were able to access specialized care more quickly[10,7]. Among the patients seen at HEC, 39.3% were referred to emergency rooms, which demonstrates the need to direct the focus of public healthcare policies towards informative work on early recognition of symptoms and the need to quickly search for a stroke reference center, preferably using the SAMU.

Time was a widely explored variable in this study, given that it is a decisive factor for the prognosis of stroke patients[21]. It was found that 67% of the patients managed to reach the HEC within the therapeutic window for VT. In a study by Panício, less than 25% of the patients arrived at the hospital within 4.5 hours[10], which may suggest that the flowchart for care proposed by SESA-ES has good application. However, it is worth mentioning that the inclusion and exclusion criteria of our study prevented patients with ictus longer than 24 hours from being referred to the HEC, which may have overestimated the percentage of patients seen within the therapeutic window.

It was also possible to separately analyze SAMU's performance within the service flowchart. In the correlation between SAMU-to-admission time and the distance from the city of origin to the HEC, there was a relationship with a trend towards linearity, but it had some points of variation, such as the city of Domingos Martins. The possible causes of these variations may be associated with the distance from the SAMU base, as well as the highway that formed the route taken in travelling to the hospital. It is worth mentioning that for 95% of the patients, their journey using SAMU was completed in less than 1 hour, which shows the effectiveness of SAMU for transporting these patients.

In analyzing the standard of care provided at the HEC, the door-to-needle time was observed. This demonstrated that 95% of the patients were assisted within 30 minutes. This highlights the efficiency of this specialized service for caring for stroke patients, since in the NINDS study the recommended time from admission to infusion of the thrombolytics was up to 60 minutes[21], i.e. twice the time spent, on average, at HEC.

Delays in receiving adequate care prevent patients from benefiting from therapeutic advances that would ensure their survival or minimize the severity of their injuries[22]. In this light, the ictus-to-admission time was correlated with the factors of gender, age and place of origin, in order to identify possible differences between the groups. However, there was no statistically significant relationship between this time and the variables analyzed. It is worth mentioning that there

was a tendency towards longer ictus-to-admission times for patients who arrived at the hospital as spontaneous demand, which suggests that this healthcare service was efficient regarding care chronology, when care was requested.

Although the numbers still remain high, the stroke mortality rate has been tending to decrease in Brazil[22]. According to Pinheiro and Vianna, this scenario is due to controlling for known cardiovascular risk factors and development of new diagnostic technologies and highly complex therapeutic procedures[3]. However, in Brazil, stroke units continue to function precariously, which compromises the implementation of these therapies[23].

Venous thrombolysis (VT) has been consolidated as a successful therapeutic option since 1995. A large study has proven the benefit of thrombolytic infusion in stroke patients[21,24]. MT has also appeared as a complementary strategy for extending the treatment of stroke. Its indication has expanded the therapeutic window to up to 6 hours after the onset of symptoms, in selected cases of occlusion of large vessels that respect the inclusion criteria of the international guidelines. In any case, time remains fundamental with regard to the results that can be obtained[14]. In the present study, acute-phase therapeutic interventions were performed on 32.44% of the stroke patients treated at HEC, which is a high rate even by international standards[25,26]. Nevertheless, this demonstrates that there is a need to expand VT and MT care, considering the efficiency of these therapies not only for reducing mortality but also for reducing the disabilities acquired by patients[27].

In a specific analysis on patients who managed to reach HEC within the therapeutic window, it was identified that 53% of them underwent clinical treatment. The perception of neurological deficit when waking up was the most prevalent variable that prevented other patients from receiving VT. The so-called "WakeUpStroke" (WUS) treatment option is designated for this type of situation, which is not uncommon in healthcare services and constitutes a limitation to thrombolytic therapy[28]. Unfortunately, the vast majority of emergency medical services do not have magnetic resonance imaging (MRI) devices available, and this is also the case with HEC. MRI would be important because it allows identification of areas of darkness that potentially have recoverable brain tissue[26]. It is worth mentioning that some studies[28,29] have already managed to obtain good results from MT applied within 16 and 24 hours of the ictus, which allows expansion of the therapeutic window to include the majority of patients who wake up with a deficit.

The main factors that culminated in delay to the VT procedure were difficulty in controlling blood pressure and in obtaining intravenous access. These situations reflect reports in the literature and corroborate the data from Raffin et al (2006), who stated that before the procedure begins, two peripheral venous accesses need to be obtained, through which the medication will be administered. In addition, use of thrombolytics implies the need for strict pressure management, due to the risk of correlated cerebral hemorrhage[30].

Our study was limited by the fact that it was carried out in a single stroke center, where patients are received from only some of the municipalities in ES. Thus, our data did not portray the reality of the entire state. Furthermore, the screening criteria for patients referred to the HEC prevented broader analysis of patients with ictus longer than 24 hours.

In conclusion, stroke is a public health problem and epidemiological studies have shown the importance of preventing and treating this disease and of promoting countermeasures against stroke in Brazil.

It was found that application of the flowchart established by SESA-ES seemed to be effective for improving the responsiveness of care for stroke victims, and that SAMU had a fundamental role in this process. It was noteworthy that it is necessary to expand the coverage of the mobile emergency service in this state, in order to achieve good outcomes throughout its area.

Moreover, the importance of the care provided by this tertiary stroke center could be demonstrated through the responsiveness and efficiency of the service, in which acute-phase therapies were ensured for 32.44% of the patients with stroke. This is a very high rate, even by international standards. Therefore, it is necessary to structure other similar units in different regions of Espírito Santo.

Further studies are needed in other regions of the state in order to better characterize the reality of stroke treatment in ES. Even with the efficiency of the service provided in the HEC stroke unit, this unit reaches a maximum of 50% of the ES population, which is not representative of the entirety of the state's healthcare service.

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ARTICLE

Formal language assessment in low-educated persons with aphasia: can the lesion effect be distinguished from the education effect?

Avaliação da linguagem em pacientes afásicos com baixa escolaridade: o impacto da lesão neurológica pode ser discriminado da baixa escolaridade?

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ABSTRACT

Background: Language tests are important in the assessment and follow up of people with aphasia (PWA). However, language assessment in the low literacy population is still a challenge. **Objective:** To investigate whether a formal evaluation of aphasia is able to distinguish the neurological effect from the effect of low educational level in people with post-stroke aphasia. **Methods:** The sample consisted of a group of 30 aphasic subjects (AG) and a control group (CG) of 36 individuals, both with an educational level of 1-4 years. The Brazilian Montreal-Toulouse Language Assessment battery was applied to all subjects. **Results:** There were statistically significant differences between the groups in 19 out of the 20 tasks analyzed. **Conclusions:** These results suggest that formal evaluation procedures are able to detect language disorders resulting from stroke, even in subjects with low educational level.

Keywords: Aphasia; Language; Education.

RESUMO

Antecedentes: Os testes de linguagem são importantes para a avaliação e o acompanhamento de pacientes afásicos. Apesar disso, a avaliação de linguagem em indivíduos com baixa escolaridade ainda é um desafio. **Objetivo:** Investigar se a avaliação formal da afasia é capaz de diferenciar o efeito da lesão neurológica *versus* o efeito da baixa escolaridade em pacientes afásicos, acometidos por acidente vascular cerebral (AVC). **Métodos:** A amostra foi composta de um grupo de 30 sujeitos afásicos (AG) e um grupo controle (CG) de 36 indivíduos, todos com um a quatro anos de escolaridade. A Bateria Montreal-Toulouse de Avaliação da Linguagem foi administrada a todos os participantes. **Resultados:** Das 20 tarefas analisadas, 19 apresentaram diferenças significativas entre os grupos. **Conclusões:** Os resultados sugerem que procedimentos formais de avaliação são capazes de identificar as alterações linguísticas ocasionadas por um AVC, também em pacientes com baixa escolaridade.

Palavras-chave: Afasia; Linguagem; Educação.

INTRODUCTION

Historically, countries with low literacy levels have had to develop research to verify the impact of low literacy on cognitive functioning and have proposed different scores for memory[1], attention[2,3], executive functions[4] and other cognitive tests[5,6]. Concerning to language, statistical differences were found in relation to educational levels in normal subjects in the tasks of oral comprehension, reading, written comprehension, naming, lexical retrieval, dictation, written naming of actions[7] and, in particular, phonological awareness[8]. A previous study also found that when comparing the scores from a normal highly educated population with those of normal people with low educational level there was a false positive result as if people with low educational had a language disorder[9]. Language is a complex cognitive function and defining procedures for assessing populations with low educational levels is complex because of the formal nature of assessments (tests). The implications of different educational levels on aphasia tests could be significant and raise questions on the appropriateness of tests for assessing these individuals[8]. On the other hand, informal assessment is

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problematic and can result in clinical issues[10], since an accurate diagnosis is critical for defining steps in the rehabilitation and follow up of people with aphasia (PWA)[11]. One approach for language assessment is the use of validated, standardized tools[12], but there is a lack of consensus over what is normal or abnormal on these evaluations.

In this respect, previous studies with aphasic populations with low educational level have proposed the use of adjusted scores for the various language functions assessed by these instruments[13,14]. Language assessment in the low literacy population with neurological injuries is still a challenge and further investigation on whether the lesion effect can be distinguished from the education effect on language impairments in post-stroke aphasic individuals is warranted.

The objective of this study was to determine whether formal evaluation of aphasia (test) is able to distinguish the neurological lesion effect from the effect of low education in post-stroke aphasic individuals.

METHODS

This comparative analytical study was carried out at the Department of Speech, Language and Hearing Sciences at Universidade Federal de São Paulo, and was approved by the Research Ethics Committee. After receiving full information about the study, written informed consent was obtained from all enrolled subjects.

The sample consisted of a group of 30 PWA (AG) and a control group (CG) of 36 individuals, all with 1–4 years of education and right-handed. The Brazilian Montreal-Toulouse Language Assessment (MTL-Br) battery[15] was applied to all subjects. The test is the only Brazilian test for assessing aphasia, but normative data are available only for populations with more than 5 years of education[14]. The battery consists of the following subtests: Structured Interview, Automatic Speech, Oral Comprehension, Written Comprehension, Copying, Written Dictation, Repetition, Reading Aloud, Semantic Verbal Fluency, Non-Verbal Praxis, Naming, Object Manipulation by Verbal Command, Phonological Verbal Fluency, Body part recognition and left-right orientation, Written Naming, Oral Text Comprehension, Number Dictation, Reading of Numbers, Written Text Comprehension, and Numerical Calculation.

The inclusion criteria for the AG were: a single stroke to the left-hemisphere and aphasia diagnosis by speech-language therapist. The exclusion criteria were: history of other neurologic or psychiatric conditions, current uncorrected hearing or visual deficits that could negatively impact the language assessment, language disorder or previous school grade repeats.

The CG was formed by applying a health questionnaire, based on which individuals with a history of psychiatric or neurologic illness or current uncorrected hearing or visual deficits that could negatively impact the language assessment, history of previous learning and/or language difficulties, use or history of use of legal or illegal psychotropic drugs and alcohol abuse were excluded.

The raw scores of the language assessment of the AG and CG were compared. The subjects in the CG were relatives and/or companions of the assessed patients.

The groups were compared for age, sex, and education using the Mann-Whitney test. There was no statistically significant difference between the groups for years of education or sex, but a difference was found for age (AG patients were older than CG subjects). The age effect was therefore controlled for by the multivariate analysis of variance (MANOVA) procedure. Analysis of covariance (ANCOVA) was employed to compare the performance of the study groups on the MTL-BR tasks. A probability (p) of less than 0.05 was considered statistically significant for all tests.

RESULTS

A total of 66 individuals were assessed, comprising 36 in the CG and 30 in the AG. Mean age in the CG was 48.83 years (SD=13.54 years) and mean education was 3.44 years (SD=4.1 years). Mean age in the AG was 65.47 years (SD=9.52 years), while mean education was 3.20 years (SD=1.16 years).

Of the aphasic patients, 11 had mixed aphasia, 5 had anomic aphasia, 4 had transcortical mixed aphasia, 3 had Wernicke's aphasia, 3 had global aphasia, 2 had transcortical motor aphasia and 2 had transcortical sensory aphasia.

The comparative performances of the two study groups on all tasks of the MTL- Br Battery, controlled for age, are shown in Table 1.

A statistically significant difference ($p<0.001$) was found between the two groups on all tasks, except for the "Object Manipulation", which proved insensitive for differentiating the lesion effect from the education effect.

DISCUSSION

The data outlined above suggests that language test like the MTL-BR can be used even in PWA with low educational level, since all but the object manipulation task distinguished PWA from normal subjects. The scores of the two groups for the "Object Manipulation" task were similar. The complexity of the mechanisms required to perform this subtest can help explain the results found. Tasks in the MTL-BR involve multimodal stimuli that can facilitate understanding by the subject and their response because they are analyzed based on a number of different processes[9,16,17]. In the Object Manipulation task, auditory, proprioceptive, and visual processing are involved. The familiarity with the objects presented and the tangible effect they evoke may have also facilitated the task

Table 1. Comparison of performance by the two groups on the MTL- Br tasks controlled for age.

MTL-BR Task[1]	Group	Mean	SD	Median	ANCOVA adjusted p-value
Structured interview	CG	25.11	1.33	25.50	<0.001*
	AG	14.50	8.90	16.00	
Automatic speech — form	CG	5.81	0.52	6.00	<0.001*
	AG	3.27	2.41	4.00	
Automatic speech — content	CG	5.75	0.55	6.00	<0.001*
	AG	3.13	2.43	3.50	
Oral comprehension — words	CG	4.94	0.23	5.00	<0.001*
	AG	3.43	1.63	4.00	
Oral comprehension — sentences	CG	11.61	1.54	11.50	<0.001*
	AG	6.30	3.31	6.00	
Written comprehension — words	CG	4.39	1.61	5.00	0.002*
	AG	2.43	1.91	3.00	
Written comprehension — sentences	CG	6.33	1.49	6.00	<0.001*
	AG	2.53	2.50	2.00	
Copying	CG	7.44	1.38	8.00	<0.001*
	AG	2.00	2.95	0.00	
Dictation	CG	14.22	5.19	14.50	<0.001*
	AG	3.30	5.31	0.00	
Repetition — words	CG	10.67	0.83	11.00	<0.001*
	AG	5.57	4.44	7.00	
Repetition — sentences	CG	21.78	0.87	22.00	<0.001*
	AG	7.40	8.58	3.00	
Reading aloud — words	CG	9.06	2.37	9.00	<0.001*
	AG	2.97	3.95	1.00	
Reading aloud — sentences	CG	19.58	3.76	21.00	<0.001*
	AG	6.03	7.95	0.00	
Semantic verbal fluency	CG	16.31	4.60	15.50	<0.001*
	AG	3.60	3.40	3.00	
Non-verbal praxis	CG	23.47	1.06	24.00	0.001*
	AG	16.00	8.55	19.00	
Naming — nouns	CG	21.42	2.67	22.00	<0.001*
	AG	10.03	8.99	11.50	
Naming — verbs	CG	5.28	1.49	6.00	<0.001*
	AG	2.73	2.38	3.00	
Object manipulation by verbal command	CG	12.97	5.26	16.00	0.098
	AG	10.10	5.63	12.00	
Phonological verbal fluency	CG	7.53	5.06	7.00	<0.001*
	AG	2.10	3.58	0.00	
Left-right orientation	CG	3.89	0.67	4.00	0.002*
	AG	2.63	1.43	3.00	
Body part recognition	GC	7.39	1.05	8.00	0.037*
	GA	5.83	2.57	6.50	
Written naming — words	CG	12.14	7.80	14.00	<0.001*
	AG	3.67	6.90	0.00	
Written naming — verbs	CG	2.89	2.07	3.00	0.001*
	AG	0.80	1.75	0.00	
Oral text comprehension	CG	5.69	2.54	6.00	<0.001*
	AG	2.00	2.38	1.50	
Number dictation	CG	4.97	1.30	5.00	<0.001*
	AG	1.90	2.23	0.50	
Reading of numbers	CG	5.22	0.64	5.00	<0.001*
	AG	2.43	2.11	2.50	
Written text comprehension	CG	6.28	2.54	7.00	<0.001*
	AG	1.30	2.83	0.00	
Numerical mental calculation	CG	3.03	1.46	3.00	<0.001*
	AG	0.83	1.12	0.00	
Numerical written calculation	CG	2.83	1.95	3.00	<0.001*
	AG	0.33	0.84	0.00	

SD: standard deviation; ANCOVA: analysis of covariance; CG: control group; AG: aphasic group; *Statistically significant value at 5% level (p<0.05).

execution. These factors likely contributed to the two groups performing similarly on the task. In addition, results of a previous study[18] have shown that there is a ceiling effect on this task in healthy individuals with low educational level.

Differences between groups were evident in all other tasks. Therefore, despite the formal nature of the test[19,20], specific deficits in comprehension and production due to brain damage can be identified.

In conclusion, the formal evaluation is able to detect linguistic disorders due to brain injury even in subjects with low levels of education.

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ARTICLE

Dialysis headache: characteristics, impact and cerebrovascular evaluation

Cefaleia da diálise: características, impacto e avaliação cerebrovascular

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ABSTRACT

Background: Headache is one of the most frequent symptoms that occur during hemodialysis sessions. Despite the high prevalence of dialysis headache, it has been little studied. **Objective:** To evaluate the characteristics, impact and factors associated with dialysis headache. The behavior of the cerebral vasculature was also compared between patients with and without dialysis headache. **Methods:** This was a cross-sectional study. Consecutive patients who underwent hemodialysis were assessed through a semi-structured questionnaire, the Headache Impact Test (HIT-6), the Hospital Anxiety and Depression Scale and the Short Form-36 Health Survey (SF-36). Transcranial Doppler ultrasonography was performed in the first and fourth hours of hemodialysis. **Results:** A total of 100 patients were included; 49 of them had dialysis headache. Women (OR=5.04; 95%CI 1.95–13.04), younger individuals (OR=1.05; 95%CI 1.01–1.08), individuals with higher schooling levels (OR=3.86; 95%CI 1.4–10.7) and individuals who had spent longer times on dialysis programs (OR=0.99; 95%CI 0.98–1) had more dialysis headache (logistic regression). Individuals with dialysis headache had worse quality of life in the domains of pain and general state of health (56.9 *versus* 76.4, p=0.01; 49.7 *versus* 60.2, p=0.03, respectively). Dialysis headache was associated with significantly greater impact on life (OR=24.4; 95%CI 2.6–226.6; logistic regression). The pulsatility index (transcranial Doppler ultrasonography) was lower among patients with dialysis headache than among those without them. **Conclusions:** Dialysis headaches occur frequently and are associated with worse quality of life and patterns of cerebral vasodilatation.

Keywords: Headache; Pain; Renal Dialysis; Anxiety; Quality of Life; Ultrasonography, Doppler, Transcranial.

RESUMO

Antecedentes: A cefaleia é um dos sintomas mais frequentes que ocorrem durante as sessões de hemodiálise. Apesar da alta prevalência, essa cefaleia é pouco estudada. **Objetivo:** Avaliar as características, impacto e fatores associados à cefaleia da diálise. O comportamento da vasculatura cerebral também foi comparado entre pacientes com e sem cefaleia da diálise. **Métodos:** Este foi um estudo transversal. Pacientes consecutivos submetidos à hemodiálise foram avaliados por meio de questionário semiestruturado, do Headache Impact Test (HIT-6), Hospital Anxiety and Depression Scale e Short Form-36 Health Survey (SF-36). Foi realizada ultrassonografia Doppler transcraniana na primeira e na quarta horas de hemodiálise. **Resultados:** Foram incluídos 100 pacientes, 49 deles tinham cefaleia da diálise. Mulheres (OR=5,04; IC95% 1,95–13,04), indivíduos mais jovens (OR=1,05; IC95% 1,01–1,08), com maior escolaridade (OR=3,86; IC95% 1,4–10,7) e que passaram mais tempo em programas de diálise (OR=0,99, IC95% 0,98–1) tiveram mais cefaleia da diálise (regressão logística). Indivíduos com cefaleia dialítica tiveram pior qualidade de vida nos domínios dor e estado geral de saúde (56,9 *versus* 76,4, p=0,01; 49,7 *versus* 60,2, p=0,03, respectivamente). A cefaleia da diálise foi associada a um impacto significativamente maior na vida (OR=24,4; IC95% 2,6–226,6; regressão logística). O índice de pulsatilidade (ultrassonografia Doppler transcraniana) foi menor entre os pacientes com cefaleia da diálise do que entre aqueles sem. **Conclusões:** A cefaleia da diálise ocorre com frequência e está associada a pior qualidade de vida e a padrões de vasodilatação cerebral.

Palavras-chave: Cefaleia; Dor; Diálise Renal; Ansiedade; Qualidade de Vida; Ultrassonografia Doppler Transcraniana.

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INTRODUCTION

Headache is one of the most frequent symptoms that occur during hemodialysis sessions. Around 70% of hemodialysis patients present headaches[1]. It has been estimated that 28 to 73% of hemodialysis patients can be considered to be suffering from dialysis headache[2-4].

The physiopathology of dialysis headache remains unclear. Factors that are known to be associated with these headaches include the type of dialysis solution used (acetate presents greater risk of dialysis headache than bicarbonate)[5]; variations in urea, sodium and magnesium levels and in arterial blood pressure[2,3,6]; levels of calcitonin gene-related peptide (CGRP) and levels of substance P during dialysis[7]. The blood-brain barrier may have an important role in the appearance of this headache. The concentration gradient between the brain and the blood that occurs during dialysis, with consequent passage of free water through the blood-brain barrier may lead to cerebral edema in some patients, thus consequently causing headache[3,8].

Despite the high prevalence of dialysis headache, it has been little studied. This leads to difficulty in recognizing its characteristics, understanding its physiopathological mechanisms and knowing how to manage it. The aim of the present study was to evaluate the frequency, characteristics and impact of these headaches and the factors associated with them. The behavior of the cerebral vasculature, as assessed using transcranial Doppler ultrasonography, was also compared between patients with and without dialysis headache.

METHODS

This was a cross-sectional study.

Patients with age 18 years and over, with chronic kidney failure attended through hemodialysis at either Hospital das Clínicas or the Clínica Multirim between September 2015 and January 2016 were included. In both of these services, bicarbonate was used in the dialytic solution and the duration of the hemodialysis sessions was four hours.

Patients were excluded in the following situations: use of hemodialysis therapy for less than six months; presence of cognitive impairment; altered consciousness or difficulty with verbal communication that caused difficulty in making assessments; presence of diseases that cause secondary headaches; or use of prophylactic medications against headaches.

This study was approved by the research ethics committee of the Health Sciences Center (CCS) of the Universidade Federal de Pernambuco (CAAE 47077715.3.0000.5208). All the patients who participated in this study signed a free and informed consent statement.

All the patients were evaluated by a neurologist with experience in diagnosing and treating headaches, who interviewed these patients and conducted clinical and neurological examinations before the hemodialysis sessions were started. Their headaches were classified in accordance with the diagnostic criteria of the beta version of the third edition of the International Classification of Headache Disorders (ICHD-3 beta)[9] and were later reclassified in accordance with the criteria of the final third edition of the International Classification of Headache Disorders (ICHD-3)[10]. Patients were considered to be making excessive use of caffeine when they reported having six or more cups of coffee per day[11].

Patients were considered to present dialysis headache if they fulfilled the criterion of having had at least three episodes of acute headache with two of the following situations of causality: 1 — the headache needed to have started during the hemodialysis session; 2 — the headache needed to have worsened during the hemodialysis session and/or to have resolved within 72 hours after the end of the session[10].

The following questionnaires were applied before the hemodialysis sessions:

- A semi-structured questionnaire that sought the following: sociodemographic data; data on the chronic kidney failure and its treatment (etiology, time when hemodialysis was started and medications used); data on the presence and characteristics of primary headaches (time when they started; duration of the attacks; frequency; pattern of pain; factors associated; and medications used); and data on the presence and characteristics of dialysis headache (the very first occurrence of dialysis headache, in relation to the start of the dialysis treatment; time at which pain generally started, in relation to the start of the hemodialysis session; duration of the attack; frequency; pattern of pain; factors associated; factors that improved or worsened the pain; and medications used).
- Headache Impact Test (HIT-6): used to estimate the impact of headaches on the patient's life[12]. The higher the score is, the greater the impact of the headache is. Scores greater than or equal to 60 are considered to have "severe impact"; scores between 56 and 59 points, "substantial impact"; scores between 50 and 55 points, "some impact"; and scores less than or equal to 49, "minimal or no impact"[13]. Patients who did not present headaches were classified in the category "minimal or no impact".
- Hospital Anxiety and Depression Scale (HADS): this allows the presence of symptoms of anxiety and depression to be diagnosed. It is subdivided into two subscales: one for anxiety and the other for depression[14,15]. Presence of anxiety and depression is defined as a score ≥8 on the respective subscale[16].
- Short Form-36 Health Survey (SF-36): this enables evaluation of health-related quality of life in eight domains: physical functioning, role-physical, pain, general state of health, vitality, social functioning, role-emotional and mental health. The lower the score is, the worse the quality of life is[17].

Evaluation via transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography was performed using the DWL-EZbox® device, by means of transtemporal windows. The middle cerebral arteries were evaluated bilaterally, at depths of between 40 and 60 mm, every 2 mm, with regard to the parameters of mean flow velocity (cm/sec) and pulsatility index (mean vascular resistance). The latter was calculated as the ratio of the difference between systolic and diastolic velocities divided by the mean velocity. This examination was performed in the first and fourth hours of hemodialysis, by the same observer, with the patient either sitting or lying down.

Statistical analysis

The Statistical Package for the Social Sciences for Windows package, version 21.0 (SPSS Inc., IBM Company, Chicago, IL, USA), was used for the statistical analysis.

The descriptive analysis included calculation of means (with standard deviation) or medians (with interquartile range) for the continuous variables, and absolute distributions (with percentage) for the categorical variables.

The Kolmogorov-Smirnov test was used to assess whether the data presented normal distribution. The numerical variables were compared between groups using the t-test if the distribution was normal; or using the Mann-Whitney test if the distribution was non-normal. The percentage distributions of the categorical variables were compared between the groups using the chi-square test or Fisher's exact test.

All the statistical tests were two-tailed and the significance level taken was based on α of 0.05.

Logistic regression was performed to determine the predictors for dialysis headache. Variables with $p<0.15$ in the univariate analysis were included in the model using a stepwise method, and those with $p<0.1$ were kept in the model. The following variables were evaluated at this stage: sex, age, schooling level, length of time for which the patient had been undergoing hemodialysis, presence of anxiety and previous migraine.

Another logistic regression was then performed to determine the factors associated with the functional impact of the headache, as evaluated using the HIT-6 scale. Variables presenting $p<0.1$ in the univariate analysis were included in the model using a stepwise method and those with $p<0.1$ were kept in the model. The following variables were evaluated at this stage: sex, age, schooling level, family income, presence of anxiety, presence of depression, previous tension-type headache, previous migraine and presence of dialysis headache.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

A total of 100 patients were evaluated and included in this study, among whom 52 were undergoing dialysis at Hospital das Clínicas and 48 at the Clínica Multirim. Their mean age was 51.8 years (±13.6); 50% were women; 53% were married; their mean schooling level was 7.7 years (±3.5); and 41% had a family income of up to two Brazilian minimum monthly wages (one monthly minimum wage was equivalent to approximately US$ 200.00).

These patients had been undergoing hemodialysis for a mean period of 54 months (±59.3) and had had their diagnosis of chronic kidney disease (CKD) for a mean period of 100.4 months (±113.3).

The main etiologies for CKD were hypertensive nephropathy (39%), diabetic nephropathy (16%), glomerulopathy (10%) and chronic tubulointerstitial nephritis (10%). A variety of causes were presented by the remaining 25%: polycystic kidney disease, tuberculosis, nephrectomy due to trauma, nephrectomy due to kidney cancer, hemolytic-uremic syndrome, scleroderma and Takayasu's arteritis.

There were 76 patients with primary headaches: 25 with migraine and 51 with tension-type headache. Anxiety was present in 28% and depression in 25%.

Forty-nine patients had headaches that fulfilled the criteria for dialysis headache. Among these patients, it had a severe impact on 16 (32.7%); a substantial impact on 4 (8.2%); some impact on 7 (14.3%); and minimal or no impact on 22 (44.9%).

Table 1 shows the characteristics of the dialysis headache. The headache pattern that was most often found was tension-type headache. In most cases, the headache started insidiously in the third or fourth hour of hemodialysis. Its intensity and frequency became lower than at the onset of the condition, over a period of months.

Table 2 presents the patients' characteristics in relation to dialysis headache. Women, younger individuals, individuals with higher schooling levels and individuals who had been on hemodialysis programs for longer times presented dialysis headache significantly more frequently (shown through logistic regression).

Figure 1 compares quality of life between individuals with and without dialysis headache. Those with dialysis headache presented significantly worse quality of life in the domains of pain and general state of health, in the SF-36 questionnaire.

Table 3 presents the associations between the patients' characteristics and the impact of their headaches. Presenting anxiety and having dialysis headache were significantly associated with greater impact from headaches (shown through logistic regression).

Among the 100 patients evaluated, 83 underwent transcranial Doppler ultrasonography. The other 17 patients did not present a transtemporal bone window that was adequate for performing the examination. Table 4 shows a comparison of transcranial Doppler measurements between patients with and without the diagnosis of dialysis headache. The

pulsatility index, which evaluates the resistance of the vessels studied, was significantly lower in the group with dialysis headache, in the right and left middle cerebral arteries in the first hour of hemodialysis and in the left middle cerebral artery in the fourth hour of dialysis. The mean flow velocities did not present any statistically significant differences.

DISCUSSION

In our study, the frequency of dialysis headache was 49%. In other studies, the prevalence of dialysis headache has ranged from 28 to 73%[2-6]. These other studies used different criteria for making the diagnosis of dialysis headache, which

Table 1. Characteristics of the dialysis headache (n=49).

Characteristic		n (%)	mean (±SD)
Start	Insidious	39 (79.6%)	
	Sudden	10 (20.4%)	
Characteristic of headache	Throbbing	36 (73.5%)	
	Pressing	11 (22.4%)	
	Stabbing	2 (4.1%)	
Intensity (VAS)			6.7 (±2.1)
Duration (minutes)			215.2 (±429.2)
Photophobia		18 (36.7%)	
Phonophobia		21 (42.9%)	
Worsening through exercise		9 (18.4%)	
Nausea		24 (49%)	
Vomiting		14 (28.6%)	
Aura		3 (6.1%)	
Autonomic signs		1 (2%)	
Start of headache in relation to dialysis (hour)	First	1 (2%)	
	Second	8 (16.3%)	
	Third	16 (32.7%)	
	Fourth	24 (49%)	
Location	Bilateral	34 (69.4%)	
	Unilateral	9 (18.3%)	
	Sometimes unilateral and sometimes bilateral	6 (12.2%)	
Headache pattern — n (%)	Tension-type	26 (53.1%)	
	Migraine	22 (44.9%)	
	Tension-type or migraine	1 (2%)	
Medication used during dialysis headache attack	Dipyrone	34 (69.4%)	
	Paracetamol	8 (16.3%)	
	Dipyrone/paracetamol	4 (8.2%)	
	Others	3 (6.1%)	
Dialysis headaches over the last 30 days		26 (53.1%)	
Number of sessions with headaches over the last 30 days			2 (±2.8)
Length of time until end of headache after end of dialysis (minutes)			180.4 (±421.1)
Behavior of headache intensity over the months	Same as in the beginning	12 (24.5%)	
	Becoming more intense	9 (18.4%)	
	Becoming less intense	28 (57.1%)	
Behavior of headache frequency over the months	Same as in the beginning	7 (14.3%)	
	Becoming more frequent	9 (18.4%)	
	Becoming less frequent	33 (67.3%)	

SD: standard deviation; VAS: visual analogue scale for pain (0–10).

makes comparisons difficult. Our study was the first to use the ICHD-3 criteria among hemodialysis patients.

We also found high prevalence of primary headaches among our hemodialysis patients. This was in line with the findings of previous studies[18,19]. However, there was no association between presentation of primary headaches and presentation of dialysis headache.

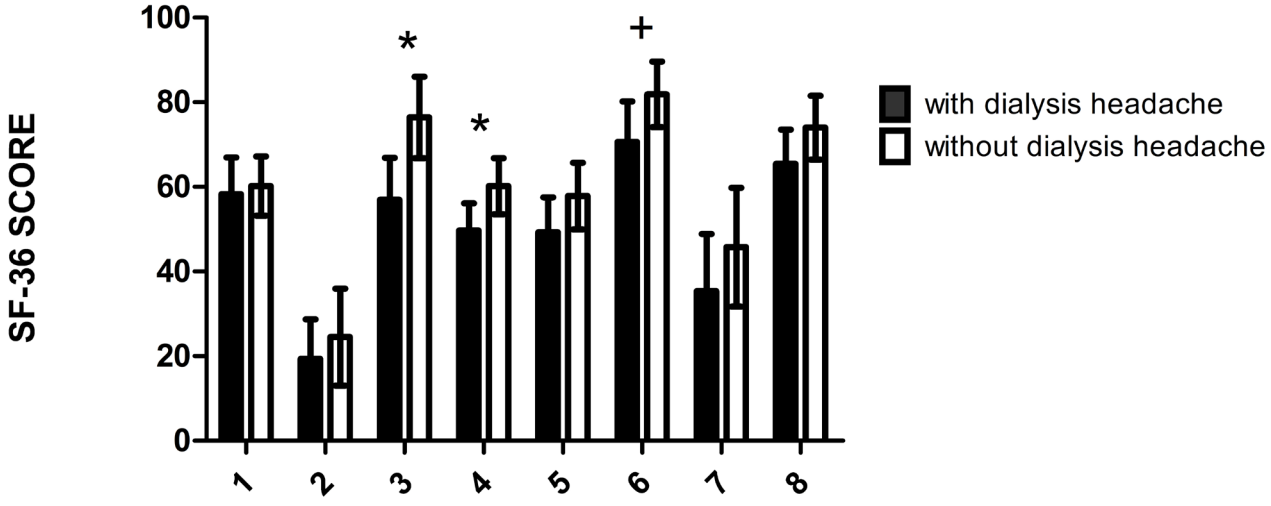
Most of our patients started to present their headaches after the second hour of dialysis. This was in line with previous reports in the literature[4,6,18,20]. The pattern of dialysis headache that was most frequently found resembled tension-type headache. This result diverges from what was found by Antoniazzi et al., who used the diagnostic criteria of ICHD-1 and found that the most frequent pattern was migraine[4]. Despite our finding of the predominance of the tension-type headache pattern, the migraine pattern was also frequently seen. The decrease in the severity of dialysis headache over time that our patients reported constitutes important prognostic information that needs to be confirmed through prospective studies.

As far as we are aware, this was the first study to evaluate the risk factors associated with dialysis headache. Women, younger individuals, individuals with higher schooling levels and individuals who had been on hemodialysis programs for longer times presented dialysis headache significantly more frequently. Higher prevalence of primary headaches such as migraine and tension-type headache among women and younger adults has previously been described[21]. We consider that the association between longer time spent on a hemodialysis program and

Table 2. Associations of sociodemographic and clinical characteristics, compared between groups with and without dialysis headache.

Characteristics		With dialysis headaches	Without dialysis headaches	p-value	*Odds Ratio* (95%CI)	p-value
		n=49	n=51	(Univariate analysis)	(Logistic regression)	(Logistic regression)
Age (years): median (IQR)		45 (39–58.9)	56 (49.5–64)	<0.01	1.05 (1.01–1.08)	<0.01
Sex	Female	34 (69.4%)	16 (31.4%)	<0.01	5.04 (1.95–13.04)	<0.01
	Male	15 (30.6%)	35 (68.6%)		Reference value	
Schooling level	Up to 7 years	11 (22.5%)	26 (51%)	0.07	Reference value	0.02
	≥8 years	38 (77.5%)	25 (49%)		3.86 (1.4–10.7)	
Length of time on hemodialysis (months): median (IQR)		36 (17-96)	24 (11-48)	0.13	0.99 (0.98–1)	0.04
Migraine		17 (34.7%)	8 (15.7%)	0.03	-	-
Tension-type headache		22 (44.9%)	29 (56.9%)	0.23	-	-
Excessive use of caffeine		3 (6.1%)	4 (7.8%)	0.73	-	-
Anxiety		18 (36.7%)	10 (19.6%)	0.06	-	-
Depression		14 (28.6%)	11 (21.6%)	0.42	-	-

IQR: interquartile range; 95%CI: 95% confidence interval.



Mean±SD; *p<0.05; +p=0.06; 1: physical functioning; 2: role-physical; 3: pain; 4: general state of health; 5: vitality; 6: social functioning; 7: role-emotional; 8: mental health.

Figure 1. Quality of life and dialysis headache.

development of dialysis headache is important clinical data for guiding these patients and for nephrologists. This finding may also have physiopathological significance. The conditions needed for developing this type of headache probably require a long time to become established.

Also as far as we know, this was the first study to assess the impact of dialysis headache. Among the headaches presented, dialysis headache was the only one that was significantly associated with a high negative impact on the patients' lives. Although patients with kidney failure have other complications and other causes of pain, such as neuropathic pain and cramps[22], presence of dialysis headache had a significant negative effect on our patients' perceptions of their health. This pain interfered to a greater extent with their quality of life.

Cerebrovascular behavior among patients with dialysis headache had not previously been reported in the literature, to the best of our knowledge. The pulsatility index, which provides a measurement of vascular resistance, was significantly lower bilaterally in the middle cerebral arteries in the first hour of hemodialysis and in the left middle cerebral artery in the fourth hour of dialysis. This suggests to us that there was a pattern of cerebral dilatation in our patients with dialysis headache.

A previous study found that there was higher plasma concentration of calcitonin gene-related protein (CGRP) before hemodialysis in patients with dialysis headache, compared with controls[7]. CGRP is a potent vasodilator and our finding may corroborate the hypothesis that it participates in the physiopathology of dialysis headache. This molecule is widely distributed in the central and peripheral nervous systems and has an important role in mechanisms favoring inflammation, nociception and hyperalgesia[23,24].

Antoniazzi and Corrado suggested that nitric oxide (NO) might participate in the physiopathology of dialysis headache[19]. NO is a vasodilator and the increase in its levels over the course of dialysis might provide an explanation for why headaches generally occur after the second hour of dialysis. This might

Table 3. Associations of sociodemographic and clinical characteristics with the impacts from headaches.

Characteristics	High impact from headache (HIT-6>55) n=21	Low impact from headache (HIT-6<56) n=79	p-value (Univariate analysis)	*Odds Ratio* (95%CI) (Logistic regression)	p-value (Logistic regression)
Age (years): median (IQR)	45 (38–53.5)	55 (44.5–61.5)	0.07	-	-
Sex — Female	18 (85.7%)	32 (40.5%)	<0.01	-	-
Sex — Male	3 (14.3%)	47 (59.5%)			
Length of time on hemodialysis (months): median (IQR)	35 (20.5-78)	27 (12-78)	0.49	-	-
Migraine	11 (52.4%)	14 (17.7%)	0.02	-	-
Tension-type headache	7 (33.3%)	44 (55.7%)	0.07	-	-
Excessive use of caffeine	2 (9.5%)	5 (6.3%)	0.61	-	-
Anxiety	13 (61.9%)	15 (19%)	<0.01	8.8 (1.9–40.8)	<0.01
Depression	9 (42.9%)	16 (20.3%)	0.04		
Dialysis headache	20 (95.2%)	29 (36.7%)	<0.01	24.4 (2.6–226.6)	<0.05

IQR: interquartile range; HIT-6: Headache Impact Test.

Table 4. Comparison of Doppler measurements between patients with and without dialysis headache.

	With dialysis headache (Mean ±SD)	Without dialysis headache (Mean ±SD)	p-value
MFV of right MCA in 1st hour of dialysis (n=83)	51.30 (±14.2)	46 (±12.2)	0.13
MFV of left MCA in 1st hour of dialysis (n=83)	51.40 (±16.3)	47 (±12.8)	0.38
MFV of right MCA in 4th hour of dialysis (n=83)	45.60 (±16.8)	41.4 (±10.9)	0.55
MFV of left MCA in 4th hour of dialysis (n=83)	43.20 (±15.2)	41.9 (±13.4)	0.98
PI of right MCA in 1st hour of dialysis (n=83)	0.97 (±0.25)	1.1 (±0.26)	0.01
PI of left MCA in 1st hour of dialysis (n=83)	0.99 (±0.31)	1.09 (±0.25)	0.02
PI of right MCA in 4th hour of dialysis (n=83)	1.08 (±0.3)	1.2 (±0.42)	0.13
PI of left MCA in 4th hour of dialysis (n=83)	1.04 (±0.33)	1.21 (±0.41)	0.02

MFV: mean flow velocity; MCA: middle cerebral artery; PI: pulsatility index.

also explain the vasodilatation pattern that we found at the end of the dialysis among the patients with dialysis headache. This state of vasodilatation among these patients may suggest that compensatory cerebral self-regulation mechanisms had failed, as previously seen among patients with intracranial atherosclerotic disease, which led to loss of vasoreactivity[25].

Our study presents some limitations. Our sample was selected according to convenience and may not have represented the population of patients who undergo hemodialysis. We did not measure the hematocrit levels of our patients. These might become altered during hemodialysis and such occurrences would be related to vascular resistance and oxygen transportation capacity, which could lead to a metabolically mediated pattern of vasodilatation or vasoconstriction[26].

The evaluation using transcranial Doppler ultrasonography was done only on the middle cerebral arteries. However, cerebrovascular phenomena may occur asymmetrically and, depending on the patient's clinical condition, these may occur more in the vertebrobasilar region. This, and the fact that few of our patients presented headaches at the time of our evaluation, may have given rise to underestimation of the vascular alterations. Such alterations might thus have been greater than what we found.

In conclusion, dialysis headaches have high frequency and generally start after the second hour of dialysis, and their pattern most frequently consists of tension-type headache. Dialysis headache has a significant negative impact on quality of life and occurs more frequently among women, younger adults, individuals with higher schooling levels and individuals who have been on hemodialysis programs for longer times. Patients with a diagnosis of dialysis headache present a pattern of cerebral vasodilatation.

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ARTICLE

Functionality and disease severity in spinocerebellar ataxias

Relação entre a função e a gravidade nas ataxias espinocerebelares

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ABSTRACT

Background: Spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterized by deterioration of balance and functionality that tends to follow disease progression. There is no established link between formal clinical markers for severity and functional/balance scores that could guide rehabilitation teams. **Objective:** To evaluate the relationship between functional scales and ataxia severity in order to identify cutoff landmarks for functional loss and estimate the mean SARA (Scale for Assessment and Rating of Ataxia) score for the risk ratings for falls on the BBS (Berg Balance Scale). **Methods:** Consecutive patients with a molecular diagnosis of SCA (total 89: 31 with SCA2 and 58 with SCA3) were assessed for functionality FIM-ADL (Functional Independence Measure-activities of daily living and Lawton-IADL (instrumental activities of daily living), balance (BBS) and disease severity (SARA). **Results:** The main disability cutoff landmarks were that the need for supervision for FIM-ADL starts with 12 points on SARA and the need for supervision for Lawton-IADL starts with 14 points on SARA. The first items to require assistance were "expression" and "shopping", respectively. At 20 points on SARA, patients were dependent on all FIM and Lawton items. The item with the greatest impact on distinguishing dependents from independents was "means of transport" in Lawton-IADL and the domain "locomotion" in FIM-ADL. The mean SARA score for patients classified as low risk in the BBS was 9.9 points, and it was 17.4 for medium risk and 25.2 for high risk. **Conclusions:** Analysis on the correlation between the severity of ataxia and functional scales can form an important guide for understanding the progression of functional dependence among individuals with SCAs.

Keywords: Spinocerebellar Ataxias; Severity of Illness Index; Postural Balance; Functional Residual Capacity.

RESUMO

Antecedentes: As ataxias espinocerebelares (SCA) são um grupo de doenças neurodegenerativas caracterizadas pela deterioração do equilíbrio e da funcionalidade, que tende a acompanhar a progressão da doença. Não existe uma ligação estabelecida entre os marcadores clínicos formais de gravidade e escores funcionais e de equilíbrio que possam orientar as equipes de reabilitação. **Objetivo:** Avaliar a relação entre escalas funcionais e de gravidade da ataxia, buscando identificar pontos de corte para a perda funcional relacionados aos escores de gravidade e aos patamares de Risco de Quedas. **Métodos:** Uma amostra consecutiva de 89 pacientes com diagnóstico molecular de SCA (31-SCA2 e 58-SCA3) foram avaliados para funcionalidade MIF-AVDs (Medida de independência funcional-Atividades da vida diária) e Lawton-AIVDs (Atividades instrumentais da vida diária), equilíbrio (EEB-escala de Equilíbrio de Berg), e gravidade da ataxia (SARA-escala para avaliação e graduação de ataxia). **Resultados:** Os principais pontos de corte de deficiência foram: com 12 pontos no SARA começa a

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necessidade de supervisão para MIF-AVDs e com 14 pontos no SARA começa a necessidade de supervisão para Lawton-AIVDs. Os primeiros itens a necessitar de assistência foram "expressão" e "compras", respectivamente. Com 20 pontos no SARA os pacientes eram dependentes em todos os itens MIF/LAWTON. O item com maior impacto na discriminação entre dependentes e independentes foi "meio de transporte" na Lawton e o domínio "locomoção" na MIF. O escore médio no SARA foi de 9,9 pontos para pacientes classificados com baixo risco na EEB, 17,4 para médio risco e 25,2 para alto risco. **Conclusões:** A análise da correlação entre a gravidade da ataxia e as escalas funcionais pode ser um importante guia no entendimento da progressão da dependência funcional em indivíduos com SCA.

Palavras-chave: Ataxias Espinocerebelares; Índice de Gravidade de Doença; Equilíbrio Postural; Capacidade Residual Funcional.

INTRODUCTION

Spinocerebellar ataxias (SCAs) are an expanding group of neurodegenerative diseases characterized by adult onset of symptoms and signs. They result from dysfunction of the cerebellum and its afferent and efferent connections, and also of other central nervous system areas. The area affected and the severity of dysfunction may vary between different types of SCA[1,2]. Thus, besides cerebellar ataxia, patients may present with oculomotor abnormalities, dysarthria, pyramidal and extrapyramidal signs, pigmentary retinopathy, peripheral neuropathy and cognitive dysfunction, among other manifestations[3,4].

At the time of writing of this paper, 48 types of SCAs had been described and classified according to the affected locus[2]. All of them share cerebellar ataxia as the main feature and leading source of disability in most patients affected[1]. As part of the ataxic syndrome, gait instability and impaired coordination are frequently the main subcomponents, thereby leading to overall functional decline and increased dependence[5].

Assessment of ataxia severity has been used to study long-term disease progression[1] and to estimate the speed of progression for different types of SCA[1,6]. Other assessments that quantify patients' independence for perform basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and their balance/risk of falls and quality of life, have also helped multidisciplinary teams to understand the natural history of the disease and its impact on these patients' daily activities[5,7-9].

The relationship between disease progression and functional loss is relatively well known, but the link between functional scales and ataxia severity has not yet been investigated with the intention of shedding light on which functions and activities are being lost and when this happens over the course of the disease. Better understanding of how functional decline occurs could be used to elaborate and implement clinical practice guidelines and to serve as landmarks for future interventions aimed at preventing and minimizing the impact of the disease.

In this study, we hypothesized that selected formal clinical markers of severity might be directly linked to functional/balance scores. Recognition of the timing and nature of activities that will require some sort of external intervention is the starting point for creation of specific guidelines, including practical and safety strategies for maintaining independence for as long as possible.

The aim of this study was to evaluate the relationship between functional scales and ataxia severity in order to identify cutoff landmarks for functional loss and estimate the mean SARA score for the risk ratings for falls.

METHODS

We performed prospective data collection between January 2017 and December 2018. This study was approved by the Research Ethics Committee of Hospital de Clínicas, Federal University of Paraná (HC-UFPR). Data were gathered from 89 consecutive patients who were followed at the Ataxia Outpatient Clinic of the Movement Disorder Unit of HC-UFPR.

The sample included subjects aged 18 years or older, irrespective of gender, with a genetically confirmed diagnosis of SCA3 or SCA2, or neurological signs characteristic of ataxia in a family member of a positively tested patient. The choice of SCA3 and SCA2 was based on the fact that these are two of the three most frequent types of SCA in southern Brazil[10]. Moreover, even though the phenotypes of these disorders do not necessarily overlap, they present with similar arrays and severity of motor and nonmotor signs, in addition to having similar ataxia severity progression rates (1.49 and 1.52 for SCA2; 1.56 and 1.60 for SCA3), as described in previous studies[1,6]. This is in contrast to SCA10, for example, which has a purer phenotype and typically a slower progression rate.

All subjects provided a signed consent statement that was in accordance with the institution's guidelines. Cases presenting a concomitant clinical disorder that could interfere with the assessments were not included.

Clinical assessment

Demographic and clinical data were collected during patients' visits, and were confirmed from the medical records when available. The same examiner assessed all cases. The standardized protocol included obtaining the following demographic data and clinical data: gender, age, age at symptom onset, disease duration, ataxia severity score, family history, details of molecular test, assessment of ataxia severity via the Brazilian version of the Scale for Assessment and Rating

(SARA) [consisting of eight items with a final score ranging from 0 (no ataxia) to 40 (most severe)][11,12] and functional scores derived from the Berg Balance Scale (BBS)[13], Functional Independence Measure (FIM) scale[14] and Lawton ADLs scale[15].

The BBS[13] consists of 14 tasks measuring static and dynamic balance and determining the risk of falls. Scores may range from 0 to 56: individuals with scores between 41 and 56 can walk independently with a low risk of falls; those with scores from 21 to 40 have the ability to walk with assistance and have a medium risk of falls; while those with scores of 20 or lower are wheelchair-bound, with a high risk of falls[13].

The FIM assesses the amount of assistance required for the individual to carry out ADLs. The maximum score for each of the 18 items is 7, which indicates complete independence, while the minimum score of 1 indicates total dependence. A score of 5 indicates the need for another person to supervise each individual task. The overall score can vary from 18 to 126[14]. In this study, patients were considered independent if they had scores of 6 or 7 for all FIM items.

Lastly, the Lawton IADL scale[15] is used to assess the ability to live independently and participate in the community (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications and ability to handle finances). The maximum score on the Lawton scale for IADLs is 21, which indicates complete independence.

Statistical analysis

The data were tabulated using Microsoft Office Excel 2016® and analyses were performed with the aid of IBM SPSS Statistics v.25.0. (Armonk, NY, USA). Categorical variables were described in terms of frequency and percentage, whereas continuous variables were described in terms of mean and standard deviation. The correlations of FIM, Lawton and Berg scores with the severity of the disease (SARA) was estimated. For this, Spearman's correlation was used, given that the values on the SARA scale did not present normal distribution. The significance level was taken to be 5%.

The magnitude of the calculated correlations was classified as described by Mukaka[16]. In order to assess the relationship between FIM items and domain classifications, Lawton Scale items and SARA scores, ROC curves were constructed and the AUC and cutoff values were computed. The Kruskal-Wallis test was also used to compare SARA scores between fall risk classification groups (BBS>40, high risk; BBS between 21 and 40, medium risk; BBS<21, high risk). Alpha was taken to be 5% for all analyses performed.

RESULTS

Among the overall sample of 89 patients evaluated, 45 (50.6%) were male and the mean age was 45.2 (±12.6) years, ranging from 16 to 55 years. There were no significant differences between the two types of SCAs with regard to age (p=0.629), age at symptom onset (p=0.189) or disease duration (p=0.672). Data on molecular characteristics were available for 59 patients (66.3%). Details of the demographic, clinical and molecular characteristics are shown in Table 1. The mean scores for disease severity, functionality and balance for the total sample and for each subdivision according to the risk of falls are shown in Table 2.

Considering the entire sample, high negative correlations were identified between SARA scores and FIM (r=-0.730, p<0.001), Lawton (r=-0.808; p<0.001) and BBS scores (r=-0.885, p<0.001).

Table 3 shows the cutoff points of the ROC curve for individual FIM and Lawton items. The first FIM items for which patients needed assistance were "expression" and "dressing lower body", with loss of independence starting at 12 points in

Table 1. Spinocerebellar ataxia types 2 and 3 — descriptive data.

Variables	SCA2	SCA3	Total	p-value
Patients-	31	58	89	
Sex–Male (%)	19 (61.3)	26 (44.8)	45 (51)	0.139
With genetic testing (%)	17 (54.8)	42 (72.4)	59 (63.3)	0.095
Expansions in altered allele	2240 (2048–2256)	70.5 (67–74)	-	-
Age (years)	44.1±12	45.8±12.9	45.2±12.6	0.629
Age at onset of symptoms (years)	31.7±9.3	34.5±10.2	33.6±9.9	0.189
Disease duration (years)	12.4±7.4	11.2±5.6	11.63±6.3	0.672
Functional scores				
SARA	16 (8.5–24.5)	17 (11–22)	16 (11–23)	0.529
FIM	108 (96.5–117)	105.5 (91.2–113)	106 (95–114)	0.18
Lawton	19 (12.5–21)	17 (14.3–19.8)	18 (13–20)	0.317
Berg	43 (10–51)	34.5 (17–47.5)	38 (15–49)	0.75

Berg: Berg Balance Scale; FIM: Functional Independence Measure (ADL); SARA: Scale for Assessment and Rating of Ataxia.

Table 2. Demographic, clinical and functional scores considering the entire sample (n=89) and subdivided according to the risk of falls.

SCA2 and SCA3 (n=89)		Groups according to fall risk			Total
		Low risk	Medium risk	High risk	
AGE (years)		41 (±11.2)	46.2 (±11.3)	50.1 (±13.4)	45.1 (±12.5)
Age at onset of symptoms (years)		32.2 (±9.5)	33.3 (±8.4)	35.4 (±11.3)	33.5 (±9.9)
Disease duration (years)		8.7 (±5.4)	12.8 (±3.9)	14.7 (±6.8)	11.6 (±6.2)
Sara score		9.9 (±5)	17.4 (±3.7)	25.2 (±5.2)	16.5 (±8.3)
FIM total score		114.8 (±8.3)	98.7 (±15.4)	88.3 (±18.7)	102.6 (±18.3)
FIM motor score		82.4 (±6.5)	69.5 (±10.7)	59.6 (±17.3)	72.1 (±15.6)
FIM cognitive score		32.3 (±2.7)	29.2 (±4.8)	28.6 (±3.4)	30.4 (±3.8)
Lawton IADL score		19.8 (±1.6)	19.8 (±1.6)	12.7 (±3.1)	16.7 (±4.1)
Berg score		49.2 (±4.7)	31.1 (±6)	10.4 (±5.6)	32.4 (±18)
Gender	Female	17 (41.4%)	10 (55.5%)	17 (56.6%)	44 (49.4%)
	Male	24 (58.5%)	8 (44.4%)	13 (43.3%)	45 (50.6%)

Berg: Berg Balance Scale; FIM: Functional Independence Measure (Activities Of Daily Living [ADL]); Lawton IADL: Lawton Instrumental Activities of Daily Living Scale; SARA: Scale for the Assessment and Rating of Ataxia.

Table 3. Cutoff points for the Receiver Operating Characteristic curve curve for Functional Independence Measure and Lawton items.

Functional independence measure			
FIM dimensions	**FIM items**	**Cutoff SARA**	**AUC**
Self-care	Eating	18.25	0.844
	Grooming	18.5	0.863
	Bathing	17.5	0.883
	Dressing upper body	16.5	0.811
	Dressing lower body	12.75	0.762
	Toileting	20.5	0.773
Sphincter control	Bladder management	18.75	0.762
	Bowel management	16.5	0.656
Transfers	Bed/chair/wheelchair	17.5	0.804
	Toilet	16.5	0.783
	Bath/shower	15.5	0.775
Locomotion	Walking/wheelchair	15.5	0.825
	Stairs	15.5	0.847
Communication	Expression	12.5	0.704
Social interaction	Problem-solving	16.5	0.708
Lawton Instrumental Activities of Daily Living Scale			
Lawton items		Cutoff SARA	AUC
Shopping		14	0.841
Mode of transportation		16.5	0.867
Housekeeping		16.5	0.854
Food preparation		18.5	0.846
Ability to use telephone		20	0.829
Ability to handle finances		18.2	0.815
Responsibility for own medications		16.5	0.844

FIM: Functional Independence Measure (ADL); AUC: area under the curve; SARA: Scale for Assessment and Rating of Ataxia. There was no statistical significance for the items of social interaction, memory and understanding (verbal/nonverbal); these were therefore omitted from the table.

SARA. The last FIM items for which patients lost independence were "toileting" and "bladder management", with the maximum of 20 points in SARA. It was not possible to verify the influence of the items "social interaction", "memory" and "understanding" on SARA scale scores, at the 5% significance level.

Regarding IADLs, "shopping" was the first activity for which patients with SCA lost their independence, starting from a score of 14 points in SARA. The last skill for which independence was compromised was "ability to use telephone", with 20 points in SARA. Figure 1 presents the decline in functionality according to FIM domains. The first domain affected was "communication", which occurred at 12.25 points (AUC: 0.69) in SARA, while the last domain affected was "transfers", at around 16.5 points. Considering the AUC estimates, it was observed that the domains of "locomotion" (AUC: 0.84), "self-care" (AUC: 0.83) and "transfers" (AUC: 0.79) were the ones with the greatest power to distinguish between dependent and independent patients. In terms of IADLs, the items that showed the greatest power to distinguish between dependent and independent patients were "mode of transportation" (AUC: 0.87), "housekeeping" (AUC: 0.85) and "food preparation" (AUC: 0.85) (Figure 2).

The association between fall risk on the BBS scale and ataxia severity showed that the mean SARA scores were 9.9 points for patients classified as low risk, 17.4 points for those of medium risk and 25.2 points for those of high risk (Figure 3). The fact that there was no overlap between the interquartile ranges that classified the risk of falls demonstrates that there was good segregation between the groups.

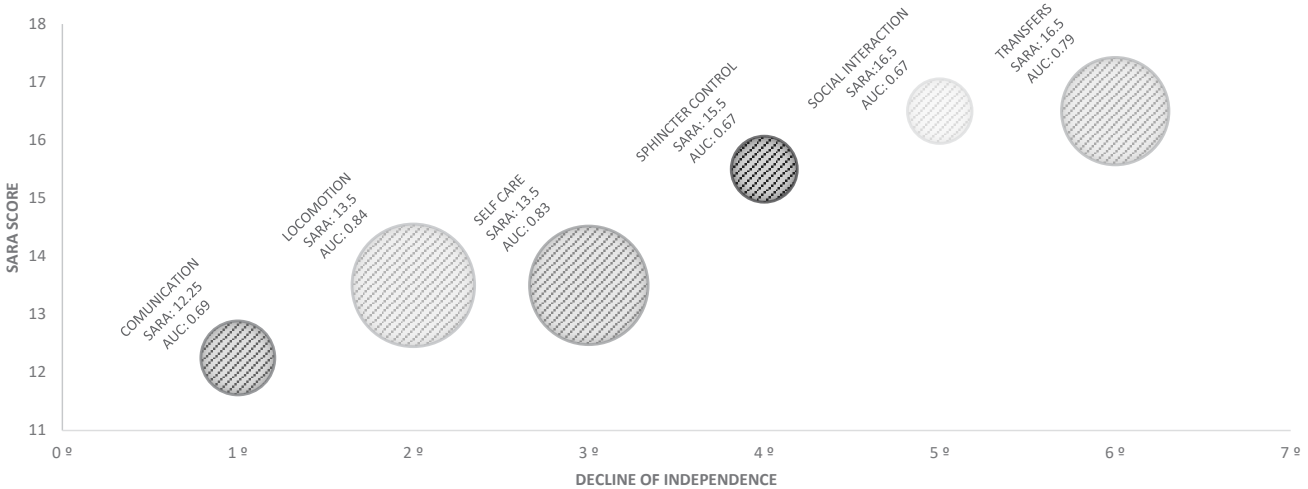
DISCUSSION

Our study confirmed that gradual loss of independence and increased risk of falls are landmarks inherent to the clinical disease progression of patients with SCAs, as observed through the high correlation between increased severity and decreased functional and balance scores. This functional decline is continuous and definitive, progressively compromising patients' autonomy and quality of life[5]. To date, we have been unable to identify any published data correlating the progression of cerebellar symptoms with loss of independence in specific areas or with the risk of falls.

The present analysis showed that, starting from 12 points on SARA, disability directly related to functional loss already leads patients to require assistance from caregivers, initially in relation to the ability to communicate; and starting from 14 points, for more complex activities. The functional scales that were used in our study provided an overview of how the loss of independence occurs and showed that when 20 points on SARA was reached, patients were already dependent for all the basic and instrumental activities analyzed.

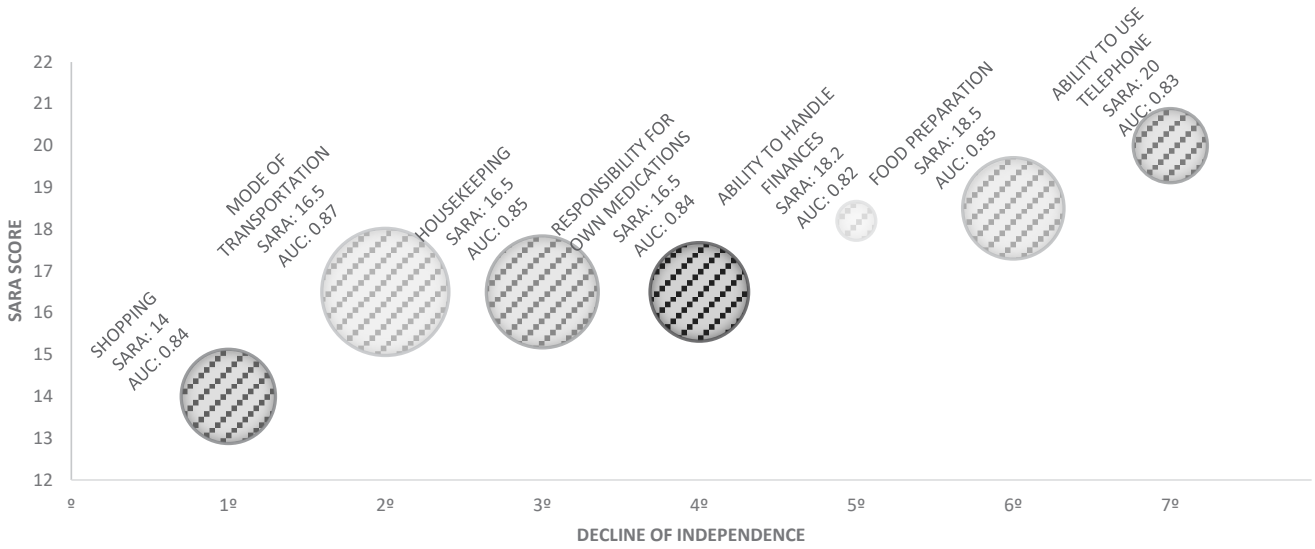
Regarding ADLs, the first item for which SCA patients required assistance from caregivers was "expression", from the "communication" domain, which was also the first to be affected. The ability to communicate ideas through speech was shown to be one of the leading sources of disability among SCA patients who, due to motor dysfunction in the muscles of the lips, tongue, palatine veil and larynx, present limitations with regard to oral expression[17]. A lack of coordinated muscle contraction for speech articulation is present in ataxias resulting from cerebellar lesions, in which the muscles are hypotonic, thus generating slow and imprecise movements in terms of strength, extension, duration and direction[18]. In addition to the primary disruption to articulation and prosody observed in ataxic dysarthria[19], many SCA patients also present Schmahmann's affective-cognitive syndrome[20], with agrammatism and telegraphic language, but without altered understanding, thus leading to difficulties in oral expression.

Loss of independence regarding expression, as measured by FIM, begins with use of "frequent repetition" to ensure that the essential needs and ideas of everyday life are understood.



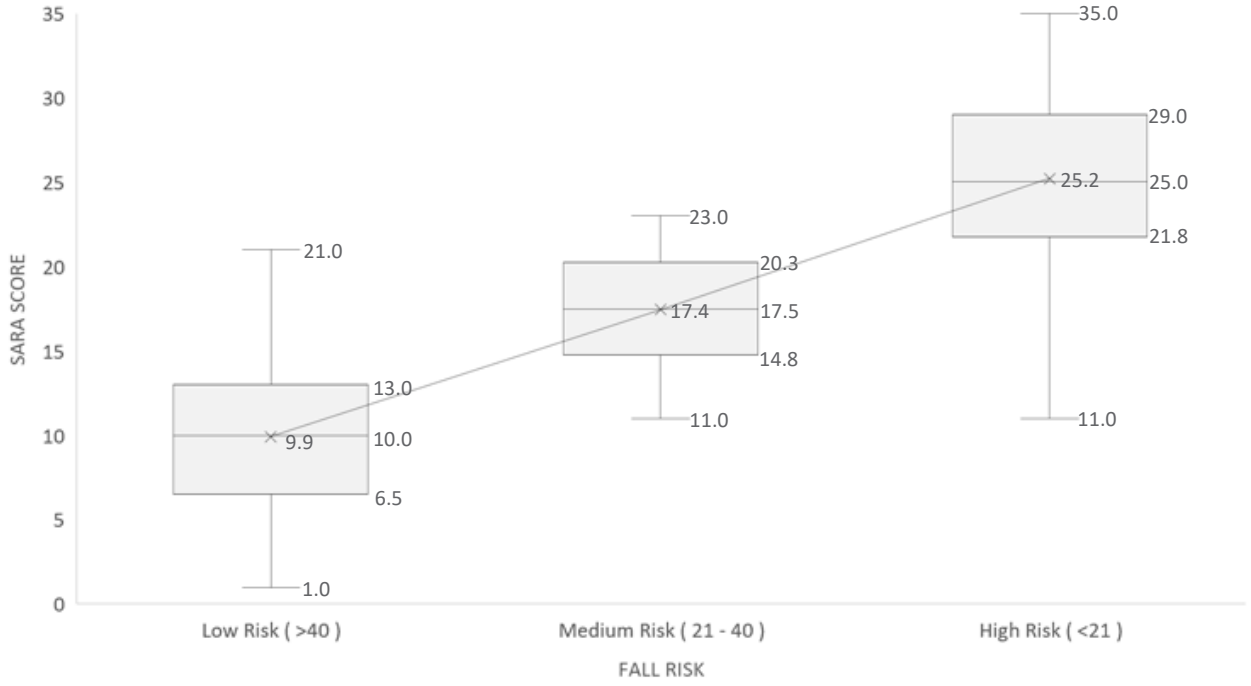
AUC: area under the curve; SARA: Scale for Assessment and Rating of Ataxia.

Figure 1. Representation of power of FIM domains to distinguish independence.



AUC: area under the curve; SARA: Scale for Assessment and Rating of Ataxia.

Figure 2. Representation of the power of Lawton scale items to distinguish independence.



SARA: Scale for Assessment and Rating of Ataxia.

Figure 3. Association between risk of falls (Berg) and severity of ataxia (SARA).

Needing to repeat frequently and striving to be understood can be tiring and discourage communication, which, in turn, becomes more compromised as the patient becomes isolated. A similar finding was shown by Lirani et al.[21], in the case of another neurodegenerative disease, Parkinson's disease. In practical terms, observation of early loss of independence with regard to expression can form a subtle alert for healthcare professionals and caregivers, in that this reflects a need for a detailed assessment of the current overall impact of the disease on ADLs.

Observation of a need for assistance with "eating", as measured via FIM, in fact refers to a wide range of tasks, such as opening containers, cutting food, passing the butter or serving drinks. It may thus be related to motor coordination difficulties, and not necessarily to dysphagia, and it might be addressed through adaptation using different food types and consistencies. Although dysphagia will settle in, among patients with ataxia, due to mechanisms that also cause dysarthria[17], the present analysis did not provide any clues as to when these two issues would arise in relation to ataxia severity.

Our study results showed that "dressing lower body" was the next item for which independence became compromised. "Dressing lower body" includes putting on socks, tying shoelaces and wearing pants/trousers. Very early on, when loss of balance becomes significant, patients adapt by sitting down in order to safely perform these activities. This adaptation is considered to represent modified independence. A need for supervision for this task is probably associated with loss of trunk balance, which increases the risk to the patient. This could explain why this specific activity, which is part of the "self-care" domain that was least compromised in our sample, was in isolation the second item to be impacted in terms of independence.

"Bath/shower", "walking/wheelchair" and "stairs" were the next items for which independence became compromised, at around 15 points on SARA. In a study by Amarante et al.[7], who evaluated patients with SCA2, the first items to become compromised were, in fact, those related to locomotion ("walking/wheelchair" and "stairs"). Difficulty in walking and climbing stairs limits mobility within different scopes, including social life and access to services in general. The bathroom/shower is one of the house spaces where the greatest numbers of falls take place[22]. Such occurrences should, very early on, serve as a warning for patients with ataxia and their caregivers. For a period, adaptations such as support bars, non-slip mats and use of a bath chair may be sufficient to provide safety, but as the disease progresses, patients will need to be supervised, especially when going into and coming out of the shower cubicle.

The FIM domains of "locomotion", "self-care" and "transfers" were the ones with the greatest power for distinguishing independence. In a study by Aizawa et al.[5], for instance, evaluating 44 patients with SCA 1, 2, 3 and 6, the greatest dependence levels were observed in those same domains.

The ability to perform certain tasks, such as "shopping", "mode of transportation" and "housekeeping" were the first IADLs that patients with SCAs failed to accomplish independently, thus corroborating the study by Santos et al.[8]. These authors evaluated the quality of life in a sample of patients with SCA10, and observed that this variable correlated well with loss of independence to perform these items. In fact, loss of independence regarding activities outside the household environment, especially those that could provide personal satisfaction, leads to progressive isolation, loss of autonomy and loss of quality of life, as also observed in individuals with Parkinson's disease[23]. In addition to the findings from the study by Santos et al.[8], we were able to show that these milestones occurred when patients had scores of between 14 and 16 points on SARA. On the other hand, autonomy inside the home, such that patients could take care of their own feeding and the "ability to use telephone" would be markers of dependency with regard to IADLs.

Our data analysis allowed us to present an average value for the SARA score for each level of stratification of the risk of falls in the BBS. These two scales use different approaches to measure the progression of facets of cerebellar signs and symptoms, and combining these parameters provides an integrated assessment of balance and the risk of falls[24].

Although these assessments of fall risk are important, Van de Warrenburg et al.[25] warned that even the initial changes to balance control can lead to falls. This issue needs to be brought up among patients and caregivers. Even though higher severity of ataxia is a predictive factor for higher frequency of falls, Fonteyn et al.[26] found that almost three quarters of their patients reported having had at least one fall in the past 12 months. In most of their patients, falls occurred at early stages of the disease, often within the first two years of the disease. In 10% of their patients, these falls were even the presenting feature[26]. Falls, along with other functional losses, tend to progress inexorably and this also leads to dependency on walking aids (walker/wheelchair). In the present study, this occurred at around 15 points on the SARA scale. Different exercise protocols enable compensation of certain ataxia symptoms, to improve balance and decrease the risk of falls. Thus, rehabilitation constitutes an ally in prolonging the independence of patients with SCA[27,28].

To gather a representative sample, the present analysis considered the patients' disease severity, regardless of the type of SCA and disease duration. Similarly, SCA3 and SCA2 results from monoallelic expansion of a CAG triplet on loci 14q21 and 12q23-24, respectively, were reported[3,29,30]. These shared cerebellar ataxia as the main clinical sign, had similar ataxia severity progression rates[1,6] and, in the present study, several of their demographic and clinical variables were matched. As such, SARA is an adequate and widely used instrument in both research and routine clinical settings[1,5-8], including for multidisciplinary team assessments and interventions. Our results highlight the importance of keeping track of clinical progression using this scale, considering that, during medical consultations, the rehabilitation team may not always be present. The SARA scores serve as a parameter that can be correlated with more functional outcomes.

Grouping together two different SCAs in a single study might be seen as a limitation, but in fact it was a strategy for optimizing the statistical power of our study. It needs to be considered that the sequences within which different items in the SARA are affected may differ. For example, there is earlier involvement of the lower limbs in SCA3[31], which could reflect specific types of impaired activities.

Future studies with larger samples that provide adequate statistical power to analyze different SCA subtypes may show whether functional differences exist among these disorders. Hopefully, such studies will also show their correlations and score thresholds on SARA. We believe that the greatest contribution of the present analysis was that it enabled a more functional and practical view of patients, using a parameter for severity that was derived from a reliable and easy-to-apply instrument such as SARA.

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ARTICLE

A holistic approach to evaluating Parkinson's disease, using the Delphi method: a linear evaluation index

Un enfoque holístico para evaluar la enfermedad de Parkinson con el método Delphi: un índice evaluativo lineal

Marcos SERRANO-DUEÑAS[1,2], Luis MASABANDA[2], Maria-Rosario LUQUIN[3]

ABSTRACT

Background: Parkinson's disease (PD) is a chronic disease that presents a multitude of symptoms, with symptoms of both motor and nonmotor nature. The Delphi method is widely used to create consensuses among experts in a field of knowledge. **Objective:** In order to reach a consensus on the values that should be assigned to the different motor and nonmotor manifestations of Parkinson's disease, a linear evaluation index (LEI) was created. Subsequently, the metric properties of this index were studied. **Methods:** 120 consecutive patients with a Parkinson's diagnosis were chosen in accordance with the UKPDSBB criteria. The Delphi method was used to reach a consensus among experts regarding the values of each of the manifestations included. Subsequently, the following attributes were analyzed: quality and acceptability of the data; reliability, in terms of internal consistency, reliability index, Cronbach's alpha and standard error of measurement; and validity, in terms of convergent validity and validity for known groups. **Results:** Twenty-five experts participated. The importance factor did not differ between the first round and the second round (chi-square test). We analyzed the responses that assigned percentage values to the 10 dimensions of the LEI. Both in the first and in the second round, the values of the scattering coefficient Vr were always close to 0. The homogeneity index was 0.36; the corrected-item total correlation values ranged from 0.02 to 0.7; Cronbach's α was 0.69; and the SEM was 4.23 (55.1%). **Conclusions:** The LEI was obtained through rigorous recommended methodology. The results showed adequate metric properties.

Keywords: Parkinson Disease; Holistic Health; Delphi Technique; Psychometrics.

RESUMO

Antecedentes: La enfermedad de Parkinson (EP) es una enfermedad crónica que presenta una multitud de síntomas, tanto de naturaleza motora cuanto no motora. El método Delphi se utiliza ampliamente para crear un consenso entre expertos de un campo del conocimiento. **Objetivos:** Con el fin de llegar a un consenso sobre los valores que deben asignarse a las diferentes manifestaciones motoras y no motoras de la enfermedad de Parkinson, se creó el "Índice de Evaluación Lineal" (*linear evaluation index* — LEI). Posteriormente, se estudiaron las propiedades métricas de este índice. **Métodos:** Se eligieron 120 pacientes consecutivos con diagnóstico de Parkinson según los criterios del UKPDSBB. Se utilizó el método Delfos para llegar a un consenso entre los expertos sobre los valores de cada una de las manifestaciones incluidas. Posteriormente, se analizaron los siguientes atributos: Calidad y aceptabilidad de los datos. Fiabilidad: consistencia interna, índice de fiabilidad, alfa de Cronbach y error estándar de medida. Finalmente, Validez: validez convergente y validez para grupos conocidos. **Resultados:** Participaron 25 expertos, el factor de importancia entre la primera y la segunda rondas (prueba chi-cuadrado), no fue diferente. Analizamos las respuestas que asignaron valores porcentuales a las 10 dimensiones del LEI; tanto en la primera como en la segunda rondas, los valores del coeficiente de dispersión Vr siempre estuvieron cerca de 0. El índice de homogeneidad fue de 0,36; los valores corregidos de correlación ítem-total variaron de 0,02 a 0,7; alpha de Cronbach fue de 0,69. El SEM fue 4,23 (55,1%). **Conclusiones:** El LEI se ha obtenido siguiendo una rigurosa metodología recomendada. Los resultados han mostrado propiedades métricas adecuadas.

Palabras clave: Enfermedad de Parkinson; Salud Holística; Técnica Delfos; Psicometría.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world and affects between 2 and 3% of people over the age of 65[1]. The symptoms of PD include both motor and nonmotor symptoms. Up to 98% of patients have nonmotor symptomatology over the course of the disease, and these symptoms have a negative impact on patients' quality of life[2].

Some of the symptoms of PD are evaluated through subjective measurements, either directly, by the doctor, or indirectly, through the patient's main caregiver[3].

There is increasing evidence that both motor and nonmotor manifestations of PD are heterogeneous. This has led researchers to establish several nonmotor phenotypes for the disease, which is indicative that when evaluating PD, both motor and nonmotor symptoms should be considered[4].

Once an overall assessment of patients with PD has been carried out, their physicians need to gauge which manifestations of the disease affect these patients the most and weight the symptoms accordingly. For example, physicians should ask themselves how seriously manifestations such as psychosis, depression and dysautonomia affect their patients, and how important bradykinesia and motor symptoms are in general.

The Delphi method (DM) is widely used to create a consensus among experts in a specific field of knowledge[5]. One crucial characteristic of this method is the anonymity of the experts involved, which allows experts to express their points of view freely, without retribution. Thus, the value assigned to each of a patient's symptoms will be considered in terms of the importance of the symptom and not the merit of who proposes this.

Given that the researchers can view the criteria created by other experts in the group, they can reconsider their point of view. This generates a controlled feedback loop that gives researchers the opportunity to change their minds. Finally, a value is assigned to the answers, and these values can be statistically analyzed and interpreted[6].

The Delphi method has been used to reach a consensus for making diagnoses of diseases such as progressive supranuclear palsy[7] and advanced PD[8].

We designed a cross-sectional study with the aim of reaching a consensus on the values that should be assigned to the different motor and nonmotor manifestations of PD. After data values had been collected, they were placed in a linear evaluation index (LEI), to evaluate patients holistically and study the resulting metric properties.

METHODS

Delphi panel

We followed the guidelines and suggestions that have been proposed for the Delphi method[5,6]. First, 30 renowned experts in the field of movement disorders and more specifically in PD were invited to participate in an online survey via e-mail. Five of them chose not to participate in the investigation: two because of conflicts of interest, two because of personal problems and one without stating a reason.

To be considered an expert, the participants needed to have achieved recognition in the field of movement disorders through having papers published in indexed journals within this field; and through having worked on movement disorders (i) in practice in a general hospital or university hospital; or (ii) in practice in a referral hospital; or (iii) in a national epidemiology/public health institution[9].

An email was sent to the experts inviting them to take a survey. There were two sections in the survey. In the first section, the experts were asked to assign a level of importance (between 0=not important and 4=essential) for each of the following 10 dimensions involved in PD. 1) age dimension (AD); 2) motor dimension (MD); 3) depression dimension (DD); 4) anxiety dimension (AxD); 5) cognitive dimension (CD); 6) apathy dimension (ApD); 7) fatigue dimension (FD); 8) nonmotor dimension (NMD); 9) psychosis dimension (PsD); and 10) sleep dimension (SD). In the second part of the survey, the experts were asked to assign a percentage value to each of the dimensions, so that the final sum resulted in 100.

Twenty-three of the 25 experts responded within the first 72 hours. After a week without a response from the remaining two experts, the survey was resent to them. Both of these two remaining experts completed the survey within the subsequent 48 hours of receiving it.

Once we had collected the data from the survey, we proceeded to analyze the responses. The proportions of each of the values assigned to the dimensions from the first section of the survey (where the experts had to give a level of importance to each of the dimensions) were collected. From the second section of the survey (where a percentage was given to the dimensions), the median, mean, standard deviation and interquartile range were collected[10]. After the results had been analyzed, the experts were given the same survey again. This time, however, they were presented with their initial responses and the responses of the other experts and were given the choice to either change the values that they had given to these dimensions in the first round of the survey or not change them. All the experts responded within the following week.

Patients

To calculate the sample size, the parameters suggested by Beavers et al.[11] were applied. The UKPDSBB clinical diagnostic criteria[12] were used to select the 120 PD patients who participated in the study. All the patients were treated in the Neurology Service of the Carlos Andrade Marín Hospital in Quito, Ecuador.

All the patients gave their informed consent to participate in the study, which was approved by the Teaching

and Research Department of the Carlos Andrade Marín Hospital and by the Bioethics Committee of the University of Navarra (Spain).

The exclusion criteria consisted of the presence of any neurological disorder that caused disability: hemiplegia, blindness or deafness; or the presence of a serious acute illness.

All the patients were evaluated in the "ON" period. Demographic data of interest were collected, including age for AD. In addition, all of them were examined by means of the following tools: SPES-SCOPA[13] to evaluate MD; HADS[14] to analyze the presence of DD and AxD; PD-CRS[15] to identify CD; AS[16] to evaluate ApD; D-FIS[17] to ascertain FD; SCOPA-PC[18] to investigate PsD; and SCOPA-SLEEP[19] for SD disorders. Lastly, using the NMSS[20], the rest of the elements of the NMD were evaluated (except for depression, anxiety, apathy, fatigue, cognition, psychosis and sleep).

Apart from the rating scales indicated above, PIMS and CISI-PD were used to assess the quality of life and clinical status. PIMS is a 10-item, 4-domain scale. Its items are scored from 0 (no change) to 4 (severe), and the total scores for the scale range from 0 to 40. Lower scores indicate less impact from PD. PIMS has been recommended for use in PD[21]. CISI-PD assesses four domains: motor signs, disability, motor complications and cognitive status. Each domain is scored from 0 (normal) to 6 (severely compromised). The sum of these scores provides an overall evaluation index[22].

The stages of the disease were evaluated using the Hoehn and Yahr (H&Y) scale[23]. Schwab and England (S&E scale)[24] was used to study activities of daily living.

In addition to generating descriptive statistics of interest, the following factors were analyzed and parameters for them were defined:

- Data quality and acceptability: (i) lost data needed to not exceed 5%; (ii) the difference between the average and median needed to not exceed 10% of the highest possible score; and (iii) the floor and ceiling effects needed to not exceed 15%[25]
- Reliability: (i) internal consistency: the homogeneity index of the items needed to be ≥0.3[26]; (ii) reliability index: Cronbach's alpha value needed to be greater than 0.7[27]; and (iii) the standard error of measurement (SEM) was obtained: the SEM needed to be equal to the standard deviation, multiplied by the square root of (1 minus Cronbach's alpha), i.e. (StD * √1-reliability coefficient)[28].
- Validity: (i) convergent validity. For this, the Spearman's correlation coefficient (*rho*S) and the values suggested by Akoglu[29] were used (0=no correlation; 0.1–0.3=weak correlation; 0.4–0.6=moderate correlation; 0.7–0.9=strong correlation; and 1=perfect correlation); and (ii) validity for known groups, for which we used the H&Y stages as a segmentation variable; values ≤0.05 were accepted as significant.

Statistical analysis of Delphi method

The data from the first round of the survey (the level of importance) were compared using the chi-square test. For the second round of the survey, in which the experts decided on what percentage to give for each of the dimensions, the dispersion coefficient V_r was gathered from both rounds. The dispersion coefficient V_r needed to have a value between 0 and 1, such that the closer it was to 0, the greater the degree of agreement between the experts also was[10].

Lastly, the scores for the second round were multiplied by the mean value of the importance factor (obtained between the first and second rounds, which turned out to be the same). The sum of these scores resulted in a value of 105.6 (this number was then made equal to 100, to obtain the final value by means of the simple rule of three). For example, the motor dimension score was 30.3, multiplied by the importance factor, which was 1.2, resulting in a value of 36.36 (Equation 1).

$$\begin{aligned} &105.6=100 \\ &36.36=X \\ &X=36.36*100/105.36 \\ &X=34.8 \end{aligned} \quad (1)$$

To obtain the LEI scores, the values for the level of importance for each dimension, from the second round of the survey, were multiplied by the average values of the percentages given by the experts. This determined a maximum final value of 105.6. Again, the rule of three allowed us to reach a value of 100. For example, if the score for the motor dimension in the second section of the survey was 30.3 and the level of importance from the first section of the survey was 1.2, the result would be 36.36 out of 105.6 which would therefore be 34.8 out of 100.

Continuing with the example of the motor dimension score, the original results had an average value of 28.1 (the maximum for the scale was 75), which yielded 13.03. Since 75 points was the maximum, 100% would be worth the maximum of 34.8 points. With CD, we proceeded by reversing the rule of three, since the higher the score was, the greater the cognition also was.

The maximum theoretical values attainable for each of the dimensions were as follows: the AD was arbitrarily determined at a maximum of 100 years old; MD, 75; DD, 21; AxD, 21; CD 134 (the minimum value in this study was 16); ApD 42; FD 32; NMD 168; PsD 21; and SD 33.

RESULTS

Forty-seven (39.2%) of the patients included were women, with a mean age of 68.5 years and a disease duration of 9 years. The average dose of levodopa was 683.5 mg/day. Seventy-four patients (61.7%) were in stage III of H&Y. Fifteen patients (12.5%) were full-time employees and 73 (60.81%) were retired. The patients' characteristics are shown in Table 1.

The main results from the Delphi study were the following: twenty-five experts responded, and when we compared the factor of importance between the first round and the second round (using the chi-square test), we did not find any significant differences. When we analyzed the answers regarding percentage values for the 10 dimensions, the V_r dispersion coefficient values were always found to be close to 0 in the first round, and they were lower in the second round (Table 2).

The homogeneity index was 0.36; the corrected-item total correlation values ranged from 0.02 to 0.7; Cronbach's α was 0.69, with minimum and maximum values of between 0.39 and 0.63; and the SEM was 4.23 (55.1%).

Through integrating the LEI, the distribution of the data was revealed to be normal (Table 3). We found that the PsD presented a floor effect of 39.16%. All other dimensions had values within the requirements (Table 4).

When we analyzed the convergent validity of the total LEI and its 10 dimensions, we found that the total LEI reached values of 0.66, compared with the PIMS; 0.74, compared with the CISI-PD; and 0.83, compared with the MD. Furthermore, there were values of -0.01 and -0.04 in relation to the DD and the PsD, respectively, with regard to the number of years of illness (Table 5).

In investigating the validity, we found that except for the PsD, all other dimensions and the total were significantly different.

DISCUSSION

From the results regarding the Delphi consensus, it can be seen that all the experts gave a similar level of importance to each of the dimensions, so there were no variations between the first and second round (chi-square test, Table 2). In weighting the level of importance of each dimension, the V_r presented adequate values, of close to 0. Therefore, the participating experts assigned very

Table 1. Description of the sample (n=120).

	Median	Mean±SD	IQR	S	K
Number of years of schooling	7	9.6±5.2	8	0.5	-0.9
Number of years of disease	8	9±5.6	7	1.4	3.3
Number of years with L-Dopa	6	7.5±5.3	6.3	1.3	2.7
Dose (mg/day) of L-Dopa	750	683.5±225.5	250	-0.1	0.5
PIMS	21	19.9±7	10	-0.5	-0.1
CISI 1	3	3.3±0.9	1	0.05	-0.02
CISI 2	3	3.3±0.9	1	0.1	0.1
CISI 3	2	1.8±1.6	6	0.3	-1.1
CISI 4	2	2.1±1.2	2	-0.05	-0.9
Total CISI	10	10.1±4.1	6	0.3	-0.3

SD: standard deviation; IQR: interquartile range; S: skewness; K: kurtosis; PIMS: Parkinson's Impact Scale; CISI: Clinical Impression of Severity Index for Parkinson's disease.

Table 2. Assignment of values and importance factor by experts.

	First round	Second round	Dispersion coefficient v_r		Importance factor		P-value ≤ comparison of the importance factor between rounds (chi-square)	Maximum final value
			First round	Second round	First round	Second round		
Age dimension	7.1	10.1	0.2	0.2	1.0	1.0	1.0	10.2
Motor dimension	32.1	30.3	0.3	0.2	1.2	1.2	0.4	34.8
Depression dimension	8.5	11.6	0.1	0.1	1.0	1.0	0.9	11.2
Anxiety dimension	4.5	7.1	0.2	0.2	0.8	0.8	0.9	6.1
Cognition dimension	5.9	9.7	0.3	0.1	1.0	1.0	0.9	9.6
Apathy dimension	5.5	6.0	0.5	0.2	0.9	0.9	0.9	5.3
Fatigue dimension	5.5	5.0	0.2	0.2	0.8	0.8	0.9	4.2
Nonmotor dimension	10.9	6.8	0.2	0.2	0.9	0.9	0.9	6.5
Psychosis dimension	9.7	5.8	0.3	0.3	0.9	0.9	0.9	5.3
Sleep dimension	9.7	7.1	0.2	0.1	1.0	1.0	0.8	6.8

The score from the 2nd round was multiplied by the factor, which gave a total of 105.6; this amount was then made equal to 100, to obtain the final value by means of the simple rule of three (e.g. motor is 30.3 x 1.2=36.36; 36.36 is to 105.6 proportionally the same as 34.8 is to 100).

similar weights to each of the dimensions. The V_r of the second round improved, thus resulting in a higher consensus being reached (Table 2). In summary, the experts considered that the ten dimensions included in the LEI were significant and assigned very closely matched levels of importance to them.

Table 3. Description of the variables that made up the linear evaluation index.

	Average crude scores±SD	Median	Mean±SD	IQR	S	K
Age dimension	68.6±11	7.1	6.9±1.1	1.5	-0.5	0.1
Motor dimension	28.1±10.3	12.1	13±4.8	6.1	0.5	0.3
Depression dimension	5.4±2.7	2.7	2.8±1.4	2.1	0.4	-0.2
Anxiety dimension	6.4±3.6	1.7	1.8±1	1.4	0.1	-0.8
Cognition dimension	63.3±18.9	4.7	4.5±1.3	2.3	0.2	-0.6
Apathy dimension	12.5±8.9	1.5	1.5±1.1	2	0.1	-1
Fatigue dimension	9.6±6.6	1.2	1.2±0.8	1.3	0.6	0.2
Nonmotor dimension	31.6±18.7	1.1	1.2±0.7	0.8	1.4	3.7
Psychosis dimension	1.5±1.6	0.3	0.3±0.4	0.8	1.4	1.9
Sleep dimension	7.6±4.6	1.4	1.5±0.9	1.5	0.3	-0.7
Total		34.6	35.2±7.6	10.2	0.2	-0.2

SD: standard deviation; IQR: interquartile range; S: skewness; K: kurtosis.

Table 4. Metric properties of the variables that made up the linear evaluation index (LEI).

	Median	Mean	Mean-median difference	10% of total	Theoretical maximum	Floor effect	Ceiling effect
Age dimension	7.1	6.9	0.2	0.10	10.2	0.83	0.83
Motor dimension	12.1	13	0.9	3.48	34.8	0.83	0.83
Depression dimension	2.7	2.8	0.1	1.12	11.2	0.83	3.33
Anxiety dimension	1.7	1.8	0.1	0.61	6.1	4.16	1.66
Cognition dimension	4.7	4.5	0.2	0.96	9.6	0.83	0.83
Apathy dimension	1.5	1.5	0	0.53	5.3	8.33	0.83
Fatigue dimension	1.2	1.2	0	0.42	4.2	8.33	0.83
Nonmotor dimension	1.1	1.2	0.1	0.65	6.5	1.66	0.83
Psychosis dimension	0.3	0.3	0	0.53	5.3	39.16	1.66
Sleep dimension	1.4	1.5	0.1	0.68	6.8	4.16	0.83
Total	34.6	35.2	0.6	10	100	0.83	0.83

Table 5. Convergent validity (Spearman's correlation coefficient *rho*S).

	PIMS	CISI1	CISI2	CISI3	CISI4	Total CISI	Number of years of schooling	Number of years of disease	Number of years with L-Dopa	Dose (mg/day) L-Dopa	S&E
Age dimension	0.08	0.21	0.25	-0.09	0.42	0.21	-0.20	0.13	0.17	0.40	-0.24
Motor dimension	0.56	0.76	0.72	0.71	0.50	0.83	-0.19	0.52	0.59	0.50	-0.37
Depression dimension	0.53	0.30	0.40	0.23	0.30	0.37	-0.31	-0.01	0.06	0.16	-0.43
Anxiety dimension	0.49	0.35	0.39	0.21	0.24	0.35	-0.27	-0.04	0.05	0.04	-0.42
Cognition dimension	-0.41	-0.45	-0.49	-0.26	-0.82	-0.60	0.59	-0.19	-0.25	-0.39	0.57
Apathy dimension	0.41	0.40	0.51	0.21	0.68	0.53	-0.47	0.17	0.26	0.36	-0.6
Fatigue dimension	0.45	0.43	0.47	0.18	0.58	0.36	-0.32	0.09	0.19	0.24	-0.56
Nonmotor dimension	0.48	0.31	0.38	0.22	0.31	0.48	-0.12	0.15	0.22	0.33	-0.45
Psychosis dimension	0.25	0.23	0.25	0.09	0.23	0.22	-0.13	-0.04	0.05	0.08	-0.29
Sleep dimension	0.33	0.32	033	0.13	0.37	0.35	-0.20	0.26	0.32	0.36	-0.33
Total	0.66	0.69	0.73	0.52	0.52	0.74	-0.26	0.37	0.46	0.46	-0.8

PIMS: Parkinson's Impact Scale; CISI: Clinical Impression of Severity Index for Parkinson's disease.

The dimension that was given the most weight in the LEI by the experts was that of the MD (34.8%), and the AD was next (10.2%). The remaining percentages (totaling 55%) corresponded to dimensions that were considered to be nonmotor. Thus, in this study, there was full incorporation of nonmotor dimensions, with the impact that they have on patients' ability to function and quality of life[30].

The quality of the data was adequate, such that 100% of the data collected could be computed. The demographic data describing the sample had characteristics of normality: minimal difference between the median and average, and values for asymmetry and kurtosis coefficients that were within the limit established (-1 to 1) for most of the variables[25,26] (Table 1).

Regarding the dimensions that make up the LEI, their descriptions revealed that both the difference between the median and average, and the coefficients of asymmetry and kurtosis were within acceptable values, except for the kurtosis of the NMD and PsD, with values of 3.7 and 1.9, respectively (Table 3).

In analyzing the viability and acceptability of the scale, we found that the PsD contradicted the norm that the floor and ceiling effects would need to be less than 15%, such that a floor effect of 39.1% was reached. Our research used the same evaluation tool as used by Visser et al.[18]; they found that 78.7% of their subjects did not have problems or had only slight presence of psychosis (Table 4).

The homogeneity index reached a value of 0.36; the standard was ≥0.30; and the corrected-item total correlation values were adequate.

Although the alpha value obtained was 0.69, i.e. it did not reach the desired threshold of 0.7, two points should be considered. First, the alpha value is highly influenced by the number of items, as can be seen in its formula (the LEI only has 10 items) (Equation 2).

$$\alpha C = \frac{N * R}{([N-1] * R + 1)} \quad (2)$$

Where: R is the mean of all the correlations and N is the number of items on the scale or questionnaire.

Secondly, as pointed out by Streiner[31], the values initially required for alpha were between 0.5 and 0.6. We consider that although the theoretical target value of 0.7 was missed by one hundredth, the internal consistency of the data was good.

The value for the SEM needs to be 50% of the standard deviation (StD), for which accuracy above 75% is proposed[32]. We calculated a value of 4.2, which was equivalent to 55.1% of the StD.

The convergent validity of the LEI (sum total) showed a strong correlation, thus: S&E escalation (*rho*S -0.8); total CISI-PD (*rho*S 0.74) and total PIMS (*rho*S 0.66) (Table 5, Figure 1).

Through using the same analysis for each dimension, we compared the results with those for quality of life, which was evaluated using PIMS; with the total CISI-PD; and against the S&E scale. We found that the AD had a weak correlation: a low correlation with PIMS (*rho*S 0.08), which was similar to what had previously been reported[33].

The MD (motor dimension) had moderate to strong correlations with the total CISI-PD (*rho*S 0.83). The DD (depression dimension) had moderate correlations, except for a very low one with the number of years of illness (*rho*S -0.01). The latter, we believe, may have been because depression and anxiety can precede the onset of Parkinson's disease. Due to high prevalence, there is one report of 52.1%, although the sample in that study was a set of PD patients who underwent DBS[34]. The AxD (anxiety dimension) had correlations similar to those for depression, and a weak correlation with the number of years of illness (*rho*S -0.04). In the same study referred to above, it was also found that anxiety could precede PD. In that sample, anxiety had a prevalence of 55.5%.

The variable of the number of years of disease generally had weak correlations with the rest of the dimensions, except with MD (*rho*S 0.52). This may have been because, in our cohort, the patients had rather few years of disease (9±5.6 years). It has been shown in the literature that the greater the number of years of illness is, the greater the cognitive impediment will be[15].

The ApD had a moderate correlation with the quality of life (*rho*S0.41). This level of correlation was slightly lower than what was obtained in other studies: *rho*S 0.56[20] and *rho*S 0.51[35].

The FD had a moderate correlation value (*rho*S 0.45), compared with the PIMS, and this was lower than what was gathered in another study in which the same evaluation tools were used (*rho*S 0.67)[36].

The NMD had moderate correlations with the PIMS (*rho*S 0.48), total CISI-PD (*rho*S 0.48) and S&E scale (*rho*S -0.45). Lastly, the PsD had weak correlations with the other variables of interest. Previously, it has been reported that the

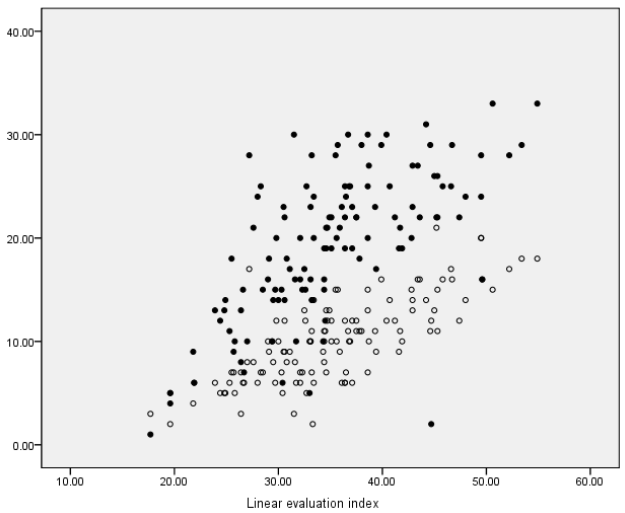

Figure 1. Scatterplot: linear evaluation index again PIMS (solid circles) and CISI-PD (empty circles).

patients' age and number of years of illness, and the presence of dementia, were similar in patients with PD, both with and without psychosis[37].

The SD reached correlations similar to what was reported in other studies, compared with the total CISI-PD (*rho*S 0.35), number of years of disease (*rho*S 0.26), number of years of levodopa (*rho*S 0.32) and dose of levodopa (*rho*S 0.36), which in the previous studies were *rho*S 0.39, 0.16, 0.18 and 0.22, respectively[38].

An expert is an informed, specialized and knowledgeable individual in the specific field. To select experts, we followed the suggestions proposed by Pawlowski et al.[39] and Robinson et al.[40].

The final panel, which was composed of a group of heterogeneous experts, granted more credibility to the process than a homogeneous panel. This is because in a heterogeneous group there is a greater range of perspectives, which results in a more comprehensive study of the matter.

The dimensions included in the LEI were those that have consistently been reported as having the greatest impact on the quality of life of patients with PD[30]. In addition to this, our study included known nonmotor symptoms, which are often not reported by patients.

One of the limitations of the present study was the relatively small size of the sample of patients, as only 120 were studied. Another limitation was that all the patients came from the same specialized medical facility for patients with Parkinson's, which is a national reference hospital.

The LEI now constitutes a tool that enables investigations during clinical consultations, without any sophisticated equipment, to provide comprehensive and objective evaluations on patients with Parkinson's disease. Therefore, it provides overall information of enormous importance for decision-making.

In conclusion, the LEI was obtained through rigorous recommended methodology. The results showed that it has adequate metric properties, despite not having achieved the ideal value for Cronbach's alpha. It is therefore a tool that has structural validity.

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ARTICLE

Melanocytic lesions of the central nervous system: a case series

Lesiones melanocíticas del sistema nervioso central: una serie de casos

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ABSTRACT

Background: Melanocytic lesions of the central nervous system (CNS) are an infrequent, broad and diverse group of entities, both benign and malignant, found in all age groups, with imaging findings ranging from well-circumscribed focal lesions to diffuse leptomeningeal involvement. On MRI, they are usually distinguished by a high signal on T1WI sequences, given the paramagnetic effect of melanin, thus making it difficult to differentiate among them. **Objective:** To describe the imaging and epidemiological characteristics of a retrospective series of CNS melanocytic lesions. **Methods:** MR images of 23 patients with CNS melanocytic lesions diagnosed between January 2012 and June 2018 were analyzed. **Results:** Most patients were female (14/23; 61%), with a median age of 47 years (range: 3 weeks to 72 years). The primary melanocytic lesions accounted for 8/19 cases (42.1%), which included neurocutaneous melanosis, meningeal melanocytomas and primary malignant melanomas. Secondary melanocytic lesions (metastatic) accounted for 10/19 cases (52.6%). There was one case of a tumor with secondary melanization, from a melanocytic neuroectodermal tumor of infancy. There were also four cases of primary ocular melanomas. The most frequent findings were the cerebral location, high T1WI signal and marked contrast-enhancement. **Conclusions:** The present review describes the wide variety of melanocytic lesions that could affect the CNS, emphasizing the MRI characteristics. Knowledge of the imaging, clinical and epidemiological characteristics of CNS melanocytic lesions is essential for their correct interpretation, given the significant overlap between lesion features and the variable prognosis.

Keywords: Central Nervous System Diseases; Melanosis; Neurocutaneous Syndromes; Magnetic Resonance Imaging; Neoplasm Metastasis.

RESUMEN

Antecedentes: Las lesiones melanocíticas del sistema nervioso central (SNC) corresponden a un grupo infrecuente, amplio y diverso de entidades, tanto benignas como malignas, encontradas en todos los grupos etarios, con hallazgos imagenológicos que van desde lesiones focales bien circunscritas hasta un compromiso leptomeníngeo difuso. A la RM se distinguen por la alta señal en la secuencia T1WI, dado el efecto paramagnético de la melanina, haciendo difícil la diferenciación entre ellas. **Objetivo:** Describir las características epidemiológicas y de de una serie retrospectiva de lesiones melanocíticas del SNC. **Métodos:** Revisión de imágenes de RM de 23 pacientes con lesiones melanocíticas del SNC diagnosticadas entre enero de 2012 y junio de 2018. **Resultados:** La mayoría de los pacientes fueron mujeres (14/23; 61%), con edades comprendidas entre las 3 semanas de vida hasta los 72 años. Las lesiones melanocíticas primarias representaron 8/19 (42,1%), incluyendo: melanosis neurocutáneas, melanocitomas meníngeos y melanomas malignos primarios. Las lesiones melanocíticas secundarias (metastásicas) representaron 10/19 casos (52,6%). Hubo un caso de tumor con melanización secundaria (tumor neuroectodermico melanocítico de la infancia). Se incluyeron cuatro casos de melanomas oculares primarios. Los hallazgos más frecuentes fueron la localización cerebral, el aumento de señal T1 y el acentuado realce con el gadolinio. **Conclusiones:** Se describe la amplia variedad de lesiones melanocíticas encontradas en el SNC, enfatizando sus características a la RM. El conocimiento de sus características imagenológicas, clínicas y epidemiológicas es fundamental para su correcta interpretación, dado la notable superposición entre las presentaciones de las lesiones y lo variable de sus pronósticos.

Palabras clave: Enfermedades del Sistema Nervioso Central; Melanosis; Síndromes Neurocutáneos; Imagen por Resonancia Magnética; Metástasis de la Neoplasia.

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INTRODUCTION

Melanocytic lesions of the central nervous system (CNS) are an infrequent and varied group of entities that range from benign to malignant lesions and from focal to diffuse leptomeningeal involvement. Their imaging appearance will depend largely on their intrinsic melanin content. They are usually classified into primary, secondary (metastases) and tumors with secondary melanization (schwannomas, medulloblastomas, some glial tumors and melanocytic neuroectodermal tumors of infancy)[1-3].

Primary melanocytic lesions are very rare, with an estimated incidence of 0.9 per 10 million people/year[2]. The latest CNS tumor classification from the World Health Organization (WHO), of 2016, includes them in the chapter "Tumors of the Non-Meningothelial Mesenchyme" and groups them into four entities: i) meningeal melanocytosis; ii) meningeal melanomatosis (often occurring in the context of dermatological syndromes, called neurocutaneous melanosis); iii) meningeal melanocytoma; and iv) meningeal melanoma[3]. However, the most frequent CNS melanocytic lesions are secondary or metastatic. Metastatic melanoma is the third most frequent source of brain metastases after lung and breast cancer[1,2].

Previous studies are scarce and generally limited to reports and case series, thus making diagnostic and management standardization difficult for these patients[4].

The purpose of our study was to review the epidemiological characteristics and MRI features of CNS melanocytic lesions, through a retrospective study on a case series.

METHODS

We conducted a descriptive retrospective study on patients with melanocytic lesions of the CNS who were identified through searching the imaging databases at our institution covering the period from January 2012 to June 2018. As this was a retrospective study, ethics committee approval and informed consent were waived.

The search was carried out among MRI reports, and those in which it was concluded that some type of CNS melanocytic lesion was present were selected. The search terms used were: "melanocytosis", "melanocytoma, "melanoma", "melanomatosis", "melanocytic", "melanocytic lesions", "melanosis" and "melanization". Subsequently, clinical and pathological data were collected when available.

Although primary ocular melanomas are not considered in the usual classifications of CNS melanocytic lesions, they were included here, given their relative high frequency in adults, with prognostic importance and distinctive imaging characteristics[5].

The MRI studies that were searched here had been performed in 3T equipment (Magnetom Skyra, Siemens, Medical Systems, Erlanger, Germany) and in 1.5T equipment (Intera, Philips Medical Systems, Best, Netherlands). All MRI protocols included the following sequences: conventional T1/T2-weighted imaging (T1/T2WI); susceptibility-weighted (T2*/SWI); diffusion-weighted (DWI/ADC maps) and contrast-enhanced T1 (T1WI-Gd). The information on all available MRI studies was collected from the radiological reports and biopsies were interpreted by certified neuropathologists (C.T.G. and S.C.B).

The features studied were the location and imaging aspects of the lesions. The imaging appearance was analyzed in the T1WI, T2WI, T1WI-Gd and DWI/ADC sequences. Analyses on gradient (GRE) or magnetic susceptibility (SWI) sequences were excluded, given the different magnets used and the difficulty in differentiating imaging between melanin and methemoglobin, given their similar paramagnetic effects[1,6].

Hyperintense lesions in T1WI were considered to be present when they presented higher signal intensity than normal brain cortex in some component of the lesion. Similarly, in T2WI sequences, the lesions were considered to be hyperintense, isointense or hypointense, according to their predominant signal, in relation to the signal intensity of the cortex. Regarding T1WI-Gd sequences, contrast enhancement was characterized as present ("+") or absent ("-") and according to its distribution, as focal, meningeal or mixed. Similarly, restricted diffusion was considered to be present when the ratio of ADC values was lower than that of the pontine white matter, in the solid component of the lesion.

RESULTS

A total of 32 patients were found in our report database. Nine patients were excluded because no preoperative MRI was available. Thus, 23 patients were included for the analysis: 14 females and 9 males, with a median age of 47 years (range: 3 weeks to 72 years). There were 18 adults and 5 pediatric patients. In 19 patients, the tumors were described as a CNS melanocytic lesion and in four as a primary ocular melanoma. The compartmental location of the lesions is described in Table 1.

Table 1. Compartmental location of central nervous system melanocytic lesions.

CNS location	Compartment
Brain (17/19; 89.4%)	Supratentorial only (8/19; 42.1%) Parenchymal-meningeal (7/19; 36.8%) Intraventricular (1/19; 5.2%)
	Infratentorial only (4/19; 21%)
Spinal (2/19; 10.5%) (one vertebral body T9; one intramedullary T2)	Both supra+infratentorial (5/19; 26.3%)
Ocular (4)	

CNS: central nervous system.

Primary melanocytic lesions accounted for 8/19 cases (42.1%): 4 pediatric and 4 adult cases, with a median age of 43 years (range: 3 weeks to 67 years). Secondary melanocytic lesions accounted for 10/19 cases (52.6%), with a median age of 51 years (range: 34–72 years). The only case of a tumor with secondary melanization had an age at diagnosis of 2 months.

The primary ocular melanomas comprised 4 cases, with ages ranging from 41 to 64 years, and a median of 42 years. The specific diagnoses, availability of histological confirmation, ages and imaging characteristics of the primary and secondary melanocytic lesions and primary ocular melanomas are described in Tables 2, 3 and 4, respectively.

Table 2. Distribution of primary melanocytic lesions and their imaging characteristics.

No.	Age	Sex	Diagnosis	Biopsy	Location	T1 signal	T2 signal	T1Gd	Restricted diffusion
1	3 weeks	F	Neurocutaneous melanosis	(-)	Supra- and infratentorial (meningeal+parenchymatous)	Hyper	Hypo	+;mixed*	(-)
2	2 years	M	Neurocutaneous melanosis	(-)	Supra- and infratentorial (meningeal)	Hyper	Iso	+; Meningeal	(-)
3	3 months	M	Neurocutaneous melanosis	(-)	Supra- and infratentorial (meningeal)	Hyper	Iso	+; Meningeal	(-)
4	5 months	M	Neurocutaneous melanosis	(-)	Supra- and infratentorial (meningeal+parenchymatous)	Hyper	Hypo	+; mixed	(-)
5	67 years	M	Melanocytoma	(-)	Spinal (dorsal cord)	Hyper	Hyper	+; focal	(-)
6	43 years	M	Melanocytoma	(-)	Infratentorial	Hyper	Hypo	+; focal	(-)
7	46 years	F	Primary malignant melanoma	(+)	Intraventricular	Hyper	Hypo	+; focal	(+)
8	41 years	M	Primary malignant melanoma (amelanocytic)	(+)	Infratentorial	Hypo	Iso	+; focal	(-)

M: masculine; F: feminine; (-): absent; (+): present; Hyper: hyperintensity; Hypo: hypointensity; Iso: isointensity; *mixed: both meningeal and focal enhancement.

Table 3. Distribution of secondary melanocytic lesions and their imaging characteristics.

No.	Age(*)	Sex	Diagnosis	Biopsy	Location	No. of lesions	T1 signal	T2 signal	T1Gd	Restricted diffusion
1	48	F	MTT melanoma-amelanocytic	(+)	Supratentorial	2	Hypo	Hypo/ iso	+; focal	(-)
2	72	M	MTT melanoma	(+)	Supratentorial	2	Hyper	Hypo	+; focal	(-)
3	50	F	MTT melanoma	(+)	Supra- and infratentorial	6	Hyper	Hypo	+; focal	(-)
4	47	F	MTT melanoma	(+)	Supratentorial	2	Hyper	Iso	+; focal	(+)
5	43	M	MTT melanoma	(+)	Supratentorial	1	Hyper	Hypo	+; focal	(-)
6	52	F	MTT melanoma	(+)	Infratentorial	1	Hyper	Hypo	+; focal	(-)
7	57	F	MTT melanoma	(-)	Supratentorial	1	Hyper	Hypo	+; focal	(-)
8	67	F	MTT melanoma	(-)	Supratentorial	1	Hyper	Hypo	+; focal	(-)
9	56	F	MTT melanoma	(-)	Infratentorial	2	Hyper	Hypo	+; focal	(-)
10	34	F	MTT melanoma	(+)	Supratentorial-spinal	2	Hyper	Hypo	+; focal	(-)

M: masculine; F: feminine; (-):absent; (+): present; Hyper: hyperintensity; Hypo: hypointensity; Iso: isointensity; (*): in years; MTT: metastatic.

Table 4. Distribution of primary ocular melanomas and their imaging characteristics.

No.	Age (*)	Sex	Diagnosis	Biopsy	Location	T1 signal	T2 signal	T1Gd	Restricted diffusion
1	64	F	Ocular melanoma	(-)	Left orbit — posterosuperior wall	Hyper	Hypo	+; focal	(+)
2	41	M	Ocular melanoma	(-)	Left orbit — medial wall	Hyper	Hypo /iso	(-)	(-)
3	41	F	Amelanocytic ocular melanoma	(-)	Left orbit — posterosuperior wall	Iso	Hypo /iso	+; focal	(+)
4	43	F	Ocular melanoma	(-)	Left orbit — posterosuperior wall	Hyper	Hyper	+; focal	(-)

M: masculine; F: feminine; (-): absent; (+): present; Hyper: hyperintensity; Hypo: hypointensity; Iso: isointensity; (*): in years.

Neurocutaneous melanosis accounted for 50% (4/8) of all the primary melanocytic lesions (Figure 1), and most of them occurred in infants younger than 6 months old. Lesions were located both supra and infratentorially, predominantly in the anterior temporal lobes and brainstem. Three of the four cases had concomitant skin nevi. Histological confirmation was not available in this group. The only case without skin lesions evolved with aggressive clinical and imaging behavior (thick and irregular leptomeningeal enhancement and signs of perivascular invasion)[1,2]. All of these cases were hyperintense on T1WI and showed diffuse leptomeningeal nodular enhancement. There was no restricted diffusion.

There were two cases of primary meningeal melanocytomas (Figure 2), both males, with lesions in the dorsal cord and at the cervicomedullary junction. Both were hyperintense on T1WI. In T2WI they presented heterogeneous signals, with hyperintense predominance in the former and hypointense in the latter. Histological confirmation was not carried out in either of these cases.

There were two cases of primary malignant melanomas (Figure 3A): one intraventricular and the other infratentorial (cervicomedullary junction), aged 46 and 41 years, respectively. In both cases, there was histological confirmation and exclusion of primary melanoma outside the CNS.

The secondary melanocytic lesion group (metastatic melanomas) showed several lesions in most of the cases, ranging from two to six lesions. Brain location predominated (9/10; 90%), while there was a single case with spinal (vertebral) involvement. In 60% there was an exclusive supratentorial location and in 20% an exclusive infratentorial location. One case was both supra and infratentorial and one was both supratentorial and vertebral. Most of the cases presented the classic melanocytic pattern of high T1WI signal intensity, while in a single one case a supratentorial amelanocytic lesion was observed (Figure 3B). Focal contrast enhancement was observed in all cases and restricted diffusion was demonstrated in only one case.

In the group of "tumors with secondary melanization", a single case of a two-month-old male infant with a mass over the left mastoid fontanelle was found. A biopsy on this mass showed it to be a melanocytic neuroectodermal tumor (Figure 4).

Primary ocular melanomas (Figure 5) were located in the left ocular globe, and mostly in the posterosuperior wall. There was retinal detachment in all cases. The imaging findings were mainly high T1WI signal intensity and focal contrast enhancement, with a single case of amelanocytic melanoma. In two cases restricted diffusion was observed.

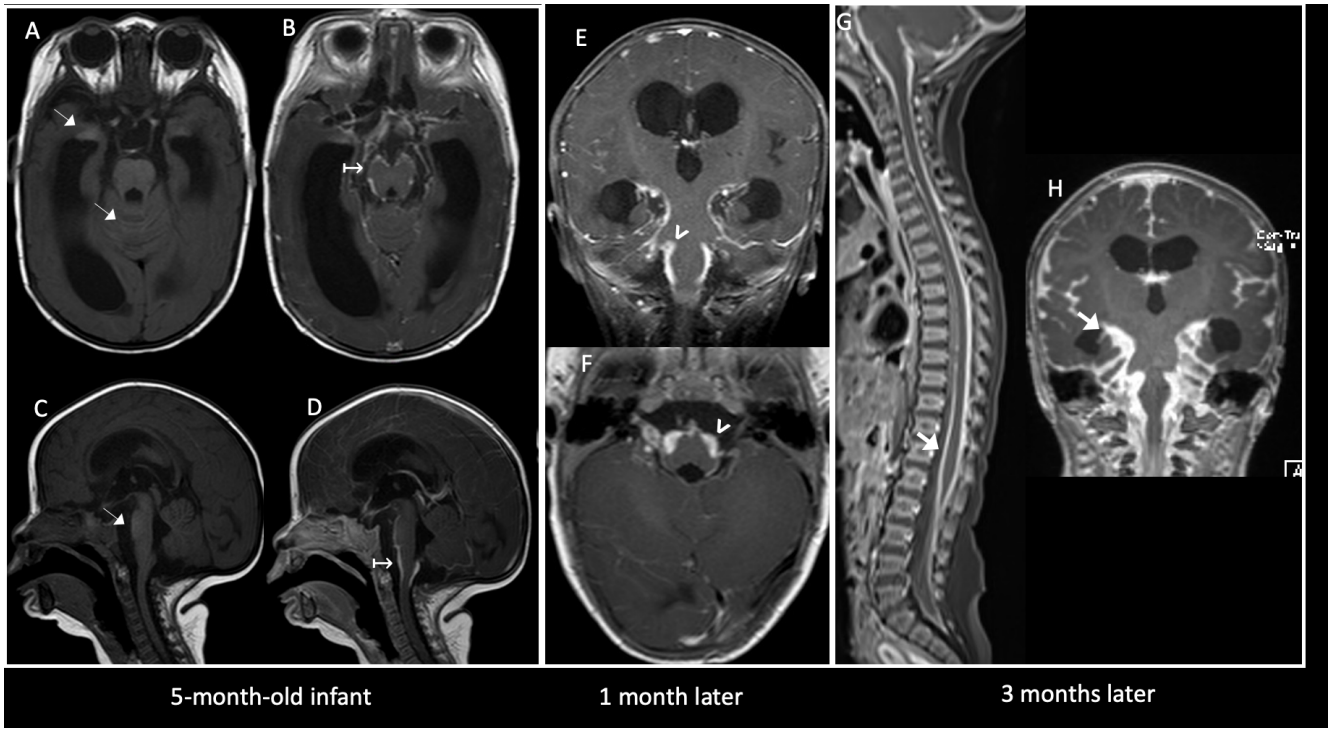

Figure 1. Neurocutaneous melanosis. A 5-month-old infant, without pigmented skin lesions, who was referred due to acute hydrocephalus. Axial (A, B) and sagittal (C, D) pre and post-contrast T1WI demonstrated subtle foci of spontaneous hypersignal in the temporal uncus, brainstem and cerebellar vermis (thin white arrows), with extensive leptomeningeal enhancement (↦). In a control one month later, progression of leptomeningeal enhancement was observed, which was predominantly infratentorial (arrowheads in E, F). A control three months later (G, H) showed aggressive spinal and encephalic progression of leptomeningeal dissemination (thick white arrows).

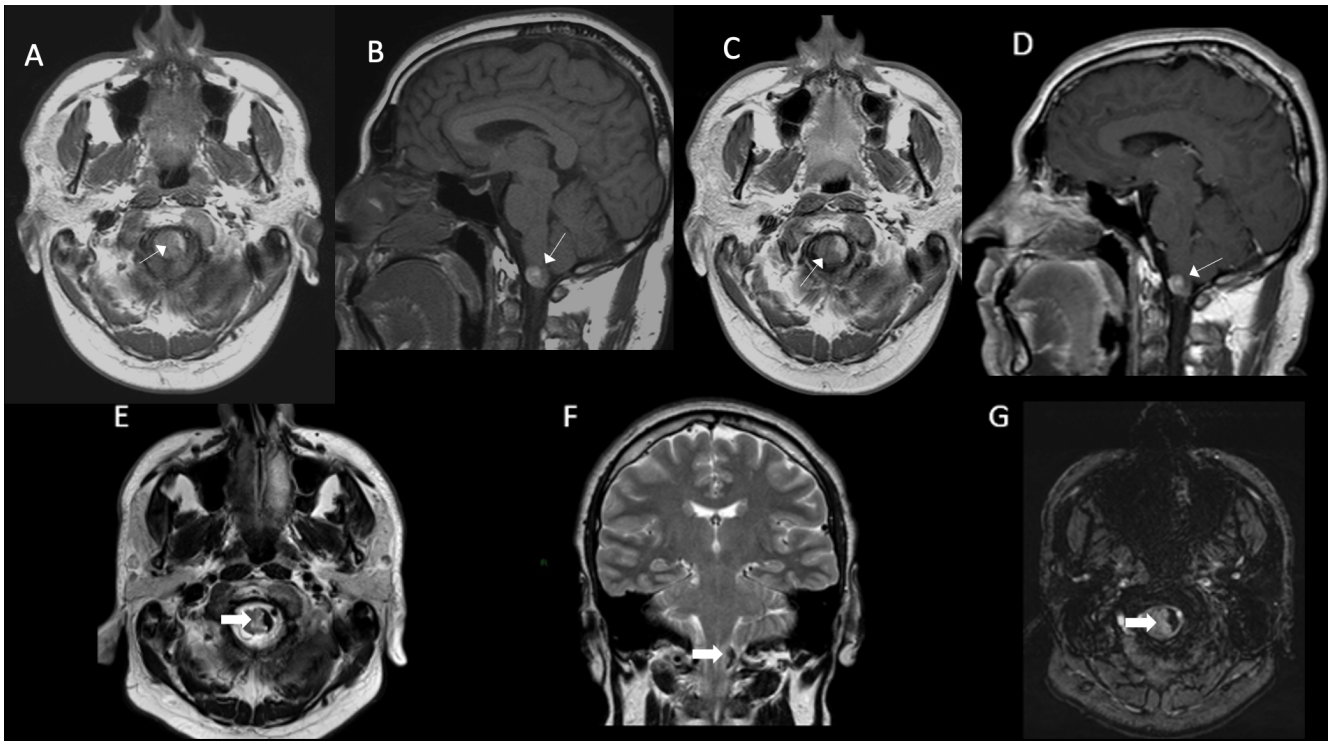

Figure 2. Melanocytoma. A 43-year-old man was referred for assessment of a cervicomedullary lesion. Axial and sagittal T1WI pre-contrast (A, B) and post-contrast (C, D) showed a spontaneously hyperintense lesion in the left lateral aspect of the cervicomedullary junction, abutting the pial surface (thin white arrows), with subtle heterogeneous enhancement (↦). T2WI axial and sagittal (E, F) showed marked hypointensity with a slight susceptibility artifact in the SWI sequence (G) (thick white arrows).

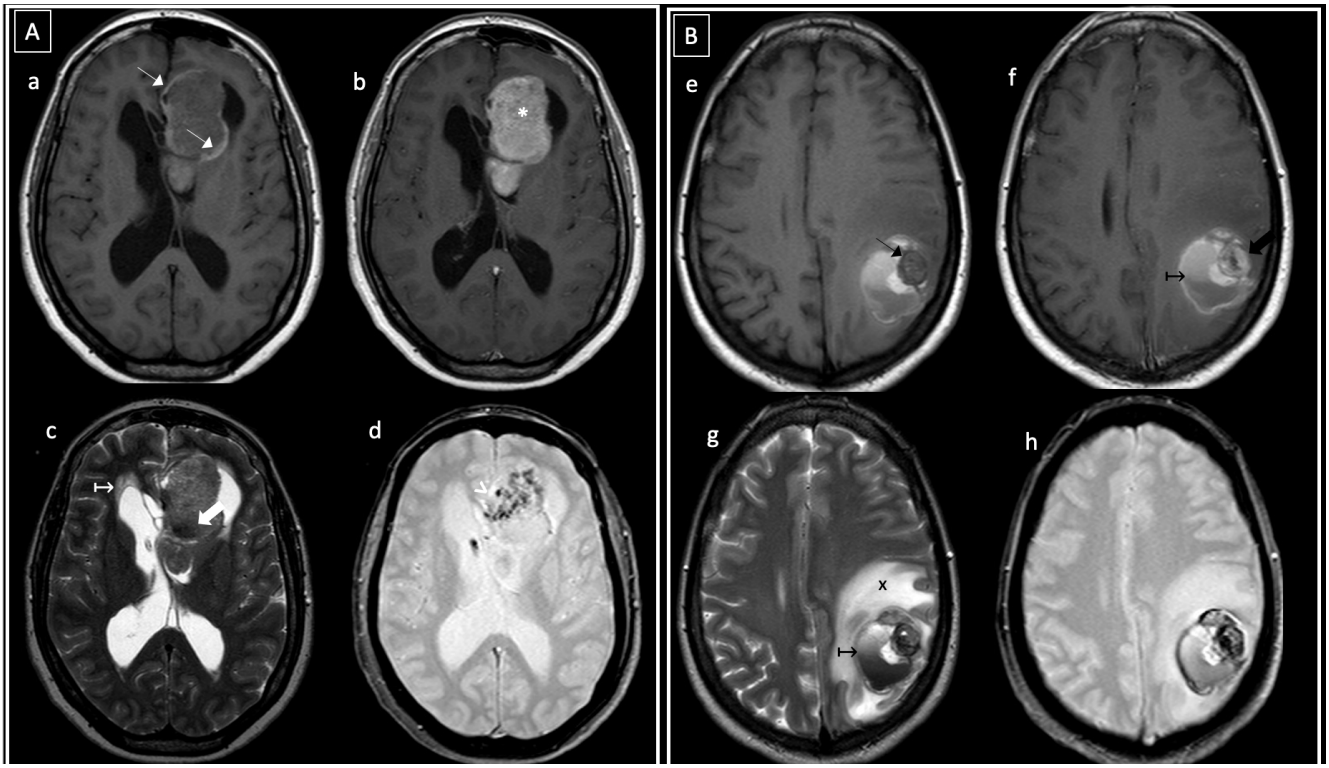

Figure 3. Intraventricular primary melanoma (A) and amelanocytic metastatic melanoma (B). In (A), a 46-year-old woman presented with headache. Axial T1WI pre and post-Gd (a, b) showed a heterogeneous left frontal intraventricular mass, with peripheral high signal areas (thin white arrows) and marked contrast enhancement (* in b). T2WI and GRE (c, d) showed hypointense foci (thick white arrows) and intratumoral magnetic susceptibility artifacts (white arrowhead). No restricted diffusion was observed (not shown). Hydrocephalus was present (white ↦ in c). In (B), a 48-year-old woman with a history of cutaneous melanoma presented with seizures. Axial MRI images (e-h) showed a hypointense-T1WI left parietal intra-axial peripheral nodule (thin black arrow in e) with heterogeneous contrast enhancement (thick black arrow in f). The lesion was surrounded by hemorrhagic products and hematocrit level (black ↦). Extensive vasogenic edema was observed (black x in g).

DISCUSSION

Melanocytes are the cells that produce and store melanin. They originate from the neural crest and, between the 8th and 10th weeks of embryonic development, they migrate to the skin, mucosa, uveal ocular layer, inner ear and CNS. In the latter, they are located in the leptomeninges, where they are preferentially distributed in the convexity of the skull base, ventral brainstem and cervical cord[2,7].

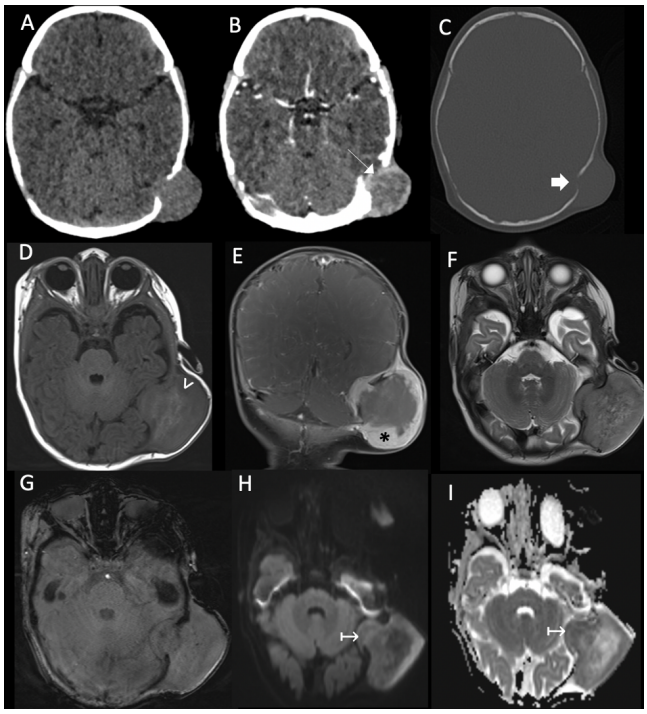

Figure 4. Melanocytic neuroectodermal tumor of infancy, in a two-month-old infant who presented with a mass over the left mastoid fontanelle. Axial pre and post contrast CT scans (A–C) showed an apparently extracranial mass at the level of the left mastoid fontanelle, with peripheral enhancement (thin white arrow in B) and osteolytic and remodeling bone changes (thick white arrow). MRI images (D–I) demonstrated a predominantly extracranial heterogeneous mass with intra and extracranial components, hyperintense areas on T1WI (white arrowhead in D) and avid peripheral contrast enhancement (* in coronal image in E). No magnetic susceptibility artifacts were observed on SWI (G). In DWI and ADC (H and I), some deep areas of restricted diffusion were presented (↦).

Melanin has a paramagnetic effect, which induces shortening of the T1 and T2 relaxation times on MRI. This gives rise to its characteristic high signal intensity in T1WI, with corresponding hypointensity in T2WI[2]. It is important to highlight that lesions with a melanin content greater than 10% will present the classic "melanocytic" pattern of T1WI hyperintensity/T2WI hypointensity signal on MRI. Lesions that appear "amelanocytic" have in fact been shown to contain some degree of melanin, in histopathological evaluations[1].

In our retrospective series, a total 23 cases were identified, with predominance of the female sex, in contrast to the slight male predominance previously reported[1,5,7]. There was a wide age range at presentation (3 weeks to 72 years), with some overlap between the different diagnoses, similar to what had previously been reported[6,8].

The location of the melanocytic lesions was consistent with what had been reported[1,2], with clear predominance of the brain over the spine. Most of these lesions were supratentorial (parenchymal-meningeal and intraventricular), followed by a combination of both supra and infratentorial and lastly, infratentorial involvement alone. We decided to include the intraocular melanomas, given their incidence, prognosis and distinctive imaging features, which allow them to be differentiated from other entities.

Regarding the imaging characteristics, the classical melanocytic pattern of T1WI hyperintensity/T2WI hypointensity signal predominated. In three cases (metastatic melanoma, ocular melanoma and primary malignant melanoma), an "amelanocytic" pattern was observed, with intermediate/low T1WI signals. Almost all the cases presented contrast enhancement, either focal, leptomeningeal or mixed, with the exception of one case of ocular melanoma with a highly melanocytic pattern. These characteristics were the most constant imaging markers described[1,2].

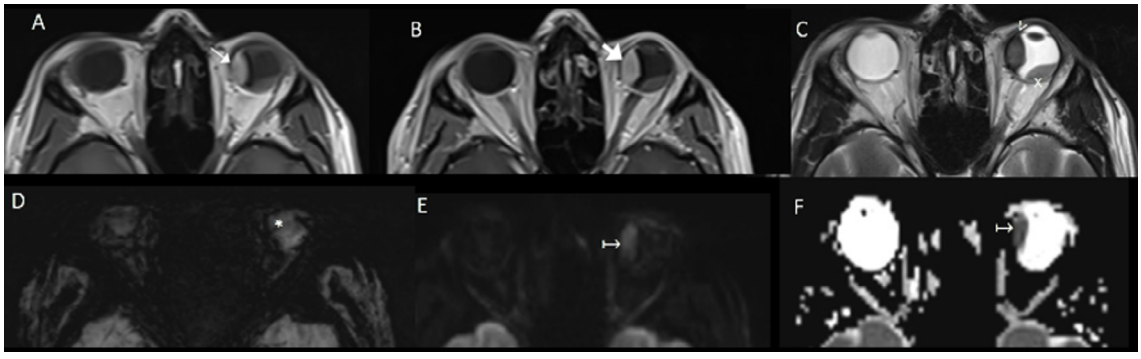

Figure 5. Left choroidal ocular melanoma, in a 41-year-old male patient with a history of progressive blurred vision in the left eye. Axial MRI images (A–F) showed a left intraocular fusiform lesion in the choroidal retinal nasal wall, with spontaneously hyperintense signal on T1WI (thin white arrow in A), with no apparent contrast enhancement (thick white arrow in B). There was low signal intensity on T2WI (white arrowhead in C), a susceptibility artifact on SWI sequence (* in D) and restricted diffusion (↦ in E and F). The melanoma was also associated with retinal detachment (x in C).

Primary malignant melanomas of the CNS are very infrequent, with estimated annual incidences of 0.7 per 10 million inhabitants[9]. They occur in adults, with a mean age at presentation of 50 years, and are located in the basal leptomeninges, around the brainstem and upper cervical cord. Their imaging appearance will depend on the melanin and methemoglobin content from prior bleeding episodes[1,2,7,9,10]. Their diagnosis is based on the absence of any other melanoma, both outside the CNS and in other CNS sites[1]. The two cases in our series consisted of a cervicomedullary junction "amelanocytic" melanoma and an intraventricular "melanocytic" melanoma. The latter has been described as an atypical site and would be explained by arrested migration of melanocytic cells, through which they are deposited within the pia mater. From their location within the pia mater, melanocytes may be incorporated into the choroid plexus[1].

Meningeal melanocytomas, previously called melanocytic meningiomas, are very rare benign lesions, with an estimated annual incidence of one case per million inhabitants, with isolated reports of malignant transformation. They also occur predominantly in the fifth decade of life and they tend to be located in the posterior fossa, Meckel's cavum and cervicothoracic spinal canal[1,11]. They are well-defined solitary lesions, with close leptomeningeal contact, variable hyperintense T1WI/hypointense T2WI signal and avid homogeneous enhancement[12-14]. Our two cases had peripheral cervicomedullary junction and dorsal medullary locations, concordant with what had previously been reported.

Neurocutaneous melanosis is a rare type of non-inherited phacomatosis, characterized by congenital cutaneous nevi and leptomeningeal melanocytic proliferation. Around 100 cases have been reported in the literature[1,15]. They were believed to be the result of congenital dysplasia of the melanocyte precursor cells in the neuroectoderm, which would cause abnormal proliferation of melanocytes in the skin and leptomeninges[15,16]. There is an association with the Dandy-Walker malformation in 8 to 10% of the cases[1] and these usually debut with hydrocephalus, related to obstruction of CSF flow or impaired reabsorption secondary to meningeal involvement. Neurological manifestations derive from intracranial hypertension and generally occur before the age of two years[15]. The imaging study of choice is MRI, in which two patterns can be observed: one of diffuse enhancement of thickened leptomeninges and a second of meningeal disease with characteristic high signal intensity on T1WI, most evident in the anterior temporal lobes (as shown in Figure 1A) and amygdala region, followed by the cerebellum, protuberance, thalamus and frontobasal parenchyma[1,15]. Malignant transformation is reported in approximately 40–60% of cases, and is indicated by progressive growth, surrounding vasogenic edema or mass effect, or development of central necrosis[1,2,15,17]. In our series, we found four cases, all under two years of age and all with diffuse supra and infratentorial leptomeningeal involvement and hydrocephalus. Two of them evolved aggressively, with greater extent and severity of lesions.

Secondary melanocytic lesions (metastatic melanoma) were the most frequently found diagnosis, similar to what had previously been reported[2]. The CNS has been described as a frequent location, and is the third after lung and breast neoplasms[1]. An even higher incidence has been described in cases in which the primary site of malignant melanoma manifests between the ages of 50–59 years[18]. These lesions present a wide variety of appearances and locations. They usually debut as several lesions and the brain is the most common location followed by the cerebellum[1]. They typically appear at the peripheral gray matter-white matter junction, with miliary and subependymal distribution patterns and some rare cases have been reported in the choroid plexus and pituitary gland[19]. Imaging appearances are quite variable, ranging from the classic "melanocytic" pattern of T1WI hyperintensity/T2WI hypointensity signal, up to the "amelanocytic" pattern. Marked contrast enhancement and peripheral edema are characteristic. Variable degrees of melanin and methemoglobin are presented, and the latter is derived from the tendency to bleed. However, there is no consensus on whether the image appearance depends on one of these compounds or on both[1,19]. The majority of our cases presented several lesions (between two and six), with an exclusive brain location predominance, "melanocytic" pattern and marked contrast enhancement.

Regarding the third group of CNS melanocytic lesions, i.e. tumors with secondary melanization, we presented a single case of an infant with a melanocytic neuroectodermal tumor of infancy. These are very rare lesions that affect newborns and children under one year of age, with a certain male predominance[1,8,20]. These lesions are of unknown etiology and histogenesis, and a probable origin in neural crest cells has been proposed[1,8]. Although some authors have included them within "neoplasms that undergo melanization"[1], other authors have included them within primary melanocytic lesions[2]. They have rapid growth, with malignant transformation rates reported between 6.5 and 14.3%[8]. They are described as well-defined round or lobulated contrast-enhancing tumors, with areas of T1WI hyperintensity/T2WI hypointensity signal, mostly located in the maxillary bone (60% of cases) and skull (10.8%), especially in the region of the anterior fontanel, dura and brain[1,20]. Our only case was a two-month-old male patient, who had a palpable mass in the left parieto-occipital region, at the level of the mastoid fontanelle, with features similar to those reported in the literature.

Lastly, primary ocular melanoma is the most frequent malignant intraocular tumor in adults, with an incidence of approximately six cases per million/year[5]. It typically originates from the uveal layer of the eye (ciliary body, iris and, especially, the choroid), although a few articles have reported a conjunctival source[5,21]. It is the second location of primary melanoma after cutaneous melanoma and although the

vast majority are primary, ocular melanoma can also have metastatic origin from a distant skin lesion[22]. Its incidence increases with age, with a peak in the 7th to 8th decade of life. It may or may not be symptomatic (visual defects and photopsia). On MRI, it presents lentiform or mushroom-shaped morphology, with a broad base of choroidal implantation and protrusion to the vitreous chamber, usually associated with retinal detachment[22]. It typically presents with the classic "melanocytic" pattern of T1WI hyperintensity/T2WI hypointensity signal, although an amelanocytic pattern may exist in up to 25% of the cases. It usually presents marked solid contrast enhancement and restricted diffusion, and the latter differentiates it from retinal detachment due to other causes[22]. The imaging features of our four cases were concordant with what had been reported in the literature, i.e. choroidal location, posterosuperior wall predominance and all associated retinal detachment. Three cases presented diffuse contrast enhancement with gadolinium, two cases restricted diffusion and one case an "amelanocytic" pattern.

In conclusion, CNS melanocytic lesions are rare and can be found in all age groups. The imaging characteristics are miscellaneous, depending on each specific diagnosis, its location and the amount of melanin contained. Nevertheless, there are some MRI features that can suggest this kind of lesions, like the high signal intensity in T1WI, low signal intensity in T2WI, restricted diffusion and either nodular or leptomeningeal contrast enhancement. In many cases, the diagnostic approach will be challenging, given the low incidence and frequent overlap of patterns. When faced with a suspicious lesion, it is essential to know the wide differentials like those described here, especially the feared metastatic melanoma, given its greater frequency and poor prognosis.

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ARTICLE

Serum levels of irisin and nesfatin-1 in multiple sclerosis

Níveis séricos de irisina e nesfatin-1 na esclerose múltipla

Mustafa ALTAŞ[1], Ali Ulvi UCA[1], Turan AKDAĞ[2], Faruk Ömer ODABAŞ[3], Osman Serhat TOKGÖZ[1]

ABSTRACT

Background: Multiple sclerosis (MS) is an inflammatory and neurodegenerative autoimmune chronic neurological disease. Currently, there are no effective serum biomarkers to verify MS diagnosis, to assess disease prognosis, and evaluate response to MS treatment. **Objective:** The present study is a preliminary assessment of irisin and nesfatin-1 serum levels in patients with relapsing- remitting MS (RRMS). **Methods:** A total of 86 participants, 42 patients with RRMS diagnosis and 44 healthy controls were included in the study. The serum irisin and nesfatin-1 parameters of the patients and control group members were analyzed. **Results:** Irisin and nesfatin-1 levels of the RRMS patients were significantly lower than the controls (z: -3.82, p<0.001; z: -4.79, p<0.001, respectively) The cut-off level of irisin is 10.390 (ng/mL) (sensitivity: 84.1%, specificity: 71.4%, AUC: 0.800), and the cut-off level of nestatin-1 is 7.155 (ng/mL) (sensitivity: 68.2%, specificity: 64.3%, AUC: 0.739) in the ROC analysis. For these cut-off levels in the case-control groups, the lower irisin and nesfatin-1 levels are the independent variables for MS patients (OR 9.723, 95%CI 2.884–32.785, p<0.001; OR 3.992, 95%CI 1.336–11.928, p<0.001) respectively. **Conclusion:** The present study revealed lower irisin and nesfatin-1 levels in patients with RRMS. These findings suggest that the decreased levels of irisin and nesfatin-1 peptides may contribute to MS pathogenesis such as inflammation, oxidative stress, and apoptosis in MS, leading to demyelination, axonal damage with neuronal loss, and gliosis.

Keywords: Multiple Sclerosis; Irisin; Nesfatin-1; Inflammation; Apoptosis; Oxidative Stress.

RESUMO

Antecedentes: A esclerose múltipla (EM) é uma doença neurológica crônica autoimune inflamatória e neurodegenerativa. Atualmente, não há biomarcadores séricos eficazes para verificar o diagnóstico de EM, para avaliar o prognóstico da doença e avaliar a resposta ao tratamento de EM. **Objetivo:** O presente estudo é uma avaliação preliminar dos níveis séricos de irisina e nesfatina-1 em pacientes com EM recorrente-remitente (EMRR). **Métodos:** Um total de 86 participantes, 42 pacientes com diagnóstico de EMRR e 44 controles saudáveis, foram incluídos no estudo. Os parâmetros séricos de irisina e nesfatina-1 dos pacientes e membros do grupo controle foram analisados. **Resultados:** Os níveis de irisina e nesfatina-1 dos pacientes com EMRR foram significativamente mais baixos do que os dos controles (z: -3,82, p <0,001; z: -4,79, p <0,001, respectivamente). O nível de corte de irisina é 10,390 (ng/mL) (sensibilidade: 84,1%, especificidade: 71,4%, AUC: 0,800), e o nível de corte de nestatina-1 é 7,155 (ng/mL) (sensibilidade: 68,2%, especificidade: 64,3%, AUC: 0,739) na análise ROC. Para esses níveis de corte nos grupos de caso-controle, os níveis mais baixos de irisina e nesfatina-1 são as variáveis independentes para pacientes com EM (OR 9,723, IC95% 2,884–32,785, p <0,001; OR 3,992, IC95% 1,336–11,928, p <0,001) respectivamente. **Conclusão:** O presente estudo revelou níveis mais baixos de irisina e nesfatina-1 em pacientes com EMRR. Esses achados sugerem que os níveis diminuídos de peptídeos irisina e nesfatina-1 podem contribuir para a patogênese da EM, como inflamação, estresse oxidativo e apoptose na EM, levando à desmielinização, dano axonal com perda neuronal e gliose.

Palavras-chave: Esclerose Múltipla; Irisina; Nesfatina-1; Inflamação; Apoptose; Estresse Oxidativo.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disease defined by its neurodegenerative and autoimmune inflammatory character with multifocal inflammation sites due to autoreactive T and B-lymphocytes and macrophage infiltrations leading to demyelination, axonal damage with neuronal loss, and gliosis in both the white and the gray matter of the central nervous system (CNS)[1].

Biomarkers for the prognosis and definitive diagnosis of MS have until recently been limited with cerebrospinal fluid analyses. To our best knowledge, there are no effective serum biomarkers for the definitive diagnosis of MS, prognosis assessment, and evaluation of the patients' responses to the treatment[2]. Currently, periodic scanning of MS patients by Magnetic Resonance Imaging (MRI) is an important tool for monitoring disease activity and response to treatment[3]. However, in evaluating disease progression and determination of prognosis, this expensive, time-consuming, and semi-quantitative imaging marker has limited sensitivity[4].

Irisin has been determined as a skeletal muscle-originated myokine with increasing serum levels during exercise in order to provide the energy necessary and glucose homeostasis through the stimulation of white adipose tissue browning[5]. But new investigations have revealed that irisin acts as both an adipokine[6] and as a potential neurokine[7]. It is well documented that irisin plays a significant role in apoptosis, inflammatory, and oxidative stress[8]. In a study performed by Bosma et al.[9] in mice FNDC4 (homology with FNDC5) may have an anti-inflammatory influence on macrophages and thus could improve colitis. New studies have noted increased or decreased irisin levels in various diseases. A study conducted by Ebert et al.[10] reported that serum irisin level was lower in chronic kidney disease. Choi et al.[11] also reported that it was lower in patients with type 2 diabetes mellitus (DM). However, Ates et al.[12] demonstrated that irisin level was higher in patients with type 1 DM. Current studies have revealed reduced serum irisin levels in breast cancer cases[13], with inhibitory effect on malignant breast cancer cells[14]. However, the physiological properties and functional roles of irisin in the brain have yet to be fully explained. Irisin is determined to be involved in metabolism regulation, neuronal differentiation, and energy expenditure besides ischemia-induced neuronal injury preserving function[15]. Moreover, a recent study has shown that a low level of serum irisin was a possible biomarker in the early prediction of ischemic stroke[16]. Recent data suggest that irisin is expressed in the brain and induces brain-derived neurotrophic factor (BDNF) expression in rat hippocampus, thus increasing brain irisin levels could preserves memory and hinders cognitive destruction in an Alzheimer's disease rat model study[17].

Nesfatin-1, a potent anorexigenic peptide playing an important role in the regulation of feeding homeostasis and energy expenditure, was first defined in 2006[18,19]. It is obtained from the precursor-peptide NEFA/nucleobindin 2 (NUCB2), present not only in the CNS but also in the periphery and reaching the brain via non-saturable transmembrane diffusion[20]. Posttranslational modification of NUCB2 by prohormone convertase produces three cleavage products, i.e. nesfatin-1, nesfatin-2, and nesfatin-3[19]. Nesfatin-1 intracerebroventricular injection or intraperitoneal application to mice resulted with reduced food intake[18,21]. The recently discovered fact that nesfatin-1 expresses neuron activation in the brainstem and hypothalamus highlights the potential role of these neurons in the transfer of information received from circulating immune factors[22]. Furthermore, nesfatin-1 has also been tested as a therapeutic agent in the treatment of infectious and autoimmune diseases. There are also some reports about nesfatin-1 effects in psychiatric disorders and neurogenic diseases. In patients with major depressive disorder[23] or epilepsy[24] elevated nesfatin-1 levels and in patients with generalized anxiety disorder[25] depleted nesfatin-1 levels were determined. Interestingly, another study reported elevated nesfatin-1 levels in schizophrenia patients[26]. Current studies revealed that in traumatic rat brains nesfatin-1 has anti-inflammatory and antiapoptotic effects[27]. Nesfatin-1 has also been observed to have a significant effect on the suppression of brain damage resulting from oxidative mechanisms[28,29].

To our best knowledge, there are no studies investigating irisin and nesfatin-1 levels in MS patients. The aim of the present study is to contribute to the existing literature by assessing serum irisin and nesfatin-1 levels, both known to have similar anti-inflammatory, antioxidant and anti-apoptotic effects and to determine whether serum irisin and nesfatin-1 levels may be used as a biomarker for making MS diagnosis, and evaluating course of disease and responses to relapsing- remitting MS (RRMS) treatment.

METHODS

After the approval of the Meram Medical Faculty, Necmettin Erbakan University institutional ethics committee enumerated as 2020/2330 and dated 21st of February 2020, a written consent form was filled out by all participants who were informed in depth about the study to be conducted. The present study is conducted according to the Helsinki good clinical practice guidelines.

Participants

Between March 2020 and September 2020, MS patients admitted to the Necmettin Erbakan University, Faculty of Medicine, Neurology MS Outpatient Clinic for control purposes were considered for the present study. Out of the MS patient population, 42 consecutive RRMS patients were selected according to the inclusion criteria. The control

group consisted of 44-age and gender matched- individuals without any previous health conditions. Forty patients (95.2%) in the RRMS group were receiving disease modifying drugs including daily oral teriflunomide 14 mg intake (5 patients), subcutaneous interferon beta-1b every other day (5 patients), subcutaneous interferon beta-1a 44 mcg three times per week (10 patients), subcutaneous glatiramer acetate 40 mg three times per week (6 patients), daily oral fingolimod 0.5 mg intake (14 patients), and 2 patients (4.8%) were naïve for treatment.

Inclusion criteria for the RRMS patient group were as follows: voluntarily enrolment, age between 18 and 55 years, RRMS diagnosis as described in the 2010 revision to the McDonald Criteria for dissemination of time as well as space and currently without relapse, no reported treatment with pulsed intravenous methylprednisolone within the last 3 months, below 5.5 according Expanded Disability Status Scale (EDSS), lack of any chronic or acute medical condition other than MS as confirmed in former medical reports and clinic examinations; no use of medications including antiaggregants, anticoagulants, corticosteroids, selective serotonin re-uptake inhibitors, antipsychotics, and no report of illicit drug or substance use or addiction.

Gender, age, and clinical data of the patients as well as height and weight of the participants were recorded at the same time. Body mass index (BMI) was calculated as (w/kg)/(h/m^2).

Measurement of irisin and nesfatin-1

Blood specimens collected from each participant were centrifuged at 3000xrpm for 15 minutes within 30 minutes subsequent to blood drawal and obtained sera was kept at -80°C until assay. Irisin and nesfatin-1 serum levels were determined through enzyme linked immunosorbent assay (ELISA) technique. The serum concentrations of irisin were analyzed via Human Irisin ELISA kits (Bioassay Technology Laboratory, Shanghai, China, catalog no: E3253Hu). The sensitivity was determined as 0.095 ng/mL; standard curve range as 0,2–60 ng/mL, intra-assay as <8%, and inter-assay as <10%. Nesfatin-1 serum concentrations were analyzed using Human Nesfatin-1 ELISA kits (Bioassay Technology Laboratory, Shanghai, China, catalog no: E3063Hu). The sensitivity was determined as 0.15 ng/mL; standard curve range as 0.3–90 ng/mL, intra-assay as <8%, and inter-assay as <10%. For the assay, manufacturer's instructions were followed throughout the study. The absorbance of the specimen was measured at 450 nm by absorbance microtiter plate reader with a double-blind procedure (ELx800TM, BIO-TEK instruments, USA).

Statistical analysis

Data analysis was conducted using *Statistical Package for the Social Sciences* software (version 15.0; SPSS Inc, Chicago, IL). Mean values are presented with standard deviation (±) or median given with range. Kolmogorov Smirnov test was used to test normality. Student's *t*-tests for parametric comparisons between the patient and control groups, Mann-Whitney U test for nonparametric comparisons, and chi-square test for the comparison of categorical data. Kruskal-Wallis nonparametric test was used for more than two groups.

Receiver operating characteristic (ROC) analysis was used to define areas, Areas Under the Curve (AUC), sensitivity, and specificity, positive and negative predictive values. Binary Logistic regression analysis was conducted to determine independent predictive risk factors for MS. P<0.05 threshold level was taken to determine statistical significance.

RESULTS

86 volunteers with a mean age of 38.0±8.9 were included in the study. Table 1 present the demographic and clinical characteristics of the patients and controls. Serum irisin and nesfatin-1 levels were significantly lower in MS patients (Z score: -3.82, p<0.001; Z score: -4.79, p<0.001, respectively) (Figure 1). BMI is significantly higher in the patients group than the controls (z: -5,287, p<0.001).

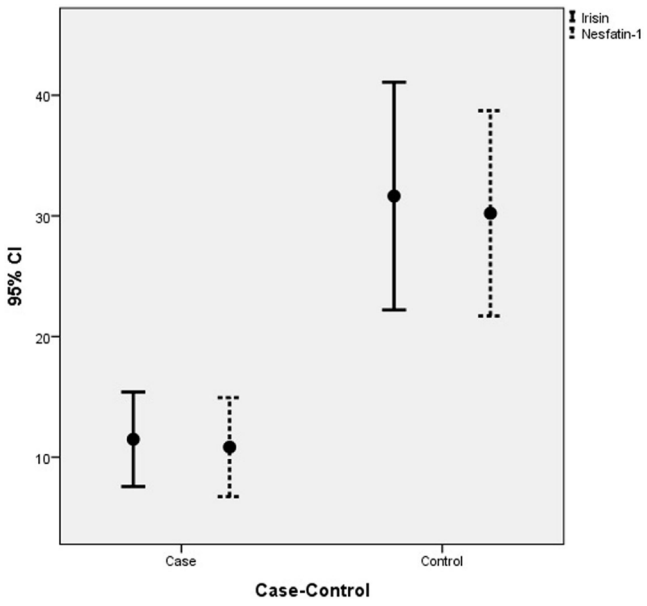
In ROC analysis of irisin (Figure 2) and nesfatin-1 (Figure 3), cut-off levels for MS were 10.390 (ng/mL) (sensitivity: 84.1%, specificity: 71.4%, PPV: 81.08%, NPV: 75.51% AUC: 0.800 (0.704–0.896), and 7.155 (ng/mL) (sensitivity: 68.2%, specificity: 64.3%, PPV: 65.85%, NPV 66.67%: AUC: 0.739 (0.636–0.842) respectively.

In the regression model, the *Odds Ratio* (OR) was 9.273 (95% confidence interval [95%CI]): 2.884–32.785, p<0.001) when the irisin <10.390 ng/mL is independent of other variables for the RRMS patients. Overall corrected percentage is 81.4% (Table 2). The OR was 3.992 (95%CI 1.336–11.928, p: 0,013) when the nesfatin-1 <7.155 ng/mL is independent of other variables for the RRMS patients. Overall corrected percentage is 80.2% (Table 2).

Table 1. The demographic and clinical characteristics of the patients and controls.

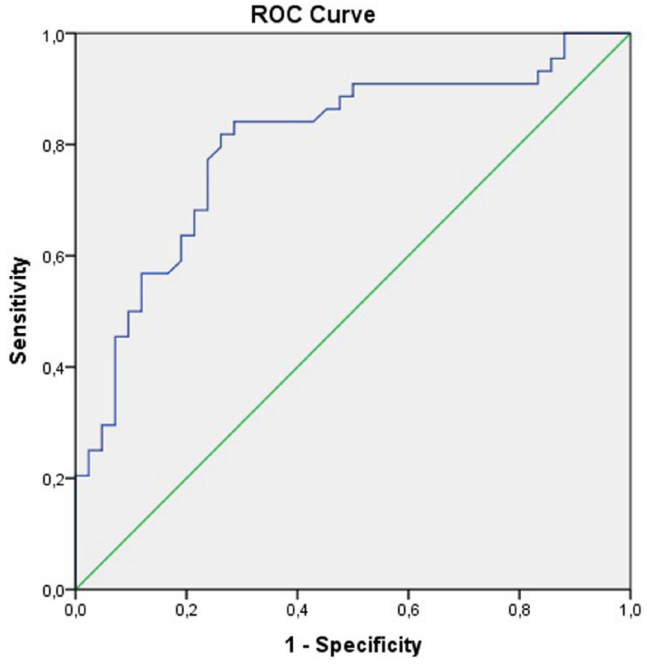
	Patients n=42	Controls n=44
Age (year) (mean/±SD)	38.12 (±8.96)	37.3 (±8.9)
Female gender (n/%)	27 (64.3%)	25 (56.8%)
BMI (kg/m^2) (median/range)	25.8 (19.11)	21.59 (10.46)
Irisin (ng/mL) (median/range)	8.21 (64.45)	14.98 (97.45)
Nesfatin-1 (ng/mL) (median/range)	5.90 (48.01)	19.65 (88.29)
EDSS (median/range)	1.5 (5.50)	
MS duration (year) (median/range)	7.0 (25.0)	
MS relapse number* (median/range)	4.0 (9.0)	

SD: standard deviation; BMI: body mass index; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis. *Number of all relapses since diagnosis.



Serum irisin and nesfatin-1 levels were significantly lower in MS patients (p<0.001).

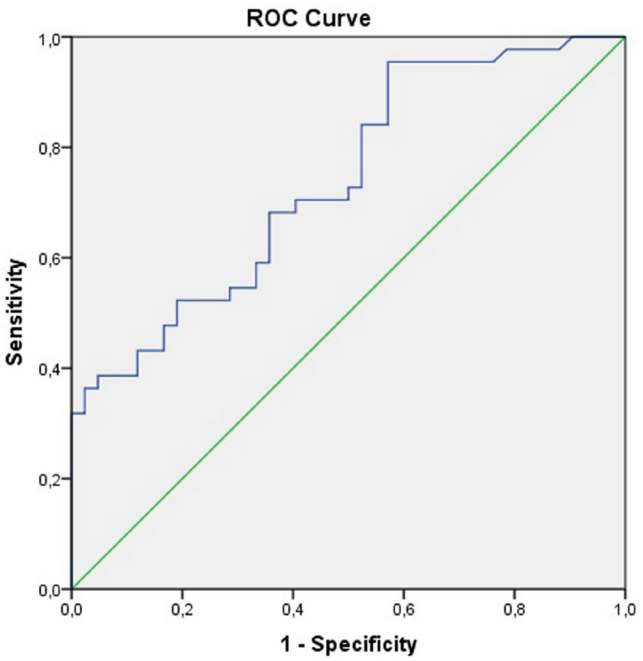
Figure 1. The mean serum irisin and nesfatin-1 levels in the case and control groups.



Cut-off level: 10.390 (ng/mL) sensitivity: 84.1%, specificity: 71.4%, AUC: 0.800. AUC: areas under the curve.

Figure 2. Receiving operating curve of irisin for the prediction of case-control.

No statistically significant correlation could be determined between serum irisin, nesfatin-1 and overall relapses number, age, BMI, EDSS, and disease duration. The comparison of the gender variable and mean irisin and nesfatin-1 serum levels revealed no statistically significant difference (p>0.05). Likewise, there isn't any significant difference between disease modifying drugs regarding to irisin and nesfatin-1 (p>0.05).



Cut-off level: 7.155 (ng/mL) sensitivity: 68.2%, specificity: 64.3%, AUC: 0.739. AUC: areas under the curve.

Figure 3. Receiving operating curve of nesfatin-1 to prediction of case-control.

DISCUSSION

The present study is the first to investigate the association between MS and serum irisin and nesfatin-1 levels. Serum irisin and nesfatin-1 levels were determined in the present study to be significantly lower in the RRMS group than the control group. However, there were no statistically significant correlations between serum irisin and nesfatin-1 levels with age, disease duration, EDSS score, and overall relapse number. This could be an indication that molecular difference in patient group begins probably in the early stages of the disease. In MS, inflammation is the primary cause and recent studies have confirmed the anti-inflammatory effects of irisin and nesfatin-1 on the damaged brain[27,28,30]. Considering the inflammatory nature of MS, lower irisin and nesfatin-1 serum levels presence in RRMS patients was surprising. Hence, it might be concluded that decreased irisin and nesfatin-1 expressions may play a role in MS pathogenesis. However; more comprehensive studies are needed to determine the underlying causes of reduced serum irisin and nesfatin-1 levels in MS patients.

The association between irisin-nesfatin-1 levels and several other diseases has been established previously in the relevant literature. Serum irisin concentration is regulated by several factors such as obesity, exercise, diet, pharmacological, and some pathological conditions[31]. In obese people high plasma irisin levels have been determined and the underlying cause was defined to be an adaptive response that attempts to compensate the imbalance in glucose and

Table 2. Binary logistic regression analysis for Irisin-Nesfatin-1 (case-control groups).

	Irisin			Nesfatin-1		
	p-value	OR	95%CI	p-value	OR	95%CI
Age	0.156	1.052	0.981–1.129	0.177	1.047	0.979–1.120
Gender	0.887	0.916	0.276–3.041	0.751	0.835	0.275–2.540
BMI	0.000	0.643	0.508–0.814	0.000	0.626	0.502–0.779
Irisin <10.390 (ng/mL)	<0.001	9.723	2.884–32.785			
Nesfatin-1 <7.155 (ng/mL)				0.013	3.992	1.336–11.928

Irisin Nagelkerke R^2: 57.0%; Nesfatin Nagelkerke R^2: 48.7%; BMI: body mass index; OR: *Odds Ratio*; 95%CI: 95% confidence interval.

lipid homeostasis[32]. Similarly, in a study conducted with Chinese DM Type 1 and Type 2 patients and healthy controls, there were nonsignificant statistically positive correlations between plasma nesfatin-1 levels and BMI[33].

In the present study, both serum irisin and serum nesfatin-1 levels were determined as predictive factors independent of BMI for RRMS disease (Table 2). Whereas serum irisin and nesfatin-1 levels are expected to be higher in MS patients who are heavier than the control group, the low levels of these biomarkers support the relationship between MS and irisin and nesfatin-1. Higher serum irisin levels were found in healthy elderly patients compared to young healthy controls[34]. Irisin is negatively correlated with age since it is a muscle growth promoter[35]. However, Li et al. could not determine a correlation between nesfatin-1 levels and age[33]. No age-related increase in serum irisin and nesfatin-1 levels was observed in the present study. The reason for this outcome could be the presence of young MS patients with a narrow age range in the present study. Circulating irisin levels in younger individuals are higher in females than males[36]. Likewise, higher nesfatin-1 plasma levels were found in women compared to men[37]. However, in the present study, no statistically significant gender related difference could be determined in terms of irisin and nesfatin-1 levels.

In a study conducted with healthy participants by Ruan et al.[38], the level of circulating irisin was approximately 12.7 times higher than the CSF irisin level. Similarly, in the study of Tan et al.[39] reported that plasma nesfatin-1 levels were about 3 times higher than the CSF nesfatin-1 levels. In the present study, CSF analysis was not performed, and serum irisin levels of RRMS patients were 1.82 times and serum nesfatin-1 levels 3.33 times lower than healthy controls. Although, detected low serum irisin and nesfatin-1 levels in MS patients give rise to thought that CSF levels can be low also, further studies are needed to determine CSF levels of these peptides in MS patients. However, how the adipomyokine signal enters the brain, whether the CSF irisin and nesfatin-1 uptake involve a saturable transport mechanism, and the level of central irisin and nesfatin-1 expression in response to diseases still remain mainly unclear[38,39]. The literature review shows that, circulating irisin and nesfatin-1 levels in healthy individuals and patients indicate significant changes in different series[38,40]. This heterogeneity can be attributed to the use of different ELISA kits, racial differences, age, gender, BMI, etc. [33,41].

The specific elements that provoke MS pathogenesis remain unknown. Evidence suggests that inflammation[27,28,30], apoptosis[42,43] and oxidative stress[44,45], are important contributors to etiology, progression, and clinical symptoms of MS. In this regard, the literature above implies that the decreased irisin and nesfatin-1 concentrations could have a significant role in MS development. In the present study, in RRMS patients a higher percentage of lower irisin and nesfatin-1 levels have been observed compared to the healthy controls below the irisin 10.390 (ng/mL) threshold levels and nesfatin-1 7.155 (ng/mL) threshold level (9.72; 3.99 times respectively). This finding could help to improve understanding of MS and enhance strategies of treatment.

However, there are some inherent limitations of the present study. First of all, the study population is relatively small. Second, only patients without relapse were included in the RRMS group. Therefore, the results of the present study should be verified with studies conducted on progressive MS patients and during relapse in RRMS. In the present study, only irisin and nesfatin-1 serum levels were measured in MS patients and the control group. Determining changes in CSF irisin and nesfatin-1 levels will greatly contribute to understanding MS pathogenesis. Moreover, further studies with increased patient series, with a prolonged evaluation process, and assessment of post-treatment levels could enable a comprehensive conception of the cause-effect relationship of irisin and nesfatin-1 peptides in MS.

In conclusion, the present study revealed lower irisin and nesfatin-1 levels in patients with RRMS. These findings suggest that the decreased levels of irisin and nesfatin-1 peptides may contribute to MS pathogenesis such as inflammation, oxidative stress, and apoptosis in MS, leading to demyelination, axonal damage with neuronal loss, and gliosis. The present study will most probably pave the way for further studies on serum irisin and nesfatin-1 levels to investigate their potential use as treatment options and the possibility to prevent or even slow down RRMS progression.

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ARTICLE

Coexistence of restless legs syndrome and multiple sclerosis aggravates anxiety and depression

A coexistência da síndrome das pernas inquietas e esclerose múltipla agrava ansiedade e depressão

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ABSTRACT

Background: Among the comorbidities that accompany multiple sclerosis (MS), restless legs syndrome (RLS) is one of the most common. Anxiety and depression are common psychological comorbidities that impact the quality of life of patients with MS (PwMS), as well as patients with RLS. **Objective:** To investigate the psychiatric burden of MS and RLS coexistence, we conducted a nationwide, multicenter and cross-sectional survey. **Methods:** Participants were assessed by using demographic and clinical parameters along with the Hamilton Anxiety and Hamilton Depression Scales (HAM-A and HAM-D). **Results:** Out of the 1,068 participants, 173 (16.2%) were found to have RLS [RLS(+)] and 895 (83.8%) did not [RLS(-)]. The mean scores for HAM-A and HAM-D were significantly higher among RLS(+) subjects than among RLS(-) subjects ($p<0.001$ for all variables). **Conclusions:** According to our data, the presence of RLS in PwMS may increase the occurrence of both anxiety and depression symptoms. Awareness and treatment of RLS in PwMS could possibly reduce the symptoms of psychiatric comorbidities originating from RLS.

Keywords: Multiple Sclerosis; Restless Legs Syndrome; Depression; Anxiety; Mental Disorders.

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Authors' contributions: SS: study concept and design, study supervision, center coordination, data collection, analysis and interpretation, drafting, revision and approval of the final version of the manuscript; MD, MT, BT, EI, MK, DT, RK, CO, MN, BKG: center supervision, data collection, analysis and interpretation, review and approval of the final version of the manuscript; NY: center supervision, data collection, analysis and interpretation, drafting, revision and approval of the final version of the manuscript; CB: center supervision; data collection, analysis and interpretation; approval of the final version of the manuscript; AS: center coordination, data collection, analysis and interpretation, review and approval of the final version of the manuscript; GBG: collection, check, input, analyses and interpretation of the whole data and coordination of study centers with the principal center; MB, SS, MAB, TG, AT, UU: data collection, analysis and interpretation.

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RESUMO

Antecedentes: Considerando-se as comorbidades que acompanham a esclerose múltipla (EM), a síndrome das pernas inquietas (SPI) é uma das mais comuns, e ansiedade e depressão são comorbidades psicológicas comuns que afetam a qualidade de vida de pacientes com EM, bem como de pacientes com SPI. **Objetivo:** Investigar a carga psiquiátrica da coexistência de EM e SPI por meio de uma pesquisa nacional, multicêntrica e transversal. **Métodos:** Os participantes foram avaliados por parâmetros demográficos e clínicos, além da versão turca das escalas de ansiedade e depressão de Hamilton (HAM-A e HAM-D). **Resultados:** Dos 1.068 participantes, 173 (16,2%) apresentaram SPI [SPI (+)] e 895 (83,8%) não [SPI (-)]. As pontuações médias no HAM-A e no HAM-D foram significativamente maiores em indivíduos com SPI (+) do que naqueles com SPI (-) ($p < 0,001$ para todas as variáveis). **Conclusões:** De acordo com nossos dados, a presença de SPI na EM pode aumentar a ocorrência de sintomas de ansiedade e depressão. A conscientização e o tratamento da SPI na EM podem reduzir os sintomas de comorbidades psiquiátricas originadas da SPI.

Palavras-chave: Esclerose Múltipla; Síndrome das Pernas Inquietas; Depressão; Ansiedade; Transtornos Mentais.

INTRODUCTION

Multiple sclerosis (MS) has been reported to be associated with many autoimmune, physical and psychiatric conditions. Among the comorbidities that accompany MS, restless legs syndrome (RLS) is one of the most common, and it is probably the only condition that has been shown to be three to fivefold more prevalent among patients with MS (PwMS) than among the general population, in the relevant case-control studies[1-4]. Moreover, anxiety and depression are common psychological comorbidities that impact the quality of life and even increase suicidal tendencies among patients with multiple sclerosis (PwMS), as well as among patients with RLS[5-10]. Nonetheless, except for two very recent studies, there has not been much effort to show how the prevalence of RLS affects both depression and anxiety among PwMS[10-12].

We aimed to investigate the interaction between anxiety/depression and RLS among PwMS in a nationwide, multicenter and cross-sectional survey. The survey included demographic, clinical and biochemical variables. Exploring the relations of some of these variables with anxiety and depression among PwMS who had coexisting RLS could possibly contribute towards understanding the causes of the high prevalence rates of this psychiatric burden and the pathophysiology of both diseases.

METHODS

Data were drawn from the 'Restless Legs of Multiple Sclerosis - Turkey' project (RELOMS-T), which had the objective of examining the consequences of coexistence of MS and RLS and was designed to represent all PwMS throughout Turkey[13]. Patients who were 18 years or older and had a diagnosis of MS or clinically isolated syndrome (CIS) in accordance with the revised 2010 version of the McDonald criteria were recruited at the MS centers of 13 university hospitals[14].

Estimation of sample size

The study was planned to represent all PwMS throughout the country. Considering the population of Turkey (80 million) and the results from MS prevalence studies that have been conducted in this country, the prevalence rate of MS is estimated to be 60/100,000 and the total number of PwMS throughout the country, 45,000. Assuming that the prevalence of RLS among PwMS was 20%, with a 95% confidence interval, an error of 3% and a total number of PwMS of 45,000, the minimum sample size was calculated to be 942 patients (Raosoft, Inc., 2004).

Study procedure

The survey consisted of face-to-face interviews with 1,089 PwMS. All the interviews were conducted by a neurologist with experience in the field of MS. A three-part questionnaire that asked about the following was used: demographic features, consisting of 8 items (age, gender, sociodemographics, height, weight and smoking status); clinical characteristics, consisting of 15 main items of MS; and lastly, the main subject of this paper, i.e. the Turkish version of the HAM-A and HAM-D, to explore the psychiatric burden of MS and RLS coexistence. This questionnaire was applied to each patient included in the study. The following patients were excluded: those under the age of 18; pregnant women; those with a diagnosis of diabetes or uremia; those with a MS relapse within 3 months from the time of interview; those who were receiving any drug used to treat RLS, including dopamine agonists, dopaminergic agents, antiepileptics such as pregabalin, gabapentin and carbamazepine, benzodiazepines and opiates for another disorder or another consequence of MS other than RLS; and those who were unable to answer the questions of the survey.

The Turkish version of the five criteria suggested by the International Restless Legs Syndrome Study Group (IRLSSG) was used in the assessment of RLS[15]: 1) an urge to move legs, usually accompanied with unpleasant sensations; 2) worsening of these unpleasant sensations at rest; 3) partial or complete relief of the urge through movement; 4) an urge

to move the legs and accompanying unpleasant sensations that only occurred in the evening or night or was worse at these times than during the day; and 5) an urge to move the legs and accompanying unpleasant sensations that were not solely accounted for as symptoms primary to another medical or behavioral condition. Only those who were found to fulfil all of these five criteria were classified as having RLS at predigit level. The interviewers conducted detailed neurological examinations to distinguish RLS from other disorders that can mimic RLS (particularly symptoms and signs of lower limb impairment due to MS), in cases of necessity.

The interview followed a two-part questionnaire for screened-positive patients who were not currently being treated for RLS. The objective of the structured first part (8 structured items) was to determine the characteristics of RLS. The second part comprised the validated Turkish form of the IRLSSG rating scale and was used to measure the severity of RLS[16].

Before interviewing each patient, written informed consent was obtained. This study was approved by the Institutional Review Board of Mersin University, and it was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

All the data were coded using the Stata Data Analysis and Statistical Software (version 15, Stata Corp LLC) data entry program and were summarized using frequency and contingency tables for categorical variables and means and standard deviation for continuous variables. The prevalence of RLS among PwMS was estimated through descriptive statistics. We used the chi-square test to test the independence of the classification criteria and an independent Student's *t*-test to compare the means. The Mann-Whitney U test was used to compare the mean ranks between the groups and the z test to compare proportions. The three questions about sleep disorders in the HAM-D and one in the HAM-A were excluded from the comparisons between RLS(+) and RLS(-) patients, to avoid bias in the scores for sleep-related questions, which are expected to be much higher in RLS(+) and hence to improve the power of the data. P values <0.05 were regarded as significant.

RESULTS

In total, 1,089 completed questionnaire forms were collected from 13 centers. Due to uncertainty regarding some demographic data, 21 patients were excluded from the study and hence 1,068 patients were enrolled. Out of the 1,068 patients, 173 (16.2%) were found to be screen-positive for RLS [RLS(+)] according to the diagnostic criteria of the IRLSSG (128 women and 45 men), while 895 (83.8%) were not [RLS(-)]. The mean age of the RLS(+) patients was 38.9 years (SS: 9.7; min: 18; max: 76). Among the 173 RLS(+) patients, all but 8 of them (4.6%) were underdiagnosed in terms of RLS. Among these 165, the mean IRLSSG rating scale score was 21.4 (SD: 6.6; min: 6, max: 37) and the impact of RLS was mild in 7 (4.2%), moderate in 62 (37.6%), severe in 80 (48.5%) and very severe in 16 (9.7%). The mean age and severity of MS among RLS(+) and RLS(-) patients were compatible. Comparisons of some of the demographic and clinical characteristics of RLS(+) and RLS(-) patients are shown in Table 1. The mean (±SD) anxiety scores of RLS(+) and RLS(-) patients were 12.7 (SD: 4.5) and 7.9 (SD: 3.5) respectively; and depression 22.4 (SD: 6.8) and 19.6 (SD: 5,8) The mean scores for HAM-A and HAM-D and the two subscales of HAM-A assessing psychic and somatic functioning were found to be significantly higher among RLS(+) subjects than among the RLS(-) subjects (p<0.001 for all variables) (Figures 1 and 2).

Table 1. Comparison of some of the demographic and clinical characteristics of RLS(+) and RLS(-) patients.

		RLS(+) patients; n=173	RLS(+) patients; n=897	p-value
Characteristics	Age (SD), y	38.9 (9.7)	37.3 (10.4)	0.058
	No. of women (%)	133 (76.9)	664 (74.1)	0.974
	BMI (SD)	25.8 (4.7)	25.8 (5.2)	0.999
	Smokers, no. (%)	64 (37)	201 (22.5)	0.001*
Clinical MS type	CIS (%)	9 (5.2)	65 (7.3)	0.320
	RRMS (%)	150 (86.7)	730 (81.6)	0.107
	SPMS (%)	3 (1.7)	70 (7.8)	0.004*
	PPMS (%)	11 (6.7)	30 (3.4)	0.041*
	Overall (%)	173 (100)	895 (100)	
	EDSS (SD)	1.98 (1.42)	1.98 (1.61)	1.000

Age: mean age of the groups; SD: standard deviation; BMI: mean body-mass index; Smokers: no. of smokers in the groups; CIS: clinically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; *indicates a statistically significant p-value.

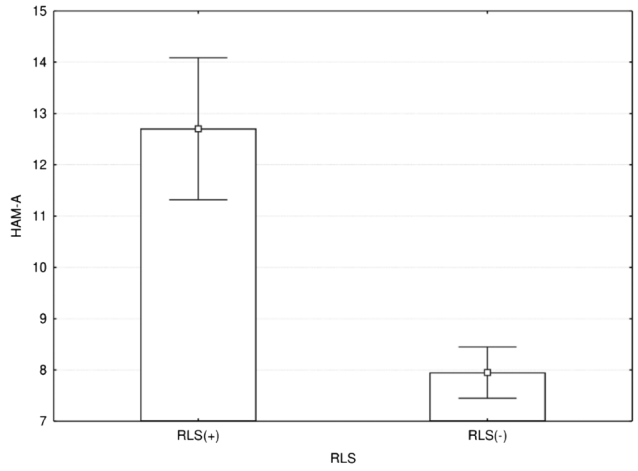

Figure 1. Anxiety scores on HAM-A among RLS(+) and RLS(-) patients. The mean HAM-A score of RLS(+) patients with multiple sclerosis was significantly higher than that of patients with multiple sclerosis without restless legs syndrome ($p<0.001$).

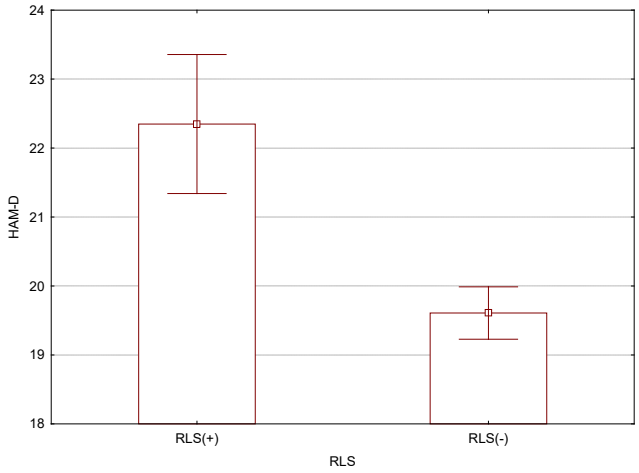

Figure 2. Depression scores on HAM-D among RLS(+) and RLS(-) patients. The mean HAM-D score of RLS(+) patients with multiple sclerosis was significantly higher than that of patients with multiple sclerosis without restless legs syndrome ($p<0.001$).

DISCUSSION

Symptoms of both diseases (MS and RLS) may cause distress and lead to psychiatric illness and a decreased sense of wellbeing. Moreover, very recently, both conditions were shown to trigger suicidal behavior independently, even in the absence of depression[7,9,12]. The data on the psychiatric aspects of this coexistence are insufficient, as also are the data on the relationship between the extent of the symptom burden, the risk of psychological symptoms and the beneficial effects of accurate treatment of RLS in PwMS with regard to any psychiatric disorder accompanying this coexistence.

Our survey was the first nationwide multicenter study, involving more than 1,000 patients, to investigate the interaction between psychiatric symptoms and RLS among PwMS. We investigated the effects of coexistence of these two neurological conditions with depression and anxiety as well as comparing their prevalence with each other. According to our data, the presence of RLS in PwMS may increase the occurrence of both anxiety and depression symptoms.

Our findings were compatible with two very recent studies in which the researchers used self-rated depression and anxiety scales and found higher anxiety/depression and lower quality of life (QoL) scores in their RLS(+) PwMS, compared with RLS(-)[10,11].

This study had its limitations. The most important limitation of our study was its inability to definitely determine and exclude the effect of other risk factors for depression and anxiety, other than RLS. We did not perform correlation analyses to eliminate the possible triggering effect of other MS symptoms and other risk factors for depression and anxiety, such as poor diet, lack of exercise, high blood sugar levels and hormone imbalances, on depression and anxiety symptoms. In this regard, although there were no differences in age and disease severity between our RLS(+) and RLS(-) groups, the data from this survey cannot be as reliable as the data from studies that are specifically designed to determine the psychiatric burden of MS or RLS and which used correlation analyses. Moreover, we did not assess the quality-of-life of patients and their level of fatigue, which have both been shown to be related to affective disorders. Comparison of patients' quality of life and fatigue measures with their psychiatric burdens would probably provide greater support for us to comment more precisely on the augmentation effect of RLS on the psychiatric symptoms of PwMS.

On the other hand, the strengths of this study lie in its design of face-to-face interviews conducted by experienced neurologists in this field, the very high number of PwMS included in the study and the power of this study to represent all PwMS throughout the country.

In conclusion, according to our data, coexistence of RLS has an additional effect on the psychiatric burden of PwMS. Although RLS mostly impairs quality of life, it is a treatable condition when recognized. Treatment of RLS in PwMS could possibly reduce the symptoms of psychiatric comorbidities originating from RLS. Thus, it is important to heighten the awareness of this comorbidity and its psychiatric burden among physicians, in order to improve the quality of life of PwMS.

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ARTICLE

The association between sleep disturbances and tooth loss among post-stroke patients

Prevalência de edentulismo e distúrbios de sono após acidente vascular cerebral

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ABSTRACT

Background: Loss of teeth has been associated with neurological and sleep disorders. It is considered to be a predictor of stroke and leads to modifications of airway patency and predisposition to obstructive sleep apnea. **Objective:** To investigate sleep quality, risk of obstructive sleep apnea and excessive sleepiness among post-stroke patients with tooth loss attending the Neurovascular Clinic of the Federal University of São Paulo. **Methods:** The prevalence rates of different types of stroke were assessed among 130 patients with different degrees of tooth loss, along with the presence of sleep disturbances, risk of obstructive sleep apnea and excessive daytime sleepiness. **Results:** The prevalence of ischemic stroke was 94.6%, with either no significant disability or slight disability. Our sample had poor sleep quality, and a high risk of obstructive sleep apnea, but without excessive daytime sleepiness. Half of our sample had lost between 9 and 31 teeth, and more than 25% had edentulism. The majority used full removable dental prostheses, and more than half of these individuals slept without removing the prosthesis. **Conclusions:** We found high prevalence of poor sleep quality and high risk of obstructive sleep apnea among post-stroke patients with tooth loss. This indicates the need for further studies on treating and preventing sleep disturbances in stroke patients with tooth loss.

Keywords: Stroke; Sleep; Sleep Apnea, Obstructive; Jaw, Edentulous.

RESUMO

Antecedentes: A perda de dentes tem sido associada a distúrbios neurológicos e do sono. É considerada um preditor de acidente vascular cerebral (AVC), com modificações na permeabilidade das vias aéreas e predisposição à apneia obstrutiva do sono. **Objetivo:** Investigar a qualidade do sono, o risco de apneia obstrutiva do sono e a sonolência excessiva em pacientes pós-AVC com perda dentária, atendidos na Clínica Neurovascular da Universidade Federal de São Paulo. **Métodos:** O estudo avaliou a prevalência de diferentes tipos de AVC em 130 pacientes com diferentes graus de perda dentária e a presença de distúrbios do sono, risco de apneia obstrutiva do sono e sonolência excessiva. **Resultados:** A prevalência de AVC isquêmico foi de 94,6%, sem deficiência significativa ou deficiência leve. Nossa amostra tinha má qualidade de sono e alto risco de apneia obstrutiva do sono, sem sonolência diurna excessiva. Metade de nossa amostra perdeu entre nove e 31 dentes, e mais de 25% tiveram edentulismo. A maioria usava próteses dentárias totalmente removíveis e, desses pacientes, mais da metade dormia com elas. **Conclusões:** Encontramos alta prevalência de má qualidade do sono e alto risco de apneia obstrutiva do sono em pacientes pós-AVC com perda dentária. Isso indica a necessidade de mais estudos sobre o tratamento e a prevenção de distúrbios do sono em pacientes com AVC e perda dentária.

Palavras-chave: Acidente Vascular Cerebral; Sono; Apneia Obstrutiva do Sono; Arcada Edêntula.

INTRODUCTION

Stroke is one of the main causes of disability and death in many regions of Brazil[1], and has been associated with tooth loss. This suggests that improving the periodontal condition of the general population could reduce overall mortality[2]. Moreover, tooth loss has been shown to be a predictor of stroke and cerebral white matter changes. It is an easy-to-assess and cost-effective indicator of periodontitis, a chronic inflammatory condition that is especially common in late life, in which the associated bacteremia can cause vascular damage[3].

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Stroke patients may present sensory-motor, musculoskeletal, perceptual and cognitive sequelae, as well as sleep disturbances. However, although sleep problems are common in patients with stroke, it is not yet known whether they appear before the event or are exacerbated by it[4]. The relationship between stroke and sleep disturbances may be both causal and bidirectional[5]. On the one hand, it has been shown that sleep disturbances such as obstructive sleep apnea (OSA) are an independent risk factor for stroke[6]. On the other hand, OSA, excessive daytime sleepiness (EDS), poor sleep quality, complaints of non-restorative sleep and restless legs syndrome (RLS) occur frequently after stroke[7].

High prevalence of respiratory sleep disorders has been reported among patients with stroke. Up to 40% of individuals with chronic stroke and 70% of those with acute stroke present these disorders[8]. Sleep-disordered breathing has been shown to have a negative impact on sleep quality after stroke, and it increases both the risk of another stroke and the risk of other cardiovascular events. OSA is associated with increased risks of diabetes, obesity and cardiovascular diseases such as hypertension, along with potentiating arrhythmias and embolisms[9].

Loss of teeth has been shown to be an independent risk factor for OSA. Each missing tooth increases the risk for OSA, such that the risk is 25% higher among those who have lost 5 to 8 teeth, 36% higher among those who have lost 9 to 31 teeth and 61% higher among those who have lost all their teeth (edentulism)[10]. Edentulism *per se* can lead to morphological modifications in the orofacial region (and of course, periodontitis) that negatively impact airway patency, thus predisposing individuals to OSA through restricting or obstructing the upper airway[11]. A combination of upper-airway anatomical abnormalities, imbalances in neural activation mechanisms and structural changes (retrognathia, posterior pharyngeal walls, a larger and/or softer tongue and palate, and tooth loss) have been implicated in the pathogenesis of OSA.

To the best of our knowledge, the overlap between tooth loss, sleep disturbances and stroke has not as yet been investigated. We hypothesized that after stroke, tooth loss may negatively influence the prevalence of OSA and symptoms such as EDS and poor sleep quality, thereby resulting in higher levels of disabilities. Therefore, the objectives of this investigation were to investigate EDS, poor sleep quality and the risk of OSA, and to assess whether there was any association between these sleep-related factors and tooth loss among post-stroke patients.

METHODS

Study design and study population

A total of 130 patients with tooth loss who had experienced a stroke were recruited to participate in this study between March 2016 and December 2017. The participants attended the Neurovascular Outpatient Clinic of the Universidade Federal de São Paulo (UNIFESP). The study protocol was approved by the Institutional Research Ethics Committee of UNIFESP. This was a cross-sectional observational study. Assessments were made by completing forms and questionnaires with the participants. Informed consent was obtained from all patients.

The inclusion criteria were the following: age ≥18 years old and having had an ischemic or hemorrhagic stroke, as verified from the medical records.

The exclusion criteria comprised: psychiatric illness (because of the possibility that prescribed medication might interfere with sleep); severe cognitive impairment; aphasia; and use of sedative or hypnotic medications. Thus, 14 participants were excluded: five due to aphasia, seven patients who did not complete the questionnaires and two due to dementia.

Data collection and clinical assessments

Data were gathered from the participants' medical records, clinical measurements and completed questionnaires, including the following information:

- Sociodemographic and clinical data: age, sex, body mass index (BMI) [calculated through the formula weight (kg)/height^2 (m^2)], neck circumference measurement, smoking status, presence of systemic arterial hypertension (SAH; defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, or regular use of antihypertensive medication), diabetes mellitus (DM; defined as fasting blood glucose concentration of 126 mg/dl or higher, or current use of antidiabetic medication) and dyslipidemia (DLP; defined in accordance with the Medical Guidelines for Clinical Practice of the American Association of Clinical Endocrinologists);
- Stroke data: quantitative measurements of stroke-related neurological deficit or stroke severity were assessed in accordance with the National Institutes of Health Stroke Scale (NIHSS)[12], which ranges from 0 to 42, such that higher scores indicate greater severity stroke; the etiological classification of stroke was made in accordance with the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[13].
- The degree of disability or dependence within the participants' daily activities was measured in accordance with the modified Rankin Scale (mRS), which ranges from 0 to 6, such that 0 describes participants without symptoms; grade 1, participants without significant disability despite symptoms; grade 2, slight disability; grade 3, moderate disability; grade 4, moderately severe disability; grade 5, severe disability; and grade 6, death.
- Sleep measurements: Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). A PSQI of ≤5 indicates good sleep quality, while >5 is associated with poor sleep quality and >10 indicates sleep disturbances. The risk of OSA was measured using the STOP-Bang questionnaire[14], in which the scores range from 0–8, such

that 0-2 represents low risk of OSA; 3–4, intermediate risk; and 5–8, high risk. Excessive diurnal sleepiness was evaluated using the Epworth Sleepiness Scale (ESS), in which the scores range from 0 to 24, such that 0–9 indicates "no sleepiness symptoms", while >9 may be "suggestive of daytime sleepiness".

- Tooth loss and occlusal contacts: a questionnaire on buccal health was completed, including the use of dentures; and a dental examination was conducted on each participant to collect anatomical characteristics such as the number of teeth and the condition of the palate, uvula and tongue.
- The modified Mallampati classification was used for airway classification. This is scored from 1 to 4 based on the anatomical features of the airway with the mouth open and tongue protruded maximally without phonation: grade I — tonsils, pillars and soft palate are all clearly visible; grade II — uvula, pillars and upper pole are visible; grade III — only part of the soft palate is visible, and the uvula is somewhat hidden; and grade IV — only the hard palate is visible[15-17]. The tonsils were classified using the Brodsky Tonsil Scale (BTS): grade 0 — previous tonsillectomy; grade 1 — tonsils were hidden in the pillars; grade 2 — tonsils were beyond the anterior pillar and occupied between 25 and 50% of the pharyngeal space; grade 3 — tonsils were beyond the pillars but not to the middle and occupied >50% and up to 75% of the pharyngeal space; grade 4 — tonsils occupied >75% of the pharyngeal space. Bite was categorized as one of three different types, in relation to the position of the first molars and the way in which the upper molars fit together with the lower ones (types I, II and III)[18].

Statistical analysis

Data analysis was performed using *Statistical Package for the Social Sciences* version 21.0 (SPSS Inc., Chicago, Illinois, USA). The results were presented as mean±SD or median and interquartile ranges (IQR, 25–75), and percentage, depending on the normality of the data. Student's *t*-test or ANOVA was used for comparison of means, and the chi-square and Fisher tests were used to compare proportions. Correlations between stroke and sleep variables and between stroke and anatomical characteristics were made using Spearman's correlation test. P values of less than 0.05 were considered significant.

RESULTS

Out of the 130 participants in the study, 52.3% were men. The participants' mean age was 59.7 (±12.5) years; mean BMI, 26.4 (±5.0 kg/m^2); and neck circumference, 46.4 (±4.3 cm). The prevalence rates of hypertension, DM and smoking were 103 (79.2%), 49 (37.7%) and 23 (17.7%), respectively.

The prevalence of ischemic stroke was 94.6% (123 patients) and hemorrhagic stroke, 5.4% (7 patients). The median NIHSS score was 2.0 (IQR 3.0), and the median mRS score was 2.0 (IQR 2.0). Among the 123 patients diagnosed with ischemic stroke, according to the TOAST classification, 29.27% had ischemic stroke of other determined etiology, 23.58% cardioembolism, 21.14% large-artery atherosclerosis, 17.7% small-vessel occlusion and 8.9% stroke of undetermined etiology.

Regarding sleep measurements, the mean score for sleep quality (PSQI) was

7.13 (±3.84), thus characterizing poor sleep quality. The participants were considered to be at high risk of OSA, according to the results obtained from the STOP-Bang questionnaire (4.11±1.57). The mean score for excessive daytime sleepiness was 8.16 (±5.22), thus indicating that there was no diurnal somnolence in this sample. Among our sample, 10.8% (14 participants) had a diagnosis of RLS.

Regarding the number of missing teeth observed, 48.9% of our sample had lost between 9 and 31 teeth, and 26.2% were edentulous. The percentage of patients using complete, removable dentures was 60.8%, and half of these patients habitually slept without removing the dentures. Ogival palate was present in 10.8% of the sample and web palate in 6.9%. Mallampati scores of III and IV were noted in 71.5%, tonsils grade I were present in 89.2%, and 82.3% had normal bite (Table 1).

Stroke severity was correlated with Mallampati scores (rho=0.174; p=0.048) and negatively correlated with BTS

Table 1. Characteristics of oral cavity, oropharynx, face and bite among patients with tooth loss after stroke (n, %).

Hard palate	Normal=14 (10.77%)	Oval=116 (89.33%)			
Soft palate	Normal=16 (12.30%)	Web=13 (10%)	Thick=7 (5.38%)	Long=94 (72.32%)	
Uvula	Normal=72 (55.38%)	Long=3 (2.31%)	Thick=32 (23.02%)	Surgery=22 (15.83%)	
Tongue	Normal=108 (77.77%)	Marked by teeth=20 (15.38%)	Hypotonic=1 (0.72%)		
Mallampati	Score I=4 (3.08%)	Score II=13 (9.35%)	Score III=19 (14.62%)	Score IV=93 (71.54%)	
Tonsils	Grade 1=5 (3.85%)	Grade 2=116 (89.23%)	Grade 3=6 (4.62%)	Grade 4=2 (0.01%)	
Face profile	Normal=37 (28.46%)	Short=77 (59.23%)	Long=15 (11.54%)		
Bite	Normal=107 (82.3%)	Open=1 (0.77%)	Deep=5 (3.85%)	Crossbite=4 (3.08%)	End to End=9 (6.92%)

(r=-0.199; p=0.023). There were also significant positive correlations between increased daytime sleepiness and disability (r=0.236; p=0.007), BTS (r=0.172; p=0.05) and number of teeth between 5 and 8 (r=0.227; p=0.009). Poor sleep quality was positively correlated with Mallampati scores (r=0.2; p=0.023). Given that the correlations were all weak, we were unable to perform a regression analysis.

DISCUSSION

This investigation on the associations between tooth loss and sleep disturbances among patients after stroke found that almost 95% of the sample had had an ischemic stroke of low severity, and there was non-significant presence of slight disability. This reflected the population of the outpatient clinic in which we recruited the participants. This finding was in line with the evidence in the literature, as 87% of stroke cases are ischemic and 13% hemorrhagic[19,20]. In addition, this finding is in agreement with the low levels of disabilities found in our sample, which is more commonly observed after ischemic events[21], and which indicates a strong probability of good recovery from the stroke. The majority of our sample comprised older men (≥40 years) who smoked and presented comorbid hypertension and diabetes. These are overlapping risk factors that predispose to both stroke and OSA. Older age, hypertension and smoking are well-known risk factors for stroke[22]. There is evidence that after the first cerebrovascular event, patients usually do not change their habits and thus have recurrent stroke[23]. High prevalence of embolic stroke was found in our sample, and this can be characterized by different phenotypes, depending on each population[24].

Despite the low severity of stroke in our sample, we found high risk of OSA and a self-perception of poor sleep quality. These factors can have a tremendously negative impact on stroke recovery, thereby increasing the risk of recurrent events. OSA (and its larger umbrella condition, namely sleep-disordered breathing, which includes central sleep apnea, sleep-related hypoventilation and Cheyne-Stokes breathing) is suspected to be present in 50–70% of patients after stroke[25]. In another investigation, our group found an association between poor sleep quality and increased risk of sleep-disordered breathing[26].

In this regard, sleep and stroke are interrelated, given that pre-existing sleep disturbances increase the risk factor for stroke. Patients with untreated OSA tend to have heightened sympathetic activity and autonomic dysregulation, and acute strokes can lead to the development of sleep-disordered breathing. Several studies comparing patients with and without OSA have found a 2 to 4.5-fold greater independent risk of a first-ever event of ischemic stroke among patients with OSA, which suggests that OSA may constitute a pre-existing condition rather than being a consequence of acute ischemic stroke. Furthermore, the risk of suffering a recurrent event may be noticeably higher among patients with OSA after stroke[27]. Treatment of sleep disorders such as OSA after stroke onset can enhance functional recovery, especially with regard to depression and sedentarism, improved concentration and attention and increased ability to perform activities of daily living.

Therefore, early diagnosis and treatment of OSA should reduce the risk of stroke. Polysomnographic (PSG) examinations are considered to be the golden standard for OSA diagnosis, but the prohibitive cost of the test and long waiting lists limit widespread access to it. Sleep specialists have proposed use of the STOP- Bang questionnaire as an alternative, more accessible screening tool, at least in the initial evaluation. The STOP-Bang questionnaire has high sensitivity (SE=95%) for identifying people at higher risk of OSA and, although its specificity is low (SP=16%), it is a simple and cost-effective instrument. In our sample, the risk of OSA was high among patients with tooth loss after stroke[28].

Patients with tooth loss are at higher risk of developing OSA, given that morphological changes in the upper airways can cause restriction and/or obstruction, thus leading to OSA and a cascade of events, such as EDS, poor sleep quality and concomitant sleep disturbances, such as restless legs syndrome[10]. Poor dental conditions (periodontal disease) and/or loss of teeth impact quality of life and affect the type of food eaten and its preparation, and this has been shown to be strongly associated with a myriad of diseases[29]. Periodontal diseases, which are one of the major causes of tooth loss, have been associated with OSA[30].

In our analysis on the oral cavity, we found Mallampati scores of III and IV in more than 70% of our sample, along with an elongated soft palate, which increases pharyngeal collapse: these are common findings in OSA cases. Anatomical and functional changes to craniofacial structures, such as a retrognathic jaw, diminished posterior pharyngeal wall, tooth loss and large soft tongue and palate have been implicated in the pathogenesis of OSA[31]. Indeed, some investigations have shown that tooth loss has the capacity to change the position of the mandible, decrease the vertical dimension of occlusion, impair functioning of the oropharyngeal musculature (e.g. loss of tone in the soft palate and pharynx and occurrence of macroglossia) and change the position of the hyoid bone. Changes to the soft palate, hard palate and mandibular position are important risk factors for OSA. Patients with an elongated soft palate have been shown to have higher rates of OSA, as assessed through PSG[32]. Another study showed that 31% of the population with tooth loss was identified as presenting high risk of OSA; however, until now, no investigations had been conducted among post-stroke participants[33]. Tooth loss plays an especially important role in terms of the respiratory process, body balance and general health of the stomatognathic system. Nevertheless, the exact mechanisms underlying this relationship remain unknown.

Currently, there is no consensus in the literature regarding the use of dentures by patients during sleep, or regarding

their benefit in relation to OSA. Almost half of our sample had lost between 9 and 31 teeth, and more than a quarter had edentulism. More than 60% of our sample reported that they continued to use their dentures during the night. Several investigations have reported that wearing dentures at night can decrease the severity of OSA[34]. Patients with tooth loss who sleep with their dentures in do not seem to show any objective changes in sleep (i.e. with regard to polysomnographic parameters).

The apnea-hypopnea index (AHI) is a measurement that forms part of PSG examinations. It is considered in making OSA diagnoses since it represents the number of apneas and hypopneas per hour of sleep. In a meta-analysis, no significant differences in the AHI of individuals using a dental prosthesis during sleep were found. This suggested that objective measurements showed that use of a dental prothesis failed to diminish AHI, and thus the severity of OSA[35]. However, contrary to the findings of that meta-analysis, another study reported that use of a dental prosthesis overnight by patients with tooth loss increased the AHI, thereby suggesting that it would be advisable to remove the denture before going to bed[36]. These contradictory findings may have been due to heterogeneity among the studies, and differences in measuring OSA.

In our sample, most of the participants slept without removing their dentures, but our results cannot be compared with the results from other studies, given that there is a lack of investigations on dental protheses after stroke. In clinical practice, we have seen that use of dentures can prevent OSA, but each specific case needs to be considered by a dentist specializing in sleep medicine. This is because a number of drawbacks exist regarding overnight use of dentures, such as resorption of the alveolar bone in the support area for the prosthesis, chronic inflammatory alterations in the patient and changes to the vertical dimension of occlusion, which can cause tension in the temporomandibular joint, with poor adaptation[32]. Therefore, additional studies are urgently required in order to evaluate the effects of tooth loss and use of dentures, in larger samples of patients.

Interestingly, a recent case report discussed the case of a patient with an oxygen desaturation index of almost 21 at baseline, who began to use removable dentures during sleep to prevent upper airway collapses. The oxygen desaturation index measures the number of times per hour that oxygen saturation decreases. This index dropped to 12.6 through use of a denture prothesis. The removable lower total prosthesis was then converted into a prosthesis in which retention was supported by means of two implants (overdenture). After 6 months, the oxygen desaturation index was 7.8. In this case, use of a total prosthesis improved this patient's respiratory stability during sleep[37].

Our sample did not present EDS, which reflected a situation of no post-stroke sleepiness, thus differing from the reports from other previous investigations. EDS may be caused by OSA or depression and is correlated with negative health outcomes after stroke. Although EDS is very common in OSA, the association between them has been reported to be weak in middle-aged adults[38].

Poor sleep quality is intrinsically related to OSA and other sleep disturbances, but recent investigations on tooth loss have found a 4% increase in the odds of having short sleep duration (i.e. less than 6 h/night) for each subsequent tooth loss. In individuals with less than 20 teeth, short sleep duration is also more prevalent[39]. In addition, loss of the teeth might be attributed to emotional distress and psychological problems, or to orofacial pain and temporomandibular disorders[40].

Our investigation had some limitations. Its cross-sectional nature precluded inferences about temporal sequence or causality. Patients with no sleep disturbances at the time of the evaluation could have developed sleep disturbances later, and evaluations of such occurrences would require a longitudinal study. In addition, this was a single-center investigation, and we did not perform any PSG examination to assess the AHI of our sample. We excluded patients with psychiatric illnesses who were undergoing treatment. After stroke, depressive episodes are common, and the medications used in treatments for these conditions could modify sleep quality and EDS. Another limitation was that airway volume was not measured during sleep. The contribution of tooth loss to airway obstruction may have been amplified through muscle hypotonia/atonia during the sleep. Nevertheless, despite these limitations, this was the first study to have evaluated the associations between tooth loss and sleep quality, risk of OSA and excessive daytime sleepiness among stroke patients in Brazil.

In conclusion, despite the complex and sometimes bidirectional relationships between tooth loss, sleep disturbances and stroke, we found high prevalences of poor sleep quality and risk of obstructive sleep apnea among patients with tooth loss after stroke. There is a paucity of effective evidence-based therapeutic strategies for OSA patients with tooth loss after stroke, and our study highlights the need for further randomized clinical trials on treatments for improving clinical management.

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VIEW AND REVIEW

Optical coherence tomography in neurodegenerative disorders

Tomografia de coerência óptica em doenças neurodegenerativas

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ABSTRACT

Structural imaging of the brain is the most widely used diagnostic tool for investigating neurodegenerative diseases. More advanced structural imaging techniques have been applied to early or prodromic phases, but they are expensive and not widely available. Therefore, it is highly desirable to search for noninvasive, easily accessible, low-cost clinical biomarkers suitable for large-scale population screening, in order to focus on making diagnoses at the earliest stages of the disease. In this scenario, imaging studies focusing on the structures of the retina have increasingly been used for evaluating neurodegenerative diseases. The retina shares embryological, histological, biochemical, microvascular and neurotransmitter similarities with the cerebral cortex, thus making it a uniquely promising biomarker for neurodegenerative diseases. Optical coherence tomography is a modern noninvasive imaging technique that provides high-resolution two-dimensional cross-sectional images and quantitative reproducible three-dimensional volumetric measurements of the optic nerve head and retina. This technology is widely used in ophthalmology practice for diagnosing and following up several eye diseases, such as glaucoma, diabetic retinopathy and age-related macular degeneration. Its clinical impact on neurodegenerative diseases has raised enormous interest over recent years, as several clinical studies have demonstrated that these diseases give rise to reduced thickness of the inner retinal nerve fiber layer, mainly composed of retinal ganglion cells and their axons. In this review, we aimed to address the clinical utility of optical coherence tomography for diagnosing and evaluating different neurodegenerative diseases, to show the potential of this noninvasive and easily accessible method.

Keywords: Tomography, Optical Coherence; Alzheimer Disease; Parkinson Disease; Multiple Sclerosis; Neurodegenerative Diseases; Amyotrophic Lateral Sclerosis; Retina.

RESUMO

A avaliação estrutural do cérebro, feita por meio dos exames de neuroimagem, é a forma mais utilizada de ferramenta diagnóstica e de acompanhamento das doenças neurodegenerativas. Técnicas de imagem mais sofisticadas podem ser necessárias especialmente nas fases mais precoces, antes mesmo do surgimento de quaisquer sintomas, porém costumam ser caras e pouco acessíveis. Sendo assim, é de fundamental importância a busca de biomarcadores não invasivos, de fácil acesso e baixo custo, que possam ser utilizados para rastreio populacional e diagnóstico mais precoce. Nesse cenário, o número de estudos com ênfase em técnicas de imagem para avaliação estrutural da retina em pacientes com doenças neurodegenerativas tem aumentado nos últimos anos. A retina apresenta similaridade embriológica, histológica, bioquímica, microvascular e neurotransmissora com o córtex cerebral, tornando-se assim um biomarcador único e promissor nas doenças neurodegenerativas. A tomografia de coerência óptica é uma moderna técnica de imagem não invasiva que gera imagens seccionais bidimensionais de alta resolução e medidas volumétricas tridimensionais reprodutivas do disco óptico e da mácula. Essa tecnologia é amplamente utilizada na prática oftalmológica para o diagnóstico e o seguimento de diversas doenças oculares, como glaucoma, retinopatia diabética e degeneração macular relacionada à idade. A redução da espessura da camada de fibras nervosas da retina e das camadas de células ganglionares em pacientes com doenças neurodegenerativas foi demonstrada em diversos estudos clínicos nos últimos anos. Nesta revisão, abordamos as principais aplicações clínicas da tomografia de coerência óptica nas doenças neurodegenerativas e discutimos o seu papel como potencial biomarcador nessas afecções.

Palavras-chave: Tomografia de Coerência Óptica; Doença de Alzheimer; Doença de Parkinson; Esclerose Múltipla; Doenças Neurodegenerativas; Esclerose Amiotrófica Lateral; Retina.

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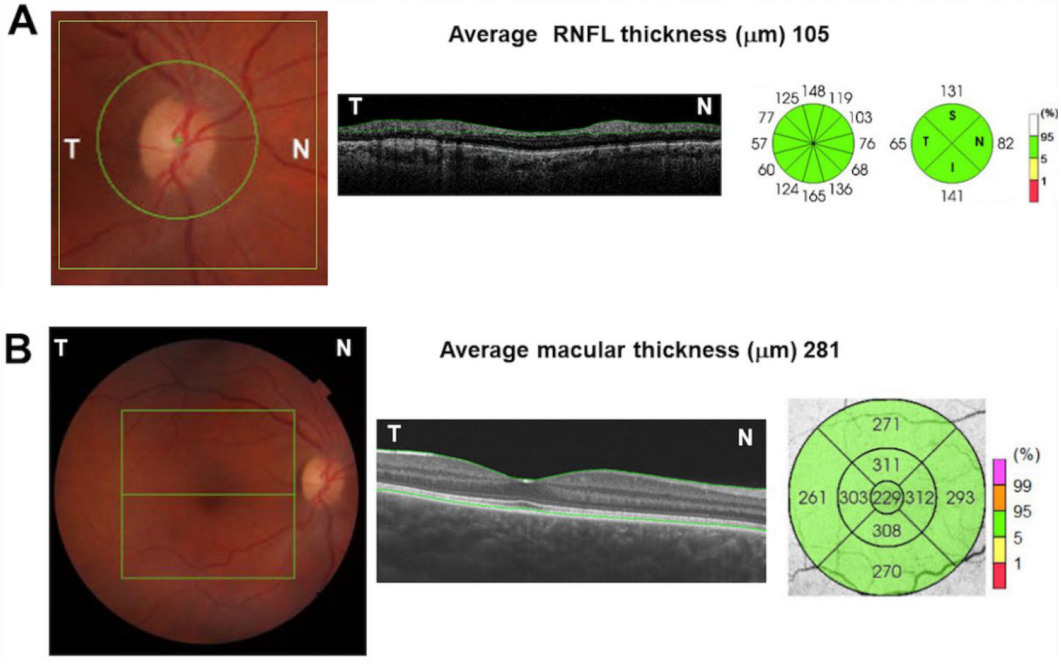
INTRODUCTION

Neurodegenerative diseases are conditions that can affect the central and peripheral nervous systems, leading to cognitive, motor, speech and even respiratory impairment[1]. These age-related disorders have become increasingly prevalent with the aging of the population worldwide over recent years[1]. Mild cognitive impairment (MCI), Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) have distinct pathophysiological mechanisms, but share progressive neuronal damage, leading to focal or overall loss of functions[2].

The most widely used diagnostic tool for investigating structural changes in the brains of patients with neurodegenerative diseases is magnetic resonance imaging (MRI)[3]. Despite its ability to detect morphological and volumetric changes in these patients, the diagnostic sensitivity of MRI is higher when the clinical disease is well-established. More advanced structural imaging techniques such as positron emission tomography, diffusion-weighted imaging and diffusion tensor imaging, magnetic spectroscopy and perfusion imaging have been applied in the early or prodromic phases of neurodegenerative diseases[3]. However, these imaging techniques are expensive, invasive and difficult to access, especially in developing countries, which makes them unsuitable for populational screening. Therefore, it is highly desirable to search for noninvasive, easily accessible, low-cost clinical biomarkers suitable for large-scale population screening, in order to focus on making diagnoses at the earliest stages of the disease. In this scenario, imaging studies focusing on the structures of the retina have increasingly been used for evaluation of neurodegenerative diseases. The retina shares embryological, histological, biochemical, microvascular and neurotransmitter similarities with the cerebral cortex, thus making it a uniquely promising biomarker for neurodegenerative diseases[4].

Optical coherence tomography (OCT) is a modern noninvasive imaging technique that provides high-resolution two-dimensional cross-sectional images and quantitative reproducible three-dimensional volumetric measurements of the optic nerve head and retina[5] (Figures 1 and 2). This technology is widely used in ophthalmology practice for diagnosing and following up several eye diseases, such as glaucoma, diabetic retinopathy and age-related macular degeneration. Its clinical impact on neurodegenerative diseases has raised enormous interest over recent years, as several clinical studies have demonstrated that these diseases give rise to reduced thickness of the inner retinal nerve fiber layer (RNFL), mainly composed of retinal ganglion cells and their axons[6].



T: temporal, N: nasal, RNFL: retinal nerve fiber layer, mm: microns; ETDRS: early treatment diabetic retinopathy study.

Figure 1. Schematic representation of the optic nerve head (ONH) and macula using spectral-domain optical coherence tomography (OCT) scanning protocols on the right eye of a normal individual. (A) 3D optic disc report, showing the ONH. Left panel: 6 × 6 mm scanned area centered on the ONH (green square) and the 3.4 mm peripapillary analyzed area for assessment of RNFL thickness. Central panel: OCT B-scan representing the cross-sectional retinal image around the ONH. The boundaries of the RNFL are represented by green lines. Right panel: Schematic representation of the peripapillary RNFL thickness measurements divided into 4 and 12-clock hour sectors with the values in microns. (B) 3D macula report, showing the macular area. Left panel: 6 × 6 mm scanned area centered on the fovea (green square). The horizontal green line represents the scanned horizontal central area. Central panel: Horizontal OCT B-scan representing the cross-sectional retinal image. The boundaries of the internal limiting membrane and the retinal pigment epithelium are represented by green lines. Right panel: ETDRS map divided in 9 sectors with the respective values of the total macular thickness measurements in microns.

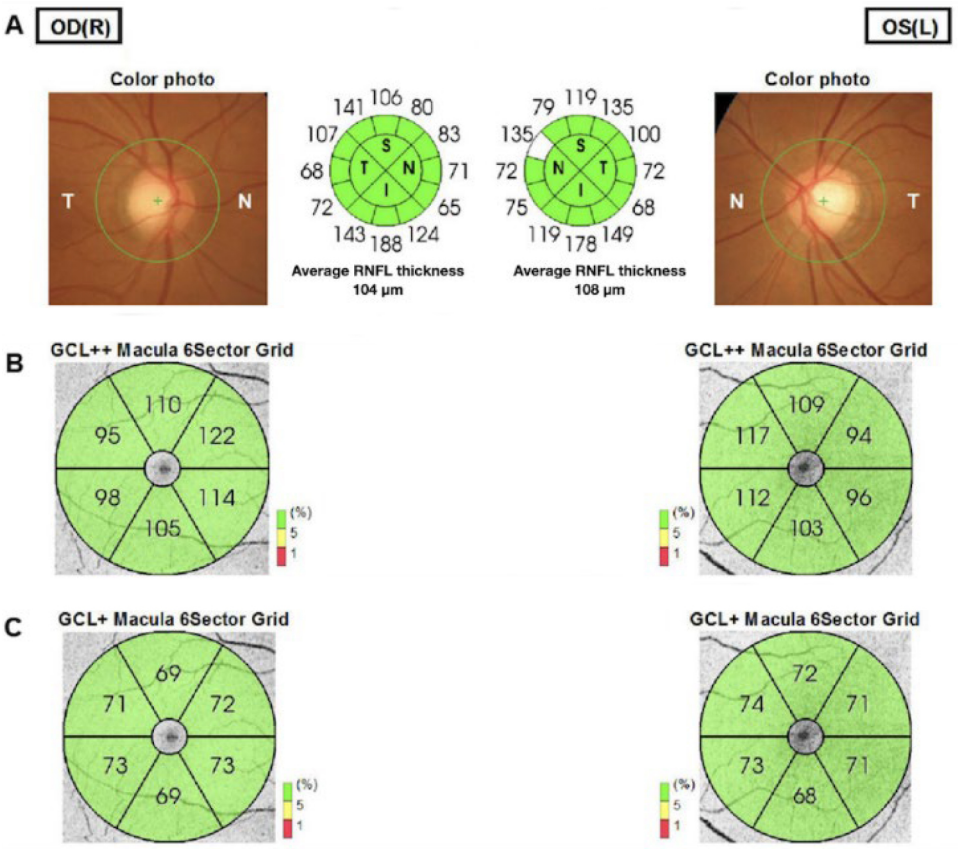


Figure 2. Swept-source optical coherence tomography (OCT) 3D wide disc and macula report (12 × 9 mm), on OCT three-dimensional images of both eyes (OU) of a 45-year-old healthy woman. (A) Peripapillary retinal nerve fiber (pRNFL) layer thickness measurements of OU. Average pRNFL thickness measurements are within normal limits: 104 microns in right eye (OD) and 108 microns in left eye (OS). (B) Ganglion cell complex (GCL++) macula thickness map divided into six sectors. GCL++ thickness measurements are within normal limits (in green) in OU. (C) Ganglion cell/inner plexiform layer (GCL+) macula thickness map divided into 6 sectors. GCL+ thickness measurements are within normal limits (in green) in OU. In this example, OCT thickness measurements did not demonstrate any signs of axonal loss and neuronal loss.

Due to the similarities of the microvascular structures of the retina and the brain, and also because of the presence of vascular abnormalities of the brain in many patients with neurodegenerative disorders, changes to retinal vascular density might also have potential as an ocular biomarker for neurodegenerative conditions. OCT-angiography (OCTA) is a noninvasive technique for imaging the microvasculature of the retina, in which light laser reflectance is used to detect the movement of intravascular red blood cells and thus reconstruct the retinal microvasculature in detail, without the use of contrast[7].

In this review, we aimed to address the clinical utility of OCT and OCTA for diagnosing and evaluating different neurodegenerative diseases, in order to show the potential of this noninvasive and easily accessible method.

PRINCIPLES OF OPTICAL COHERENCE TOMOGRAPHY

OCT is a noninvasive diagnostic technique that generates in vivo cross-sectional images of the retina. It uses near-infrared light, based on low-coherence interferometry, to create a cross-sectional image of the retina. The first commercially available versions of OCT used time-domain (TD-OCT) technology, which requires long acquisition times and provides axial and lateral resolutions of 15 mm. Improvements have been achieved over the past two decades with the emergence of spectral-domain OCT (SD-OCT) technology. This provides three-dimensional high-resolution cross-sectional retinal images with an axial resolution up to five times greater and imaging speeds approximately 60 times greater than TD-OCT[8].

The retinal layers are automatically identified by the OCT device. It considers the differences in reflectivity and signals generated by each retinal layer. Thus, peripapillary RNFL (pRNFL) is defined as the distance between the internal limiting membrane and the retinal ganglion cell/inner plexiform layer. These layers are located between the RNFL and the inner nuclear layer. The total macular thickness is calculated considering the distance between the internal limiting membrane and the retinal pigment epithelium[8].

The OCT device automatically estimates the pRNFL and the macula thickness measurements. In most OCT devices,

pRNFL thickness measurement reports are obtained through a 6 × 6 mm scanned area centered on the optic nerve head, consisting of 521 A-scans horizontally and 256 vertically. The measured area consists of a 3.4 mm diameter circle centered on the optic nerve head (Figure 1A). The measurements made are the average thickness, the thicknesses of the four quadrants (superior, temporal, inferior and nasal) and the thicknesses of the 12 clock hour segments (in mm). The macular analysis protocols consist of a scanned area of 6 × 6 mm, with 512 A-scans horizontally and 128 vertically. The macular analysis is based on a 6 mm circular map divided into a nine-segment map. The measurements made are the average macular thickness and the thickness of each of the nine sectors (in mm)[8] (Figure 1B).

OPTICAL COHERENCE TOMOGRAPHY IN MILD COGNITIVE IMPAIRMENT

MCI is recognized as a possible intermediate phase between senescence and dementia that denotes the presence of subjective and mild complaints of cognitive impairment, compared with healthy older people, without impacting the performance of activities of daily living[9]. Individuals in whom memory is one of the impaired domains (amnestic MCI - aMCI) have higher conversion rates to dementia. This is also seen when there is an association with vascular and parkinsonian symptoms[10]. Given the difficulties in clinically differentiating aMCI from the early stages of AD, an increasing number of studies have aimed to enable a more precise and earlier etiological diagnosis using techniques such as neuroimaging and serum/cerebrospinal fluid biomarkers[10]. In this context, OCT may play a role as another potential biomarker.

Several previous studies have indicated that MCI patients present decreased pRNFL thickness[11-13]. Compared with AD patients, the reduction in pRNFL thickness seems to be less pronounced in MCI patients, thus suggesting that a direct correlation exists between the severity of the disease and the amount of axonal impairment. These findings are in accordance with a recently published study by our group[14]. In this study, we found that most OCT parameters were significantly lower in individuals with aMCI, especially the macular ganglion cell complex thickness measurements. Moreover, the macular thickness parameters were significantly correlated with the severity of cognitive impairment[14].

Some recent previous studies showed changes in the retinal microvascular network in individuals with aMCI, with significant reductions in vessel density in the superficial capillary plexus and deep capillary plexus, in addition to decreased blood flow[15-17]. These studies also showed that parafoveal and peripapillary densities were positively correlated with low scores in the Montreal Cognitive Assessment (MoCA). The reductions in both vessel and perfusion densities of the superficial capillary plexus seen in OCTA have been positively correlated with measurements of brain volume using volumetric MRI, in individuals with MCI and AD[17].

OPTICAL COHERENCE TOMOGRAPHY IN ALZHEIMER'S DISEASE

AD is the most common neurodegenerative disorder in the elderly. Visual abnormalities occur frequently among AD patients and include decreased perception of contrast and movement, reduction of color vision and even loss of vision[18]. These abnormalities may be due to disorders in primary areas, notably the primary visual cortex[19,20]. Nevertheless, several studies have shown signs of specific impairment of the retina and the optic nerve in AD patients[21-23].

A wide range of studies have shown RNFL thinning in AD, in comparison with controls[11,12,22,24-31]. In general, the pRNFL thickness is diffusively decreased, affecting all sectors around the optic disc, which suggests that the axonal loss in AD patients results from a diffuse degenerative process in the ganglion cell layer[11,24,27-29].

In 2006, Iseri et al.[25] were the first to evaluate the total macular thickness, in 28 eyes from 14 AD patients. They showed that these patients had significantly reduced macular thickness in the nasal, temporal and inferior fields, as well as reduced total macular volume. Moschos et al.[31] showed that the inner macular sectors are the ones most affected. This was supported by data from a study by Cunha et al.[24], in which 45 eyes from 24 AD patients were included. That study showed thickness reductions in all sectors, except for the outer inferior sector, occurring preferentially in the inner macular areas. The ganglion cell layer and its axons contribute approximately one third of the total retinal thickness in the macula and seem to be the layer most affected in AD, according to previous tomographic and histopathological studies[21,23,24,32]. Recent technological enhancements of OCT have allowed greater segmentation of the macular retinal layers, consequently allowing the inner layers to be studied with greater precision. Assessment of the inner retinal layer is crucial, mainly because these layers (i.e. the macular RNFL and ganglion cell/inner plexiform layers) reflect the neuronal loss in patients with AD (Figure 3).

Some studies have found a correlation between OCT findings in AD patients and results from the Mini-Mental State Examination (MMSE)[25,30]. Cunha et al.[24,32] showed that greater pRNFL thinning, denoting axonal loss, and lower total macular and ganglion cell layer thicknesses, representing neuronal loss, were correlated with worse cognitive performance in the MMSE. Hence, OCT can be useful not only for assessing neuronal and axonal loss in AD patients, but also for measuring the cognitive decline in these patients.

A recent meta-analysis, involving 30 cross-sectional studies with 1257 AD patients, 305 MCI patients and

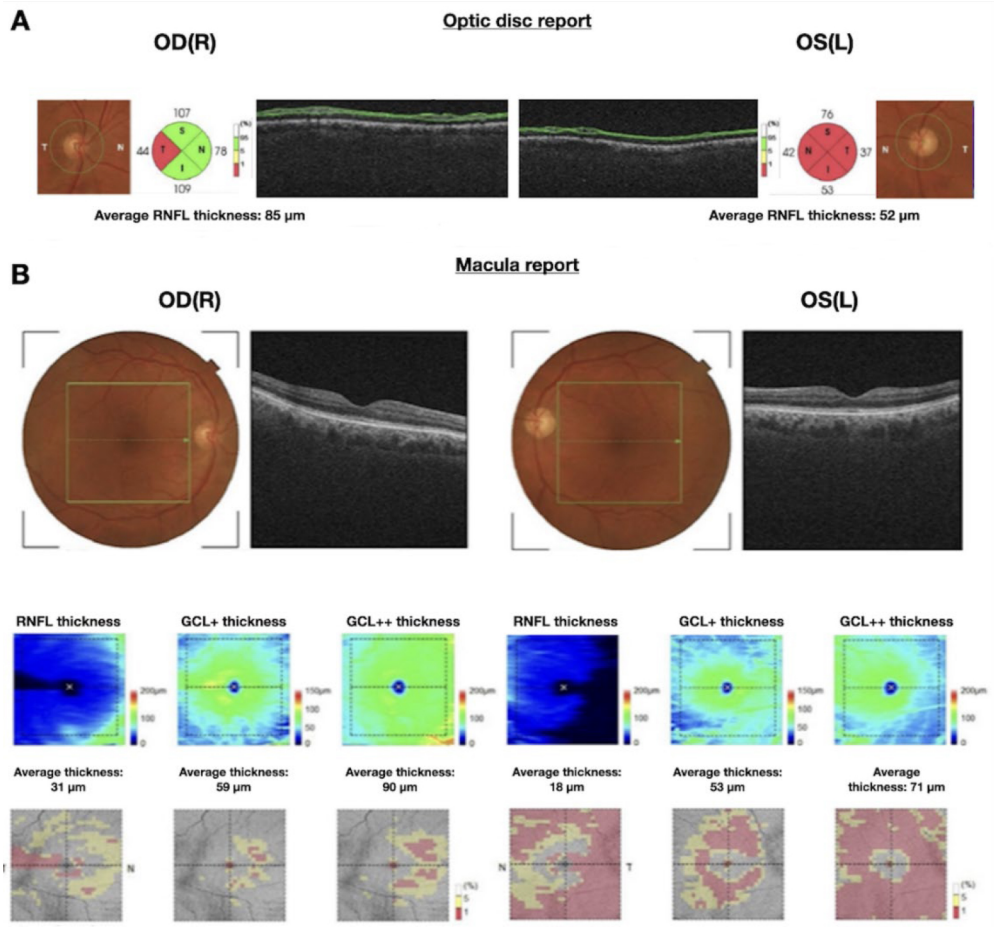


Figure 3. Example of optical coherence tomography (OCT) 3D optic disc and macula report, on OCT three-dimensional images of both eyes (OU) of a 75-year-old male with a three-year diagnosis of Alzheimer's disease and Mini-Mental State Examination test score of 15/30. (A) Optic disc report (6 × 6 mm) of OU, including total average peripapillary retinal nerve fiber layer (RNFL) measurements (in microns). Note the values outside of normal limits in the temporal quadrant in the right eye and in all four quadrants in the left eye (in red). (B) Inner macular thickness report (7 × 7 mm) of macular RNFL, ganglion cell/plexiform layer (GCL+) and ganglion cell/plexiform layer plus RNFL (GCL++) thickness measurements (in microns). Note the values outside of normal limits (in red) for all three parameters in OU, thus showing greater severity of neuronal loss in the left eye.

1460 controls[6], confirmed the association between OCT-based retinal measurements of the ganglion cell-inner plexiform layer, ganglion cell complex, macular volume and thickness and choroidal and RNFL thicknesses of AD patients, which were all significantly different from the controls.

OCTA can also be helpful in assessing retinal changes in AD, as shown in an increasing number of studies. Using OCTA, Bulut et al.[33] were the first to show decreased vascular density in the whole macular, foveal and parafoveal zones in AD patients, compared with controls, along with enlargement of the foveal avascular zone. Other authors have observed that OCTA findings correlate with cognitive function and that overall vascular density is lower in AD patients than in controls[34,35].

In addition, one of the first uses of OCT as a potential biomarker was among adults with preclinical AD. In 2018, using SD-OCT macular parameters, Santos et al.[36] conducted a 27-month longitudinal study on midlife adults with preclinical AD with multiple risk factors. In comparing them with healthy control subjects, significant reductions in macular RNFL and in the outer nuclear layer and inner plexiform layer volumes were noted over the follow-up period. This was one of the first reports on neuronal layer volumetric changes assessed by means of OCT in subjects with preclinical neurodegenerative disease, and it highlighted the potential use of OCT as biomarker.

OPTICAL COHERENCE TOMOGRAPHY IN MULTIPLE SCLEROSIS

MS is the most prevalent chronic inflammatory disease of the central nervous system (CNS)[37]. Visual loss is one of the most frequent symptoms and is typically related to retrobulbar optic neuritis (ON), which is characterized by sudden onset of visual loss accompanied by eye pain that is worsened or triggered by eye movements[38].

In the acute phase, OCT in ON can be useful for detecting and quantifying optic disc edema, which is observed through

increased pRNFL thickness. In accordance with a previous study, the mean average pRNFL thickness in patients with ON secondary to MS is 113 µm, ranging from 87 to 271 µm[39]. If these measurements are greater than 270 µm, it indicates very pronounced edema, which would be atypical for MS. OCT can also be used to monitor resolution of edema and to evaluate macular edema or serous retinal detachment, which are typical of other inflammatory conditions such as neuroretinitis and posterior or postoperative uveitis.

Another important application of OCT is in detection of subsequent axonal loss after the outbreak of ON[40]. A systematic review and meta-analysis on OCT-based retinal layer atrophy measurements in MS showed that RNFL is thinner in the peripapillary and macular regions in MS patients with ON and without ON, compared with controls[41]. There was no statistical difference in the thickness of the combined outer nuclear layer and outer plexiform layer when MS patients were compared with controls. Quantitative layer segmentation data showed that inner retinal layer atrophy was severe after ON and was also significantly reduced in the eyes of patients with MS who had never had ON, compared with control eyes. It has been shown that a single episode of ON does not imply greater risk of a progressive decrease in RNFL thickness, thus suggesting that thinning might occur as a result of recurrent episodes of ON[42]. However, axonal loss and reduction of pRNFL thickness can occur regardless of a previous history of ON, thus denoting the existence of subclinical axonal loss, possibly linked to irreversible damage caused by the neurodegenerative nature of MS[40,41].

The reduction in the thickness of the pRNFL is most evident around three months after an ON episode and tends to stabilize around 12 months. However, longitudinal studies have shown an annual atrophy rate of -1.4 µm/year: higher in MS patients with ON (-0.91 µm/year) than in MS patients without ON (-0.53 µm/year)[41].

Another important matter is the association of axonal loss (pRNFL thickness) and neuronal loss (macular ganglion cell complex thickness) with the intensity of visual functional loss, measured in terms of visual acuity, computerized visual field examination and color vision. Patients with greater axonal and neuronal loss after an ON outbreak are the ones who are expected to present the greatest impairment of visual function[43].

Endothelial dysfunction, probably secondary to inflammation, and a chronic state of impaired CNS venous drainage seem to play an important role in the development and course of MS[44]. There is emerging evidence that OCTA may serve as an effective tool for detecting pathological alterations that occur in the retinal vasculature of patients with MS. Several studies using OCTA have shown that the retinal vessel density of both macular and peripapillary areas were reduced in MS patients[45-48]. Thus, OCTA has the ability to detect subclinical vascular changes and is a potential biomarker for diagnosing MS and measuring its progression.

OPTICAL COHERENCE TOMOGRAPHY IN PARKINSON'S DISEASE

PD is the most common type of parkinsonism and the second most common neurodegenerative disease affecting the elderly population. The ocular changes that have been described in PD include visual dysfunction (visual acuity, dynamic contrast sensitivity and color discrimination), pupil abnormality, lens opacity, motion perception, visual processing speeds, facial recognition problems, chronic visual hallucinations and retinal neuronal loss and dysfunction[49,50]. These visual disorders are thought to be related to α-synuclein deposition and dopamine deficiency in the retina, thus mirroring the defining pathological features of PD in the brain[49,50]. Alpha-synuclein is an abundant neuronal protein that regulates synaptic vesicle trafficking and subsequent neurotransmitter release. When aggregated, it forms insoluble fibrils known as synucleinopathies, under pathological conditions, and this may lead to various cellular disorders. Dopamine is released by a unique set of amacrine cells of the inner nuclear layer and activates D1 and D2 dopamine receptors, which are distributed throughout the retina. Reduction in retinal dopamine has mostly been correlated with reduced color vision, visual contrast sensitivity and visual acuity[51]. Overall, visual impairment has been considered to be a consequence of PD progression, but a number of visual features can be observed in early PD and could even be present in the prodromal phase.

Recent advances have led to increasing interest in the role of the retina as a potential biomarker for making an early diagnosis of PD, and also as a means of measuring disease progression and evaluating novel therapeutic strategies. If early dopamine dysfunction leads to retinal structural abnormalities that could be detected through imaging of the retina, OCT could serve as a potential biomarker for making early diagnoses and prognoses in PD.

In 2004, Inzelberg et al.[52] were the first to show RNFL thinning through OCT, in ten PD patients. Subsequent studies confirmed their findings and also showed reductions in macular volume and thickness[53,54]. However, several other studies reported that RNFL thickness was similar in patients and controls[55-57]. The akinetic-rigid subtype of PD was found to have thinner RNFL than the tremor-predominant subtype[58], and the thickness of the RNFL was found to have a negative correlation with the severity of PD measured according to the Hoehn-Yahr stage and the Unified Parkinson's Disease Rating Scale (UPDRS) scores[55,56,59]. RNFL thickness has also been correlated with cognition[60] and the presence of hallucinations[57]. Recent longitudinal studies have shown a progressive decrease in RNFL thickness, and this was accompanied by progressive visual dysfunction[61,62].

A segmented retinal layer measurement might provide better knowledge of retinal thinning in PD. A recent meta-analysis demonstrated that the ganglion cell layer and inner

plexiform layer are the macular layers most affected in PD[63]. Changes to the retina in PD patients suggest vascular and dopaminergic mechanisms, but further studies are needed in order to support this theory. Although there are many challenges regarding OCT assessments in PD patients, pooled data from a recent systematic review confirmed that robust associations between retinal OCT measurements and PD exist[64], thus emphasizing the usefulness of OCT as a potential imaging biomarker in PD. Moreover, combination of OCT with OCTA may yield better diagnostic ability than either of these alone, hence providing additional biomarker methods for measuring PD onset and progression[65].

OPTICAL COHERENCE TOMOGRAPHY IN AMYOTROPHIC LATERAL SCLEROSIS

ALS is a neurodegenerative disease that classically affects the corticospinal tract and the motor neurons in the anterior horn of the spinal cord, and it is the most common motor neuron disease. Although it is essentially a motor disease, non-motor symptoms are common and may even precede the motor symptoms. About 10 to 75% of the patients with this disease have cognitive impairments and 15 to 41% of the cases progress to dementia[66].

Non-motor nervous system involvement in ALS has been demonstrated through neuroimaging, electrophysiological and histopathological tests. These draw attention to possible involvement of the anterior optic pathway and, more specifically, of the retina and the optic nerve[67-70]. Histopathological analysis on ALS eyes and mice with the UBQLN2(P497H) mutation, as well as OCT measurements, showed findings of intraretinal deposits and axonal loss, which were supportive of involvement of the anterior visual pathway[71].

In a study on 20 ALS patients and 25 matched healthy controls, the average pRNFL thickness found to be significantly reduced in ALS patients, compared with controls (102.57±13.46 compared with 97.11±10.76; p=0.04). A positive correlation was also found between the functional abilities of ALS patients, as assessed using the ALS Functional Rating Revised Scale (ALSFRS-R), and the average pRNFL thickness in most quadrants[72]. In a follow-up study on ALS patients, Rojas et al.[73] showed that in ALS follow-up patients, compared with ALS baseline patients, there was significant macular thinning in the inner and outer macular ring in inferior areas and significant RNFL thinning in the superior and inferior quadrants in the follow-up patients. Another interesting correlation was found between RNFL thickness and fractional anisotropy measurements of the corticospinal tract in a diffusion tensor imaging study[74], which showed that in fact retinal involvement is associated with overall neurodegeneration in ALS. Fractional anisotropy is a useful measurement of connectivity in the brain, derived from the diffusion tensor imaging data. It measures the degree of anisotropy of water molecules and allows inferences regarding alterations to the axonal diameter, fiber density or myelin structure.

In addition to RNFL abnormalities, other changes to retinal layer thicknesses and retinal blood vessels have also been described in ALS[75]. The outer and inner nuclear layers were found to be significantly thinner in ALS patients than in controls, and the outer wall thickness of retinal vessels was significantly thicker in ALS patients. Interestingly, no study reported any thinning of the ganglion cell layer, which has been extensively studied due to its relationship with optic nerve damage in other diseases such as AD and PD[75]. OCT could probably not only serve as a biomarker and progression marker tool, but also provide a new opportunity to delve into the pathogenesis of the disease.

OPTICAL COHERENCE TOMOGRAPHY IN OTHER NEURODEGENERATIVE DISEASES

OCT has been studied in Friedreich's ataxia (FRDA), the most common autosomal recessive ataxia worldwide, and in the rarer ataxia syndrome of autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). Patients with FRDA may have a measurable degree of pRNFL thinning, as determined using OCT, which can be a useful tool for following up these patients[76]. ARSACS is a rare neurodegenerative disorder caused by mutations in the SACS gene, and thickened retinal nerve fibers seen on fundoscopy form part of the clinical picture. In this regard, OCT appears to be a more sensitive and specific means for detecting RNFL thickness. In a large cohort of genetically confirmed ataxia cases, all 17 ARSACS patients were visually asymptomatic and did not have any previous history of ophthalmological complaints, and all of them presented pRNFL thickness loss on OCT, whereas this finding was detected via fundoscopy only in 12 of them. This is a useful tool for identifying cases of ARSACS among other causes of ataxia[77].

Adrenoleukodystrophy (ALD) is a disease linked to the X chromosome that presents with different neurological phenotypes, ranging from very severe cerebral forms to less severe adrenomyeloneuropathy. Progressive myelopathy is the main cause of disability in these patients. However, the visual system may be involved and neurodegeneration of the spinal cord in ALD has been correlated with pRNFL thickness[78]. In a cross-sectional and longitudinal study on 11 symptomatic adult ALD males, Bianchi-Marzoli et al.[79] showed that OCT can reveal retinal abnormalities in the most disabled patients, particularly in the inferior pRNFL and inner macula.

OCT has also been used in relation to other neurodegenerative movement disorders, such as Wilson's disease, Huntington's disease and atypical parkinsonian syndromes. In Wilson's disease, which is an inherited autosomal recessive

disorder that leads to pathological copper accumulation in different organs, thinning of the pRNFL and macular thickness has been detected via OCT[80], especially in patients with brain imaging abnormalities[81]. A significant negative correlation was found between OCT parameters and neurological impairment according to a specific scale for patients with Wilson's disease[82]. Eye movement disorders are key clinical features in Huntington's disease. OCT performed on 26 Huntington's disease patients showed that RNFL thickness was significantly reduced, compared with controls, and there was a significantly negative correlation with disease duration. Macular volume also correlated negatively with disease duration and motor scores[83]. Another cross-sectional study on eight Huntington's disease patients showed that both choroidal and retinal macula were altered in the disease[84]. Other studies followed[85,86], including an OCTA study[87], which affirmed the usefulness of OCT as a potential biomarker of neurodegeneration in Huntington's disease patients. Studies on multiple system atrophy and progressive supranuclear palsy have shown conflicting results, but there is evidence of RNFL thickness reduction, also correlated with disease severity, and to a worse extent than in PD patients[88].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered to be a genetic form of small-vessel disease that causes subcortical dementia. In a cross-sectional study involving 17 CADASIL patients, RNFL thickness was significantly reduced, compared with controls[89]. In a more common form of dementia, frontotemporal dementia, OCT can also be useful, considering that RNFL thickness reduction has been shown[90].

Lastly, OCT has been evaluated as a potential optical guidance system for deep brain stimulation. The results showed that catheter-based OCT had the resolution and contrast necessary for targeting. Evidence has also been provided to show that vacuoles in spongiform encephalopathies are another structure that OCT can detect with high contrast[91]. This exemplifies the possible future clinical applications of OCT in disorders that goes beyond the visual system.

LIMITATIONS AND CONCERNS

Over the last decade, there has been significant focus on research addressing OCT applications for diagnosing and following up many neurodegenerative diseases. Table 1 summarizes the main findings from the most important papers on OCT use in MCI, AD, MS, PD and ALS. Use of OCT to define a biomarker may have an impact on population screening for neurodegenerative diseases, especially among patients with risk factors, given that it is an easily accessible and minimally invasive test. Another important clinical application of OCT is in evaluating the therapeutic effects of certain drugs on ocular parameters and the possibility of prevention of neuronal degeneration in these patients. To cite an example, Mello et al.[92] compared the macular and choroidal thickness parameters in patients with PD with or without treatment using pramipexole, a dopamine agonist. Their results showed that thinning of many macular parameters occurred, especially macular RNFL and the ganglion cell layer + inner plexiform layer, in patients with PD without pramipexole

Table 1. Main optical coherence tomography and optical coherence tomography-angiography findings in neurodegenerative disorders.

Structural parameters	Main findings	Key references
Mild cognitive impairment		
pRNFL	Progressively thinned from controls to mild cognitive impairment and from mild cognitive impairment to Alzheimer's disease	Lee et al.[11], Paquet et al.[12], Gao et al.[13], Almeida et al.[14]
Macula	Decreased ganglion cell complex thickness, compared with controls	Almeida et al.[14]
	Correlation between OCT abnormalities and cognitive impairment	Almeida et al.[14]
Microvascular	Decreased vessel density and blood flow correlated with lower MoCA scores	Zhang et al.[15], Criscuolo et al.[16], Yoon et al.[17]
Alzheimer's disease		
pRNFL	Diffuse thickness reduction, compared with healthy controls	Chan et al.[6], Lee et al.[11], Paquet et al.[12], Parisi et al.[22], Cunha et al.[24], Iseri et al.[25], Kesler et al.[26], Kirbas et al.[27], Lu et al.[28], Marziani et al.[29], Moreno-Ramos et al.[30], Moschos et al.[31]
	Correlation between thinning and lower MMSE results	Cunha et al.[24], Iseri et al.[25], Moreno-Ramos et al.[30], Cunha et al.[32]

Continue...

Table 1. Continuation.

Structural parameters	Main findings	Key references
Macula	Diffuse thinning, especially in the ganglion cell complex	Chan et al.[6], Lee et al.[11], Cunha et al.[24], Kirbas et al.[27], Lu et al.[28], Marziani et al.[29], Moschos et al.[31]
	Reduced volume, compared with controls	Chan et al.[6], Iseri et al.[25]
	Correlation with MMSE results	Cunha et al.[24], Iseri et al.[25], Moreno-Ramos et al.[30], Cunha et al.[32]
	Decrease in macular RNFL, outer nuclear layer and inner plexiform layer volumes, in preclinical AD relative to controls	Santos et al.[36]
Microvascular	Decreased vascular density	Bulut et al.[33], Zhang [34], Song [35]
	Foveal avascular zone enlargement	Bulut et al.[33]
	Correlation with cognitive function	Bulut et al.[33], Zhang et al.[34], Song et al.[35]
Multiple sclerosis		
pRNFL	Increased thickness in the acute phase of optic neuritis	Costello et al.[39]
	Chronic thinning in patients with and without optic neuritis	Parisi et al.[40], Petzold et al.[41], Garcia-Martin et al.[42]
	Thinning is correlated with visual loss	Trip et al.[43]
Microvascular	Reduction in the retinal and macular vessel densities	Lanzillo et al.[45], Lanzillo et al.[46], Spain et al.[47], Wang et al.[48]
Parkinson's disease		
pRNFL	Inconsistent findings	Inzelberg et al.[52], Altintas et al.[53], Hajee et al.[54], Albrecht et al.[55], Mailankody et al.[56], Lee et al.[57]
	Thinner RNFL in akinetic-rigid Parkinson's disease, compared with tremor-predominant type	Altintas et al.[53]
	Negative correlation between UPDRS and RNFL	Albrecht et al.[55], Mailankody et al.[56], Moschos et al.[59]
	Correlation between pRNFL thinning and nonmotor symptoms	Lee et al.[57], Yildiz et al.[60], Ma et al.[61], Satue et al.[62]
Macula	Decreased volume and thickness	Altintas et al.[53], Hajee et al.[54]
	Ganglion cell-inner plexiform layer abnormalities	Chrysou et al.[63]
Amyotrophic lateral sclerosis		
pRNFL	Diffusely reduced thickness, compared with controls	Rohani et al.[72], Rojas et al.[73]
Macula	Thinning in outer and inner sectors	Rojas et al.[73]
Microvascular	Inconclusive findings	Cervero et al.[75]

OCT: optical coherence tomography; pRNFL: peripapillary retinal nerve fiber layer; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; RNFL: retinal nerve fiber layer; UPDRS: Unified Parkinson's disease rating scale.

treatment, compared with those who were using pramipexole. Their findings suggested that pramipexole treatment seems to prevent retinal degeneration in PD.

However, we need to address some drawbacks regarding this technology. First, the use of OCT to detect neuroaxonal loss, seen in patients with neurodegenerative diseases, may be influenced by the presence of other ocular diseases that are prevalent in the elderly population, such as glaucoma and age-related macular degeneration. Moreover, other previous ocular diseases can also provide impaired results that do not have any correlation with the neurodegenerative disease itself.

Second, normative data from OCT devices has the clinical purpose of helping doctors to recognize an abnormal OCT examination and this involves volumetric analyses on the pRNFL and macular thickness values. In some neurodegenerative conditions, especially in the very early phases, OCT may exhibit values within normal limits. To the best of our knowledge, the individuals who were included for the normative databases were not screened to exclude those who had family histories of neurodegenerative disorders or who had previously undergone cognitive tests. This might have impacted on the diagnostic ability to detect neuronal loss, especially in the very early phases and even in borderline

cases. We believe that it is necessary for physicians to take into account analyses on OCT data values from patients with neurodegenerative diseases, based on published studies on these specific populations. We also recommend that companies supplying OCT technology should maintain awareness of these limitations and look for solutions to mitigate this problem, thus improving the diagnostic capability of OCT in relation to these specific groups of diseases.

Another important suggestion is that, after a certain age, especially in cases with a higher risk of onset of a neurodegenerative disease, patients should undergo serial analysis using OCT, to observe whether any significant reduction of these parameters might occur over the years.

Another major concern, especially in developing countries such as Brazil, is the limited number of OCT tests that are done in socioeconomically vulnerable populations. OCT tests need to be more available for population screening.

In conclusion, OCT is a handy noninvasive tool for diagnosing and following neuroaxonal loss in many neurodegenerative diseases and could be potentially used to provide an easily accessible ocular biomarker in these patients.

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VIEW AND REVIEW

Gut microbiome in neuropsychiatric disorders

O microbioma intestinal nas doenças neuropsiquiátricas

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ABSTRACT

Background: Neuropsychiatric disorders are a significant cause of death and disability worldwide. The mechanisms underlying these disorders include a constellation of structural, infectious, immunological, metabolic, and genetic etiologies. Advances in next-generation sequencing techniques have demonstrated that the composition of the enteric microbiome is dynamic and plays a pivotal role in host homeostasis and several diseases. The enteric microbiome acts as a key mediator in neuronal signaling via metabolic, neuroimmune, and neuroendocrine pathways. **Objective**: In this review, we aim to present and discuss the most current knowledge regarding the putative influence of the gut microbiome in neuropsychiatric disorders. **Methods**: We examined some of the preclinical and clinical evidence and therapeutic strategies associated with the manipulation of the gut microbiome. **Results**: targeted taxa were described and grouped from major studies to each disease. **Conclusions**: Understanding the complexity of these ecological interactions and their association with susceptibility and progression of acute and chronic disorders could lead to novel diagnostic biomarkers based on molecular targets. Moreover, research on the microbiome can also improve some emerging treatment choices, such as fecal transplantation, personalized probiotics, and dietary interventions, which could be used to reduce the impact of specific neuropsychiatric disorders. We expect that this knowledge will help physicians caring for patients with neuropsychiatric disorders.

Keywords: Gastrointestinal Microbiome; Metagenomics; Nervous System Diseases; Transplantation; Precision Medicine.

RESUMO

Antecedentes: Os transtornos neuropsiquiátricos são uma importante causa de morte e invalidez no mundo. Os mecanismos subjacentes a esses transtornos incluem uma constelação de etiologias estruturais, infecciosas, imunológicas, metabólicas e genéticas. Avanços nas técnicas de sequenciamento do DNA têm demonstrado que a composição do microbioma entérico é dinâmica e desempenha um papel fundamental não apenas na homeostase do hospedeiro, mas também em várias doenças. O microbioma entérico atua como mediador na sinalização das vias metabólica, neuroimune e neuroendócrina. **Objetivo**: Apresentar os estudos mais recentes sobre a possível influência do microbioma intestinal nas diversas doenças neuropsiquiátricas e discutir tanto os resultados quanto a eficácia dos tratamentos que envolvem a manipulação do microbioma intestinal. **Métodos**: foram examinadas algumas das evidências pré-clínicas e clínicas e estratégias terapêuticas associadas à manipulação do microbioma intestinal. **Resultados**: os táxons-alvo foram descritos e agrupados a partir dos principais estudos para cada doença. **Conclusões**: Entender a fundo a complexidade das interações ecológicas no intestino e sua associação com a suscetibilidade a certas doenças agudas e crônicas pode levar ao desenvolvimento de novos biomarcadores diagnósticos com base em alvos moleculares. Além disso, o estudo do microbioma intestinal pode auxiliar na otimização de tratamentos não farmacológicos emergentes, tais como o transplante de microbiota fecal, o uso de probióticos e intervenções nutricionais personalizadas. Dessa forma, terapias alternativas poderiam ser usadas para reduzir o impacto dos transtornos neuropsiquiátricos na saúde pública. Esperamos que esse conhecimento seja útil para médicos que cuidam de pacientes com diversos transtornos neuropsiquiátricos.

Palavras-chave: Microbioma Gastrointestinal; Metagenômica; Doenças do Sistema Nervoso; Transplante; Medicina de Precisão.

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INTRODUCTION

Over the past decade, microbiomics have emerged as a new field led by advances in culture-independent methods and next-generation sequencing technologies. These methods have provided a broader understanding of how the interaction between microbes and humans can profoundly influence host homeostasis and different disease states[1]. The literature has reflected the growing number of studies on the putative influence of the microbiome on human health and disease (Figure 1). In humans, bacteria are the most prevalent domain, and it has been estimated that the ratio of microbes to human cells in an adult is nearly 1:1[2]. The human microbiome is defined as the compendium of microbial communities (including bacteria, archaea, viruses, protozoa, and fungi) living in a given body niche[3,4].

It has been demonstrated that the gut microbiome can be shaped by prenatal conditions, lifestyle, aging, host genetics, antibiotic use, and even geography. Moreover, it has been shown that microbial aggregates on the large intestine can modulate a wide range of host physiological processes related to immune system maturation, food metabolism, energy production, and brain development[5,6].

The crosstalk between the gut microbiome and the brain is known as the gut microbiota-brain axis (MBA), which involves immunological, neuroendocrine, metabolic, and stress-response pathways[7]. This axis appears to be a cardinal mediator in a repertory of complex traits that range from metabolic to neuropsychiatric conditions[8]. Despite the vast contribution of animal models to elucidate biological mechanisms underlying host-microbiota interactions, there are difficulties in translating the findings in animal experiments to human research. Also, differences in methodologic standards, metadata curation, and reference databases management (https://portal.hmpdacc.org/; https://www.sanger.ac.uk/resources/downloads/bacteria/metahit/) can be potential pitfalls for study comparison, interpretation, and reproducibility[9].

Since cohorts in microbiome studies tend to be small and heterogeneous, it is difficult to know which observations are generalizable to larger patient populations. Metabolomic, proteomic, and big data analyses of microbiome function will be critical to determine if the conclusions of these studies can apply to the clinical setting. Further experimental studies using *in vitro* or *in vivo* models are needed to understand the direct impact and causal relationships between host and microbes in order to control both known and potential hidden confounders. In this way, it still not currently possible to determine whether changes in the microbiota could be merely an epiphenomenon rather than the primary cause of the problem. Thus, few clinicians currently recognize that the gut microbiome is relevant to human neurophysiology because the nature of the relationship between microbiota and disease is still unclear.

In this context, we aim to present and discuss the current literature on the putative biological significance of the gut microbiome in neuropsychiatric disorders. We hope to show why this field is emerging as a possible source of therapeutic targets in these disorders and how it can be incorporated into personalized medicine strategies[4]. We will describe only the major studies related to each disease; however, additional references are presented in Tables 1–5.

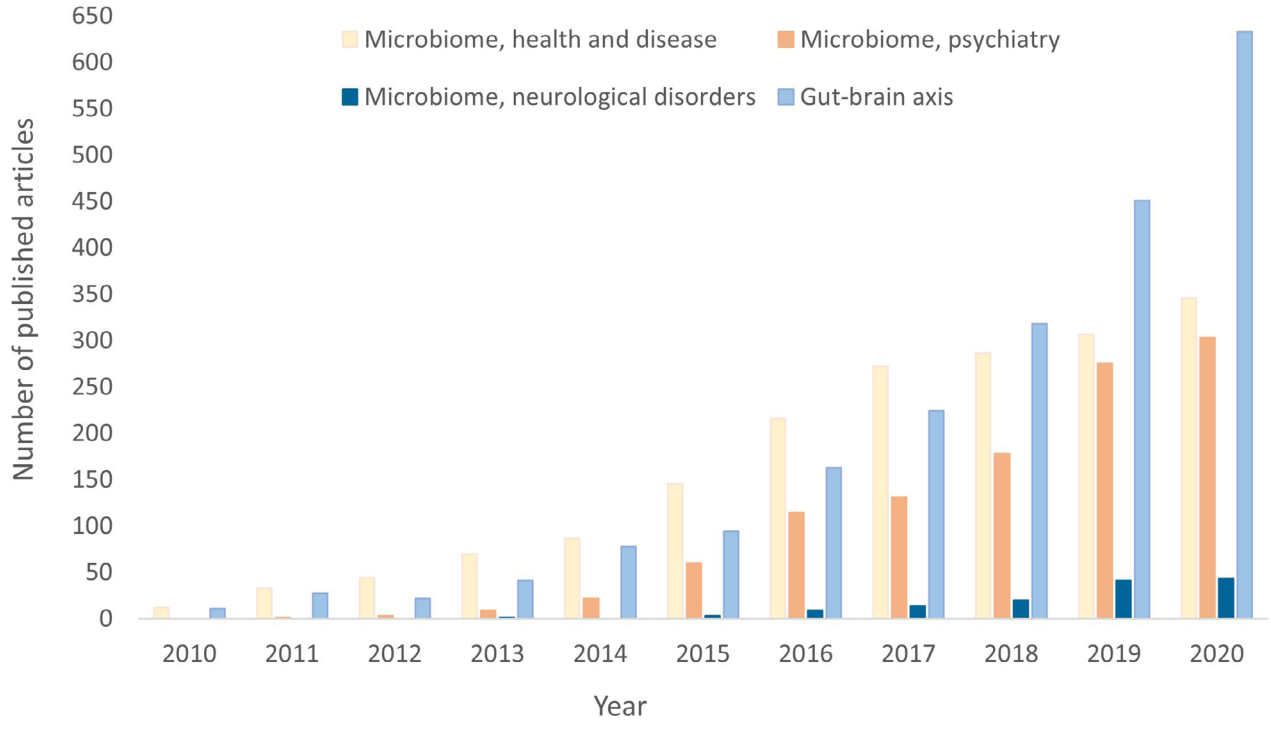

Figure 1. Citations in PubMed related to microbiome research over the last decade.

Table 1. Summary of the main studies about gut microbiome in multiple sclerosis.

Title of the study	Sample size	Main findings	References
Cross-reactivity between related sequences found in *Acinetobacter sp.*, *Pseudomonas aeruginosa*, myelin basic protein, and myelin oligodendrocyte glycoprotein in multiple sclerosis	n=71 (26 patients with MS; 20 patients with unilateral hemiplegia due to a cerebrovascular accident; 25 controls)	Antibodies to mimicry peptides from *Acinetobacter*, *P. aeruginosa*, myelin basic protein, and myelin oligodendrocyte glycoprotein were significantly elevated in patients compared to controls.	Hughes et al.[23]
Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models	n=142 (stool samples from 71 patients with MS and 71 controls)	Increased *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* in patients, which induced pro-inflammatory responses. Reduced *Parabacteroides distasonis* in patients with stimulated anti-inflammatory IL-10-expressing human CD4+CD25+ T cells and IL-10+FoxP3+ Tregs in mice. Microbiota transplants from patients into germ-free mice induced more severe experimental autoimmune encephalomyelitis compared with controls.	Cekanaviciute et al.[24]
Gut microbiota in multiple sclerosis: Possible influence of immunomodulators	n=15 (7 patients with MS and eight controls)	Lower abundance of *Faecalibacterium* in patients. Different community composition in patients treated with Glatiramer acetate regarding *Bacteroidaceae*, *Faecalibacterium*, *Ruminococcus*, *Lactobacillaceae*, *Clostridium*, and other Clostridiales. Untreated patients had an increase in the *Akkermansia*, *Faecalibacterium*, and *Coprococcus* genera after vitamin D supplementation compared to the other groups.	Cantarel et al.[26]
Alterations of the human gut microbiome in multiple sclerosis	n=103 (60 patients with RRMS and 43 controls)	Increased abundances of *Prevotella* and *Sutterella* in patients using a disease-modifying treatment and decreased *Sarcina*, compared with untreated patients.	Jangi et al.[27]
Associations between the gut microbiota and host immune markers in pediatric multiple sclerosis and controls	n=24 (15 pediatric patients with RRMS and nine controls).	There was no difference in immune markers (Th2, Th17, and Tregs) between patients and controls, although there were divergent gut microbiota associations. There was a positive correlation between richness and Th17 in patients. *Bacteroidetes* were inversely associated with Th17 in patients, and *Fusobacteria* correlated with Tregs in controls.	Tremlett et al.[28]
Immunological and Clinical Effect of Diet Modulation of the Gut Microbiome in Multiple Sclerosis Patients: A Pilot Study	n=20 (20 patients with RRMS with a follow-up of 12 months)	In the group with HV/LP diet compared to the western diet group, the *Lachnospiraceae* family was more abundant, IL-17-producing and PD-1-expressing T CD4+ lymphocytes were significantly decreased. The relapse rate in 12 months and the EDSS score were significantly reduced.	Saresella et al.[29]

Th2: T helper 2 cells; Th17: T helper 17 cells; Tregs: Regulatory T cells; RRMS: relapsing-remitting multiple sclerosis; MS: multiple sclerosis; HV/LP: high vegetable/low protein; EDSS: expanded disability status scale.

GUT MICROBIOME STRUCTURE AND FUNCTION: INTESTINAL AND SYSTEMIC IMPACT

The gastrointestinal (GI) tract is considered the organ that harbors the highest amount of commensal microorganisms, reaching 10^{13} bacteria/mL[2]. Bacteroidetes, Firmicutes, Actinobacteria, Verrumicrobia, Proteobacteria, and Fusobacteria have been identified as the core enterotypes at the phylum level, which consist of more than 1000 species[3]. These consortia tend to remain steady throughout adult life, but preclinical evidence in both animals and humans have revealed that pre- and post-natal colonization of the gut has specific signatures and interindividual variations (~20%), depending on critical events such as maternal conditions, perinatal infections, mode of delivery, breastfeeding, diet, antibiotic exposure, and host genetics[5,6].

Different approaches comparing germ-free mice and conventionally colonized controls demonstrated that the

Table 2. Summary of the main studies about gut microbiome in stroke.

Species	Diagnosis (n, age)/ Stroke model (n)	Biological sample	Methods	Main shifts in gut microbiota composition (genus/phylum)	References
Human	- 531 Finnish males - 45–70 years old - From the general population of the METabolic Syndrome In Men (METSIM) study	- Stool - Fasting blood samples	- 16S rRNA gene amplification - NMR spectroscopy - liquid chromatography with on-line tandem mass spectrometry (LC-MS/MS)	- ↑ Prevotella and Peptococcaceae were associated with ↑ plasmatic TMAO - ↑ Unclassified Clostridales was associated with ↑ plasmatic TMAO and ↑ glutamine levels - ↑ *Tenericutes* and *Christensenellaceae* were associated with ↑ acetate levels, ↑ HDL levels, ↓ BMI, and ↓ TG - ↑ *Christensenellaceae* associated with ↓ leucine and ↓ isoleucine - ↑ *Blautia* and *Dorea* were associated with high serum levels of glycerol, monounsaturated fatty acids, and saturated fatty acids - ↑ *Methanobacteriaceae* and *Coprococcus* was associated with lower levels of TGs	Org et al.[37]
Human	- 349 Dutch ischemic and hemorrhagic stroke patients, median age 71 years - Collected within 24 h of hospital admission - 51 Dutch outpatient age- and sex-matched non-stroke controls, median age 72 years	- Plasma protein biomarkers - Rectal swabs	- H-NMR spectroscopy - LC-MS - 16S rRNA amplicon sequencing	-↑ *Escherichia/Shigella, Peptoniphilus*, *Ezakiella*, and *Enterococcus* (potentially invasive aerobic bacterial genera) in patients with ischemic stroke and cerebral hemorrhage. - ↑ *Blautia, Subdoligranulum*, and *Bacteroides* in controls and patients with a TIA. - Stroke patients displayed a higher prevalence of TMA-producing bacteria and lower plasma levels of TMAO - Loss of butyrate-producing bacteria in stroke patients	Haak et al.[38]
Human	- 30 Chinese patients with cerebral ischemic stroke (21 males, nine females) - 30 healthy Chinese control (18 males, 12 females) - Mean age in CI was 60.47±10.57 vs. 64.17±12.67 in the control group	- Fecal samples - Blood levels of HDL, LDL, GLUC, UA, TG, and HCY	- Amplification of the V1-V2 region of the 16S rRNA gene	- ↑ Short-chain fatty acids producers such as *Odoribacter*, *Akkermansia*, *Ruminococcaceae_ UCG_005*, *norank_p_ Flavobacteriaceae*, *norank_p_ Parcubacteria*, and *Victivallis* in the CI group.	Li et al.[39]
Human	- 12 Swedish patients with symptomatic atherosclerotic plaques (who had undergone carotid endarterectomy for minor ischemic stroke, transient ischemic attack or amaurosis fugax) - 13 Swedish sex- and age-matched controls.	- Stool samples - Serum b-Carotene and lycopene	- Shotgun metagenomics.	- ↑ *Collinsella* was enriched in patients with symptomatic atherosclerosis - Genes encoding peptidoglycan synthesis were enriched in patients - Depletion of genes encoding phytoene dehydrogenase in patients - ↓ b-carotene (antioxidant) in patients	Karlsson et al.[41]
C57BL/6J and Rag1/ mice	- Two distinct models of acute MCA occlusion: fMCAo and fMCAo	- Mice feces	- 16S rRNA amplicon	- ↓ Species diversity and bacterial overgrowth of *bacteroidetes* were identified as hallmarks of poststroke dysbiosis - Dysbiotic microbiome induces: ↓ intestinal motility, intestinal barrier dysfunction, a pro-inflammatory T-cell polarization in the intestine, and ischemic brain - Therapeutic FMT improves stroke outcome	Singh et al.[42]

Continue...

Table 2. Continuation.

Species	Diagnosis (n, age)/ Stroke model (n)	Biological sample	Methods	Main shifts in gut microbiota composition (genus/phylum)	References
Human	- Chinese patients with large-artery atherosclerotic ischemic stroke and TIA (322 provided blood samples and 141 provided fecal samples). - Chinese asymptomatic controls (231 provided blood samples and 94 provided fecal samples). - 18 to 80 years	- Blood TMAO levels - Fresh fecal sample	- LC-MS - Pyrosequencing of 16S rRNA tags	- ↑ Opportunistic pathogens, such as *Enterobacter*, *Megasphaera*, *Oscillibacter*, and *Desulfovibrio* in stroke and transient ischemic attack group. - ↓ Commensal or beneficial genera including *Bacteroides, Prevotella, and Faecalibacterium* in patients group. - ↓ TMAO level in the stroke and transient ischemic attack patients	Yin et al.[45]
Human (males) and C57BL/6 mice	- Stroke cohort: 104 Chinese patients with acute ischemic stroke and 90 healthy Chinese individuals - Validation cohort: 83 Chinese patients and 70 healthy Chinese individuals - 18 to 80 years. - Experimental Stroke MCA occlusion (mice) - Stroke Dysbiosis Index (SDI) model	- Fecal samples	- 16S rRNA gene V4 region	- ↑ *Butyricimonas*, *Un Rikenellaceae*, *Un Ruminococcaceae*, *Oscillospira*, *Bilophila*, *Un Enterobacteriaceae* and *Parabacteroides* and ↓ *Fecalibacterium*, *Clostridiaceae*, and *Lachnospira* in patients with higher SDI - SDI was significantly higher in stroke patients than in healthy controls - A higher SDI increased the probability of unfavorable outcomes. - Mice that received FMT from high-SDI patients developed severe brain injury with elevated IL-17+ γδ T cells in the gut compared to mice receiving FMT from low-SDI patients	Xia et al.[46]

TMA: trimethylamine; TMAO: trimethylamine N-oxide; BMI: body mass index; TG: triglycerides; HDL: high-density lipoprotein; MCA: middle cerebral artery; fMCAo: post-filament MCA occlusion model; cMCAo: permanent distal MCA occlusion model; FMT: fecal microbiota transplantation; TIA: transient ischemic attack; H-NMR: proton nuclear magnetic resonance. Un: unclassified. SDI: Stroke Dysbiosis Index. CI: cerebral ischemic stroke. HDL: high-density lipoprotein; LDL: low-density lipoprotein; GLU: blood glucose; UA: uric acid; TG: triglycerides; HCY: homocysteine.

Table 3. Summary of main studies about gut microbiome and dementias.

Species	Diagnosis (n, age)	Intervention	Biological Sample	Methods	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
Human	- 25 American AD patients and 88 asymptomatic control group. - Age- and sex-matched (mean ±70.3)	NA	- Fecal samples - CSF biomarkers included Aβ42/Aβ40, phosphorylated tau (p-tau), the ratio of p-tau/ Aβ42, and chitinase-3-like protein 1 (YKL-40)	- 16S rRNA sequencing (V4)	- Decreased richness and diversity in the AD group - ↑ In the phylum Bacteroidetes and Bacteroides at genus level in the AD group - ↓ Actinobacteria phylum and Bifidobacterium genus in the AD group. - Significant associations between CSF biomarker YKL-40 and abundance of *Bacteroides*, *Turicibacter*, and *SMB53* (family *Clostridiaceae*) in the AD group	Vogt et al.[52]
Human	- 97 Chinese subjects: 33 AD, 32 aMCI, and 32 HC - Aged 50 to 85 years	NA	- Fecal samples	16S rRNA Miseq sequencing (V3-V4 region)	- ↓ Microbial diversity in the AD group - *Proteobacteria* was highly enriched in the AD group - The models based on the abundance of family *Enterobacteriaceae* could distinguish AD from both aMCI (AUC=0.688) and HC (AUC=0.698)	Liu et al.[53]

Continue...

Table 3. Continuation.

Species	Diagnosis (n, age)	Intervention	Biological Sample	Methods	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
Human	- 17 American participants (11 had mild cognitive impairment and 6 were cognitively normal) - Age: 64.6±6.4 years	- MMKD versus for 6-weeks separated by 6-weeks washout periods	- Fecal samples - Short-chain fatty acids (SCFAs), Aβ-40, Aß-42, total tau, and Tau-p181 before and after diet interventions	- 16S rRNA gene sequencing (V4 region) - HPLC	- ↑ Abundance of Proteobacteria in MCI group - At the family level MCI group had ↑ abundance of *Enterobacteriaceae* and *Mogibacteriaceae* - ↑ Abundance of genera *Phascolarctobacterium* and *Coprococcus* in MCI group. - Proteobacteria correlate positively with the Aβ-42/Aβ-40 ratio in the MCI group - ↑ Abundance of *Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae,* and *Erysipelotriaceae* on MMKD - MMKD slightly reduces fecal lactate and acetate while increasing propionate and butyrate	Nagpal et al.[56]

AD: Alzheimer's disease; aMCI: amnestic mild cognitive impairment; MCI: mild cognitive impairment; HC: healthy controls, CN: cognitively normal; AUC: area under the ROC curve; CSF: cerebrospinal fluid; YKL-40: chitinase-3-like protein 1; MMKD: Mediterranean-ketogenic diet; AHAD: American Heart Association Diet; SCFAs: Short-chain fatty acids; Aβ: Amyloid β; Tau-p181: phosphorylated tau 181; HPLC: high-performance liquid chromatography; NA: not applicable.

Table 4. Summary of the main studies about gut microbiome in epilepsy.

Species	Diagnosis (n, age)/ Epilepsy model (n)	Intervention	Biological Sample	Methods	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
Swiss Webster mice	- 6-Hz-induced seizure model of refractory epilepsy - Kcna1 $^{-/-}$ mouse model for TLE and SUDEP - 3–4-week-old male and female mice	KD for 14 days	- Fecal and blood samples - FMT	- 16S rDNA profiling - Metabolomics - Bacterial FISH	-↑ Relative abundance of *Akkermansia muciniphila* and *Parabacteroides* - ↑ GABA/glutamate in the hippocampus - ↓ γ-glutamylated amino acids in both colonic lumenal content and sera	Olson et al.[61]
Human	- 12 Swedish children with drug-resistant epilepsy, 3 to 15 years old - 11 healthy Swedish controls (patients' parents)	- Classic KD for three months	- Blood levels of glucose and β-hydroxybutyric acid - Fecal samples	Shotgun metagenomic	- ↓ *Bifidobacterial*, *Actinobacteria*, *E. rectale* and *Dialister* - ↑ Relative abundance of *E. coli*	Lindefeldt et al.[62]
Human	- 20 Chinese patients with refractory epilepsy - 14 males, six females - Median age 4.2 years	- Classic KD for six months	- Fecal samples - Blood glucose and ketones levels	- V3 and V4 amplification of the 16S rRNA gene	- Overall, KD reduced gut biodiversity - ↓ Abundance of Firmicutes and Actinobacteria and ↑ Bacteroides - *Clostridiales, Ruminococcaceae, Rikenellaceae, Lachnospiraceae,* and *Alistipes* were enriched in the refractory group	Zhang et al.[63]
Human	- 14 Chinese children with refractory epilepsy-30 age-matched healthy infants	- Classic KD for one week	- Fecal samples	16S rRNA sequencing	- 64% of epileptic infants improved (50% decrease in seizure frequency) - ↑ *Bacteroides, Prevotella,* and *Bifidobacterium* after treatment. - ↓ *Proteobacteria* after KD	Xie et al.[64]
Human	- 8 Korean children with refractory epilepsy aged 1 to 7 years - 32 age-matched healthy controls	NA	-Fecal samples	- 16S rRNA gene (V3-V4) sequencing	- ↓ *Bacteroidetes, Proteobacteria* and ↑ *Actinobacteria* in epileptic group - ↓ Microbial richness in epileptic patients. - Biomarkers for refractory epilepsy were: *Enterococcus faecium, Bifidobacterium longum,* and *Eggerthella lenta*	Lee et al.[66]

Continue...

Table 4. Continuation.

Species	Diagnosis (n, age)/ Epilepsy model (n)	Intervention	Biological Sample	Methods	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
Human	- 30 Turkey patients with idiopathic focal epilepsy (16 men, 14 women, mean age of 41.3 years) - 10 healthy controls (mean age 31.7)	NA	- Fresh stool samples	- 16s rDNA (V3-V4) sequencing	-↑*Proteobacteria* in patients - ↑*Campylobacter, Delftia, Haemophilus, Lautropia, Neisseria* in IFE group	Şafak et al.[67]
Human	- Chinese patients (males and females) with epilepsy - Drug-resistant (n=42) - Drug-sensitive (n=49) - 65 healthy controls - 5 to 50 years old	NA	- Fecal samples	- V3-V4 amplification of the 16S rRNA gene	- ↑ Abundance of *Verrucomicrobia* and rare microbiota in patients with DRE - ↑ *Bifidobacteria* and *Lactobacillus* in patients with ≤4 seizures per year	Peng et al.[68]
Human	- Chinese participants. - Exploration cohort: 55 patients and 46 controls - Validation cohort 13 patients and ten controls - Ages ranged from 15 to 60 years - Create a model to distinguish DRE from DSE	NA	- Fecal samples	- 16S rRNA (V3-V4) sequencing	- ↓ Alfa diversity in patients - At the phylum level, patients had: ↑ *Actinobacteria* and *Verrucomicrobia*, and ↓ *Proteobacteria* - At the genus level, patients demonstrated: ↑ *Prevotella_9*, *Blautia*, and *Bifidobacterium* - The phylum *Cyanobacteria* and genus *Parabacteroides* were depleted in the DRE group - Fecal microbiota could serve as a potential biomarker for disease diagnosis	Gong et al.[69]
Human	- Pilot study - 45 patients with DRE - Mean age 44 years	A mixture of 8 bacterial species (probiotics) daily for four months	Levels of cD-14, interleukin 6, and γ-aminobutyric acid were analyzed	NA	28.9% of all patients displayed a greater than 50% reduction in the number of seizures	Gómez-Eguílaz et al.[70]
Human	- 6 Dutch patients with DRE - 10–16 years old	- Antibiotics exposure	NA	NA	- Patients without seizures (short-term) during antibiotic treatment	Braakman and van Ingen[71]

TLE: temporal lobe epilepsy; SUDEP: sudden unexpected death in epilepsy; FISH: Bacterial Fluorescence *In Situ* Hybridization; KD: ketogenic diet; DRE: drug-resistant epilepsy; FMT: fecal microbiota transplantation; DRE: drug-resistant epilepsy; DSE: drug-sensitive epilepsy; IFE: idiopathic focal epilepsy NA: not applicable.

Table 5. Summary of the main studies about gut microbiome in Parkinson's disease.

Species	Diagnosis (n, age)	Intervention	Biological Sample	Methodology	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
Human	- 55 Finnish patients with PD (mean age 67.63±5.21 years) - 56 controls (mean age 66.38±6.73 years)	NA	- Fecal and plasma samples	- V3-V4 regions of the 16S rRNA gene - Gas chromatograph	- ↑ Calprotectin and ↓ SCFAs in the stool of participants with PD (sex-dependent manner) - Fecal zonulin correlated positively with fecal NGAL - Butyric acid levels were higher in PD patients with the *Prevotella* enterotype	Aho et al.[74]
Human	- 64 Finnish patients with Parkinson's (mean age 65.2±5.52) - 64 Finnish control individuals (mean age 64.45±6.9)	NA	- Fecal samples	16S rRNA gene sequencing (V3-V4 region)	- Progressed PD patients had a Firmicutes-dominated enterotype more often than stable patients or control subjects - ↓ Abundance of *Prevotella* in faster-progressing PD patients	Aho et al.[75]

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Table 5. Continuation.

Species	Diagnosis (n, age)	Intervention	Biological Sample	Methodology	Main shifts in gut microbiota composition (genus/phylum)/ Outcome	Reference
	- Samples were collected twice, on average 2.5 years apart					
Human	- 51 Chinese PD patients (mean age 62.4±8.2 years) - 48 age-matched, healthy controls (mean age 62.2±9.2 years)	NA	- Fecal samples	- 16S-rRNA gene sequencing (V4 region)	- PD patients showed decreased species richness, phylogenetic diversity, β-diversity, and altered relative abundance in several taxa - ↑ *Akkermansia* and ↓ *Lactobacillus* in PD patients	Li et al.[76]
Human	- 72 Finnish PD patients (mean age 65.3±5.5) - 72 control subjects (mean age 64.5±6.9)	NA	- Fecal samples	- 16S rRNA gene Pyrosequencing (V1–V3 regions)	- ↓ Abundance of *Prevotellaceae* in feces of PD patients (by 77.6% as compared with controls) - The relative abundance of *Enterobacteriaceae* was positively associated with the severity of postural instability and gait difficulty	Scheperjans et al.[77]

PD: Parkinson's disease; SCFAs: short-chain fatty acids; NGAL: neutrophil gelatinase-associated lipocalin; NA: not applicable.

abnormal composition of the gut microbiota led to functional and structural changes in the gastrointestinal tract. A variety of morphological defects on mucosa-associated lymphoid tissue and intestinal microvasculature, including reducing the number of Paneth cells, Peyer's patches, and villi size, were already described in mice models[10]. Similarly, the loss of microbial diversity can negatively affect the expression of genes related to nutrient absorption, mucosal cellularity, and barrier fortification[11]. *In vitro* and *in vivo* studies have examined the importance of Toll-like receptors (TLRs) present on the surface of intestinal epithelial cells and immune T cells[12]. The signaling transmission mediated by TLRs can also modulate mechanisms encompassing the host's tolerance to commensal bacteria and the inhibition of pro-inflammatory cytokines such as the tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1B (IL-1B)[13]. These findings have been classically associated with several GI disorders, including inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC), as well as irritable bowel syndrome (IBS), functional dyspepsia (FD), and colorectal cancer (CRC)[14,15]. Besides, observational studies have indicated that the loss of beneficial microorganisms affects ecological interactions among local populations and drive systemic diseases. Some of the metabolic processes that are impaired in patients with obesity, diabetes mellitus, and non-alcoholic fatty liver disease are associated with the synthesis of vitamins, xenobiotic transformation, and bacteria-derived molecules production, including secondary bile acids and short-chain fatty acids (SCFA) production[16,17].

INTESTINAL MICROBIOTA AFFECTS BRAIN FUNCTION AND HAS IMMUNOMODULATORY PROPERTIES

The human gut contains its own neural system, consisting of more than one hundred million neuron cells (10^8)[18]. Crosstalk between the central nervous system (CNS) and the gut microbiome is known as the gut microbiota-brain axis, and it is orchestrated at different anatomical levels. It occurs through an intricate network of afferent and efferent circuits alongside the vagus nerve, enteric nervous system, and hypothalamic-pituitary-adrenal axis. Thus, the gut connectome integrates neuroendocrine, enteroendocrine, neuroimmune, and metabolic signaling pathways responsible for regulating functions associated with digestion, tract motility, and brain development. Furthermore, gut microbes can control host responses to vascular injury and autoimmunity by modifications in both the blood-brain barrier (BBB) and brain lymphatic system[7,15].

Additionally, evidence from intervention studies in germ-free mice, where a diverse microbiota is absent, has also shown the great potential that microorganisms have in regulating microglia differentiation and maturation. Other features commonly displayed in gnotobiotic models are the abnormal expression of proteins related to synaptic plasticity, such as the brain-derived neurotrophic factor and the impairment in global cognition responses. For instance, in a study carried out by Möhle et al., the authors pointed out that adult hippocampal neurogenesis and global cognition responses can be restored after oral supplementation with probiotics via expansion of Ly6C+ monocytes[19,20]. Notably, it

has been reported that microbial metabolites such as SCFAs, secondary bile acids, precursors of the lipid biosynthesis (propionate), and specific amino acids (tryptophan) are critical in modulating the release of host cytokines and hormones such as peptide YY, vasoactive intestinal peptide, glucagon-like peptide-1 (GLP-1), and melatonin, as well as neurotransmitters such as serotonin (5-HT), catecholamines, and gamma-aminobutyric acid (GABA). All of these affect brain functions related to feeding, stress response, emotional behaviors, aging, and cognition[17,21]. Furthermore, intestinal dysbiosis appears to be linked to the development of brain autoimmunity driven by specific T cell subtypes, pro-inflammatory cytokines, endothelial barrier impairment, and neurodegeneration[7,22]. The next section will explore some of the neuropsychiatric disorders thought to be influenced by microbiome disturbances.

MULTIPLE SCLEROSIS

Previous studies have linked T helper 17 cells (Th17) to MS pathogenesis through its effect in exacerbating experimental autoimmune encephalomyelitis (EAE). Regulatory T cells (Treg) have an essential role in suppressing inflammation in the CNS in EAE models[22,23]. Cekanaviciute et al. have identified increased EAE disease scores and deficient IL-10+ Treg induction in mice colonized with microbiota from patients with MS[24]. Furthermore, some butyrate-producing bacteria, mainly belonging to the Firmicutes phylum, have also been implicated in the pathogenesis of MS. Butyrate is known to inhibit pro-inflammatory pathways and prevent systemic exposure to intestinal antigens[25]. Bacteria, such as *Faecalibacterium* from the Firmicutes phylum, were found to be reduced in MS patients[26].

In a study of adult patients, Jangi et al. found a higher abundance of *Methanobrevibacter* and *Akkermansia* with a lower prevalence of *Prevotella*, *Butyricimonas*, *Colinsella*, and *Slackia* in patients with MS compared to healthy controls. Combining microbiome results with the immunogenetics characteristics of patients with MS, they found a positive correlation between *Methanobrevibacter* and *Akkermansia* and a negative correlation of *Butyricimonas* with *MAPK14*, *MAPK1*, *LTBR*, *STAT5B*, *CASP1*, and HLA-DRB1 — genes associated with potentiation of the immune response in MS[27].

Tremlett et al. studied the microbiome in pediatric MS. A phylum-level analysis found a negative association between Bacteroidetes and CD4+ T cells and Tregs and a positive association between Actinobacteria and CD4+ T cells and Tr1 (IL-10), which represent some of the most common bacterial phyla of the human microbiota. The evenness of the gut microbiome also had a strong and negative association with Th17 and T helper 2 (Th2) response in the control group[28].

More recently, the interaction between microbiome and diet in MS has attracted attention. A study found an association between a lower number of relapses and a lower disability status scale after one year of a high vegetable/low protein diet (HV/LP diet) when compared with a classical Western diet characterized by regular consumption of red meat, processed meat, refined grains, sweetened food, salt, and saturated and omega-6 fatty acids. The HV/LP group had higher levels of bacteria from the *Lachnospiraceae* genus, and they were positively related to Treg cells[29]. Table 1 summarizes the most relevant microbiome findings in patients with MS.

AUTOIMMUNE ENCEPHALITIS

Immuno-mediated encephalitis is an emergent group of syndromes characterized by the development of acute or subacute progressive encephalopathy (less than three months onset) that occurs due to an abnormal antibody response against cell-surface, intracellular synaptic, or intraneuronal (nuclear or cytoplasmic) antigens[30,31].

Most of what is known about the impact of intestinal dysbiosis in patients with autoimmune encephalitis (AE) comes from studies conducted in rodents. It has been suggested that changes in the intestinal microbiota could increase the susceptibility to AE through different mechanisms. Thus, increases in abundance and richness of specific pathobionts can provoke pro-inflammatory T cell cross-reactivity due to molecular similarities with neural proteins[22]. Microbiome products of diet fermentation such as the SCFAs have a major impact on gene expression of transcription factors via epigenetic mechanisms. Indeed, in a case-control study conducted by Gong et al., fecal samples were examined in 30 patients at different phases of anti- N-methyl-D-aspartate receptor (NMDAR) encephalitis. Patients in the acute phase had low Firmicutes to Bacteroidetes (F/B) ratios than the control group[32]. These results support the theory that an imbalance in commensal microbes negatively impacts the production of SCFAs. Also, main SCFAs such as acetate (C2), propionate (C3), and butyrate (C4) can alter a variety of cellular mechanisms involving the activity of G-protein coupled receptors (GPRs), the inhibition of histones deacetylases (HDACs), and nuclear factor-jB (NF-jB), and the biosynthesis of retinoic acid, which are all essential in maintaining Treg differentiation and hence reducing neuroinflammation[33,34].

Enrichment of the genus *Fusobacterium* was also reported in the anti-NMDAR AE. Fusobacteria species comprise gram-negative anaerobic bacilli, which are considered normal microbiota in oral cavity, GI, and urogenital tract. However, recent studies report that *F. nucleatum* can present pathogenic properties that have been implicated in oral and extraoral diseases, including neurological disorders[32]. It is believed that adhesion and invasion via hematogenous translocation are the primary strategies used by *F. nucleatum* to activate inflammatory and oncogenic genes, thus contributing to disease development and progression[35].

MICROBIOME AND STROKE

Studies have shown that up to 50% of patients with stroke suffer from GI complications, which has a strong association with patient recovery, deterioration of neurological functions, and mortality[36]. These features regarding stroke make it an interesting condition to look for associations between brain and gut microbiota. Indeed, several studies have shown a link between stroke outcomes and microbiota regulation of the immune system and metabolism[37-39] (Table 2).

The bidirectional communication between the brain and gut after stroke involves the vagus nerve, release of damage-associated molecular patterns (DAMPs), cytokines from the injury site of the brain and gut, and migration of inflammatory or immune cells from the gut to the injury site[40]. This communication occurs by complex signaling pathways from the vagus nerve to the enteric nervous system, the neuronal-glial-endothelial interactions, and DAMPs and cytokines-induced activation of gut inflammatory and immune cells[40].

Several studies show significant changes in the microbial diversity in fecal samples of patients after an ischemic stroke, leading to gut alterations including dysbiosis, dysmotility, hemorrhage, and sepsis[40,41]. Furthermore, Singh et al. showed a reduction in microbiota diversity after stroke events that might be associated with stress response, impaired motility, and tissue necrosis[42]. These changes may cause gut permeability modifications and the increase of circulating lipopolysaccharides (LPS) molecules, which may influence systemic inflammation and immune response after stroke.

Circulating IL-17 released by γδ T cells and IL-10 released by regulatory T cells (Tregs) were associated with increased ischemic brain injury and neuroprotective properties, respectively, after ischemic brain injury[43]. There is some evidence that these inflammatory molecules are regulated by gut microbiota, promoting a strong interrelation between brain and gut and influencing several neurological diseases[40,43]. After a stroke, dysbiosis leads to an imbalance of T-cell subpopulations (Th1, Th2, Th9, Th17, Treg, and follicular T helper cells) that trigger several types of autoimmune and inflammatory disease[40]. For example, Th1 (production of IL-2 and interferon-gamma) and Th2 (IL-4, IL-5, and IL-13) induce inflammation; Th9 (IL-9 and TGF-β) and Treg (IL-10 and IL-35) have a neuroprotective function; Th17 activates matrix metalloproteinases and causes blood-brain barrier breakdown by secreting IL-17A, IL17-F, and IL-22[40]. Benakis et al. demonstrated that antibiotic-treatment-induced dysbiosis could influence stroke outcome in *vivo* models by regulating T cells in the small intestine[43]. Some studies also observed improved stroke outcomes by fecal microbiota transplantation to control post-stroke dysbiosis[43]. Most interestingly, treatments involving reduction of *Clostridiaceae* and *S24-7 spp.* showed to be relevant to neuroprotection after stroke in mice[43].

Zeng et al. recently raised the possibility that the microbiome might be a novel risk factor for stroke[44]. With a risk stratification approach and comparing higher- versus lower-risk patients, they found an increased risk of stroke associated with enrichment of opportunistic pathogens (e.g., *Proteobacteria*, *Bacilli*, *Enterobacteriaceae*), low abundance of butyrate-producing bacteria (e.g., *Lachnospiraceae, Ruminococcaceae*), and reduced concentrations of fecal butyrate[44,45].

Xia et al. developed a stroke dysbiosis index (SDI) based on the patient's gut taxonomic differences compared to healthy individuals[46]. They observed that high SDI values predicted severe brain injury in patients with stroke. Furthermore, to investigate a putative causal effect of intestinal dysbiosis, the authors performed experiments using a middle cerebral artery occlusion model in animals colonized with microbiota from affected individuals. They observed that mice transplanted with intestinal microbiota from high-SDI patients also developed an exacerbated inflammatory response, hence, worsening the acute brain injury associated with stroke[46].

Although the results are encouraging, as described above, additional studies with larger samples and different ethnic backgrounds are needed to validate these findings. However, if further confirmed, a careful approach, including microbiome screening as a possible preventive target for stroke management is needed.

GUT MICROBIOTA: THE RELATIONSHIP WITH DEMENTIA

Studies in germ-free animals exposed to microbial infections, human post-mortem brain samples, and microbiome analysis of living humans have revealed that disorder of the gut microbiota may underlie the development or exacerbation of Alzheimer's disease (AD) pathology[47]. Also, available data suggest that the gut microbiota in AD is characterized by a substantial reduction in beneficial microbial diversity and presence of pathogenic species such as Proteobacteria phylum, especially the *Enterobacteriaceae* family[48]. These shifts in microbial diversity may activate immune cells and stimulate overproduction of toxic metabolites or pro-inflammatory cytokines, which contribute to the destruction of the GI mucosa. It is well known that chronic inflammation and immune dysregulation precede cognitive decline by years[49]. Increased inflammation makes gut microorganisms move from the GI tract through cells overlying the Peyer's patches into blood and other tissues (a process known as atopobiosis)[47]. Likewise, systemic inflammation can increase BBB permeability, exposing the brain to cytokines that can lead to neuroinflammation and neuronal cell death, promoting neurodegenerative diseases[48,50]. Initially, the brain can resist, but the regenerative capacity, together with the microglia's ability to clear toxic metabolites, decreases with time[49].

The outer membrane component of Gram-negative bacteria is LPS, capable of triggering systemic inflammation by increasing

pro-inflammatory cytokines[48,51]. Lipopolysaccharides may also modify gut homeostasis and promote gut inflammation and permeability. The abundance of Gram-negative intestinal bacteria, such as the *Enterobacteriaceae* family in individuals with AD, results in increased translocation of LPS from the gut into the circulation, which in turn may contribute to AD pathology[52]. Indeed, a study involving post-mortem brain tissue from patients with AD showed that LPS fragments co-localized with amyloid plaques in the hippocampus and neocortex[53].

Surprisingly, bacteria can produce their own amyloid, which maintains cellular junctions, promotes the formation of biofilms, and confers resistance against physical or immune destruction[47]. Microbial and cerebral amyloids are structurally similar and can be recognized by the same TLR2/TLR1 receptor system[50]. They might activate signaling pathways known to play a role in neurodegeneration and AD pathogenesis[50,51]. The hypothesized mechanism is that bacteria-derived amyloids leak from the GI tract and accumulate in the brain, resulting in an increase of reactive oxygen species and activation of nuclear factor-κB, which upregulates the pro-inflammatory microRNA-34a[51]. Subsequently, microRNA-34a downregulates the expression of TREM2 (triggering receptor expressed on myeloid cells 2), leading to impairment of phagocytosis and contributing to the peptide accumulation β-amyloid1-42[51]. Both amyloids and LPS are potent activators of the receptor for advanced glycation end-products (RAGE) and Toll-like receptors (TLR), and their co-activation amplifies pro-inflammatory signaling leading to sustained chronic inflammation in AD[50,51].

Commensal microbiota produces an assortment of neuroactive molecules, such as serotonin, kynurenine, GABA, catecholamines, histamine, and acetylcholine, among others[50]. The consequence of a dysbiotic bowel in the metabolism of tryptophan and kynurenic pathways is documented in AD[50]. Gut microbes may regulate the serotonergic system directly by producing serotonin or degrading the serotonin precursor, tryptophan[49]. *Escherichia coli*, an Enterobacteriaceae member, plays an essential role in regulating production and availability of serotonin, acting as a transmitter both in the CNS and in the enteric nervous system[51]. Nevertheless, gut-derived serotonin only exerts indirect effects on brain functions. Despite that, the gut is the only source of tryptophan, derived either from the diet or microbial production. Tryptophan crosses the BBB to become available for serotonin synthesis in the brain[49]. Gulaj et al. found reduced plasma concentration of tryptophan and kynurenic acid in 34 patients with AD, suggesting that dysregulation of the kynurenine route is present in AD[54].

Lactobacillus and *Bifidobacterial* genera can metabolize glutamate to produce GABA. Changes in gut microbiota might compromise the endogenous production of this inhibitory neurotransmitter[51]. Alterations in GABA signaling are linked to cognitive impairment and AD neuropathy[49]. Likewise, *Lactobacillus, Lactococcus, Streptococcus*, and *Enterococcus* may produce histamine, which acts as a neurotransmitter essential for modulating neuroinflammation through TNF-α expression in the brain[55]. Furthermore, an N-methyl-D-aspartate (NMDA)-targeting neurotoxin that was observed to be raised in AD brains may be produced by gut cyanobacteria[49].

The role of diet in these mechanisms is still poorly understood but probably extremely important[47]. Dietary patterns similar to the Mediterranean diet and Dietary Approaches to Stop Hypertension have been associated with a reduced risk of AD[56]. In contrast, a Western-style diet represents a risk factor. The variety and composition of a diet and long-term dietary habits may influence the gut microbiota composition and shape the microbial community[51]. A newly proposed insight is that the transplantation of fecal microflora from healthy people to patients with AD can help restore the intestinal microbiota and reduce the negative impact of the dysbiotic microbiome on the gut and brain functions[47]. The influence of gut microbiota on brain function is being investigated continuously. Table 3 presents additional studies on the role of gut microbiota and dementia.

EPILEPSY, KETOGENIC DIET, AND THE INTESTINAL MICROBIOME

About one-third of patients with epilepsy have seizures refractory to anti-seizure drugs (ASD)[57]. Non-pharmacological approaches, especially the ketogenic diet (KD), are alternatives in cases of pharmacoresistant epilepsy. The KD has been used for about one hundred years, demonstrating efficacy in reducing seizure frequency, mostly in children with difficult-to-control epilepsy[58].

The KD appears to be a powerful contributor in modulating downstream effects on an individual's gut metagenomic composition and metabolomic profile[59]. In a dietary intervention study conducted by Ang et al., two cohorts composed of obese patients and mice were followed up during short- and long-term periods. In humans, a baseline diet and a KD with only 5% of carbohydrates content were used. Mice were submitted to three different diet types: low-fat diet (LFD), high-fat diet (HFD), and KD. Results from a 16S amplicon-based metagenomic approach of stool samples and metabolomic profile in humans demonstrated a significant reduction in the relative abundance of Actinobacteria phylum and a marked decrease in different bifidobacterial species, suggesting that the KD is sufficient to shift the gut microbiota composition. Similar findings were seen in a mice model, where ketone bodies like βHB had a direct effect in suppressing microbial proliferation of bifidobacteria. Moreover, fecal microbial transplantation from patients into germ-free mice demonstrated that the colonization of KD-associated microorganisms drove the reduction of selected members of *Bifidobacterium adolescentis*, therefore modulating the induction of Th17 cells.

These findings reveal a separate pathway whereby carbohydrate restriction, rather than high-fat intake, is the main contributor to gut microbiome structure and immune response[60].

Olson et al. demonstrated that the taxonomic composition of the gut microbiome in mice is altered after treatment with KD. They also raised the possibility that some KD-associated species such as *Akkermansia muciniphila* and *Parabacteroides merdae* and particular molecules predicted seizure protection with high accuracy and were necessary to reduce brain electrical activity[61]. Taken together, these findings are likely to be correlated with a decrease in the metabolism of ketogenic gamma-glutamylated (GG) amino acids and, therefore, to low concentrations of these amino acids in the colon, blood, and CNS. Likewise, this phenomenon can boost GABA bioavailability on the hippocampus, increasing seizure threshold in mice and contributing to the anti-seizure effect. Finally, based on these bacterial species and molecules, researchers could identify microbiome-based treatments such as microbiome transplant, live biotherapeutic products, and targeted pharmacological approaches that protect against seizures in mice[61].

To further examine the potential of KD in shaping the intestinal microbiome in patients with epilepsy, Lindefeldt et al. analyzed the taxonomic and functional profile in children with difficult-to-control epilepsy using whole metagenomic sequencing[62]. The study consistently showed that i) there were differences in the composition of the patient's gut regarding healthy controls before starting the intervention; ii) those differences were reflected in the reduction of relative abundances of butyrate-producing organisms such as *Eubacterium rectale* and *Dialister* during and after treatment with KD where variations were more noticeable; iii) KD decreased *Bifidobacterium* and *Dialister* had an impact not only on the production of non-digestible carbohydrates (e.g., lactate) but also on the final conversion to SCFAs (mainly acetate), which are crucial in brain physiology; finally, iv) shifts on gut microbiome associated with KD promoted the growth of *Escherichia coli*, which could trigger gut inflammation in epileptic patients[62]. These results are in line with a study carried out by Zhang et al., who explored the potential of microbial biomarkers in patients with refractory epilepsy who followed a KD for six months[63]. Overall, they observed low diversity and richness ratios in individuals undergoing a KD as well as an increase in the relative abundance of Bacteroidetes and reduction of Firmicutes and Actinobacteria phyla. They also reported a high abundance of *Clostridia* class organisms in non-responders. This class has been associated with tryptophan catabolites, which in turn are responsible for hormone secretion, neurotransmission, gut motility and permeability, and anti-oxidative effects[63]. Another work involving epilepsy and KD had a similar outcome and reported significant gut dysbiosis in the refractory group. Nonetheless, the enterotype Bacteroidetes was accumulated in both the healthy and epileptic groups after at least one week of high-fat diet therapy. This phylum has been related to seizure modulation by secretion of inflammatory cytokines, including IL6 and IL17. Also, *Cronobacter* was the predominant genus identified only in affected children, which decreased over the treatment period[64].

It has been observed that patients with epilepsy are presumably prone to gut dysbiosis and, hence, to chronic inflammation of the intestinal epithelium[65-67]. In a cohort of 91 individuals, Peng et al. revealed that patients with more than four seizures per year had a predominance of *Ruminococcus* and rare bacteria genera compared to a drug-sensitive group. These findings lead to various hypotheses: i) the use of several antiepileptic drugs (AED) induces intestinal dysbiosis; ii) the prevalence of rare microorganisms modulate metabolic pathways involving ABC transporters, therefore conferring chemoresistance to the treatment; iii) *Bifidobacterial* and *Lactobacilli* genera stimulate the production of GABA and are prevalent in the drug-sensitive group[68].

So far, all of the studies involving different epilepsy phenotypes either in humans or mice report changes in the intestinal microbiome at baseline or after a KD[69]. Still, there is little overlap across these studies in the exact microbial signatures that have been identified (Table 4). Thus, additional high-powered and well-controlled studies are needed to explore the issue better and propose new treatment options[70,71].

PARKINSON'S DISEASE AND MICROBIOME

It is well known that patients with Parkinson's disease (PD) present severe non-motor symptoms at the prodromal phase of the disease, which are determinants of the quality of life in these individuals. Sensorial, neuropsychiatric, sleep dysfunction, and GI symptoms (constipation) are the most common phenotypes describe in this category[72]. Several studies using breath testing demonstrated that a considerable proportion of patients with PD have intestinal bacterial overgrowth and absorption issues, leading to intestinal constipation. On the other hand, 16S ribosomal RNA analysis from colonic biopsies and stool samples of adults with PD showed decreased SCFAs-producing bacteria such as *Blautia*, *Coprococcus*, and *Roseburia*[73,74]. Furthermore, depletion or increase in *Prevotella* and *Lactobacillus* genera was reported in several case-control studies performed in these patients[75,76]. This class of beneficial microorganisms is involved in BBB integrity, permeability, and neuronal inflammatory signaling[73]. Moreover, the increase in *Enterobacteriaceae* members was directly proportional to the severity of symptoms like stability, gait, and rigidity[77]. Conversely, in a study conducted in individuals with PD, the oral microbiome was analyzed. Male patients exhibited an increase in the abundance of *Prevotella*, which is considered an opportunistic pathobiont on the mouth, suggesting a strong role of these genera in periodontal disease[78]. Taken together, these findings support that modifications in bacteria density, taxonomic levels (dysbiosis), and mucin production may, in turn, boost the neuroglia system, triggering damage to the intestinal and brain barriers, leading to alpha-synuclein

protein misfolding and finally aggregation. Likewise, chronic systemic exposure to LPS leads to the selective death of dopaminergic neurons in the substantia nigra[73,79,80].

The vagus nerve (VN) has also been implicated in the pathogenesis of PD. Some researchers suggest that the VN can modulate neuroimmune and inflammatory signals either via top-down or through the microbiota-gut axis[79]. Thus, it has been proposed that the VN could transport alpha-synuclein to the CNS and vice versa. After examining 9,430 vagotomies in Swedish patients, Liu et al. demonstrated that truncal, but not selective vagotomy, had a protective effect against PD development[80]. In contrast, recent studies in mouse models mimicking motor and non-motor symptoms of early and late stages of the disease point out that changes in the immune response to gut bacteria could affect motor symptoms in PD[81]. In an experimental study performed by Sangjune et al., the authors demonstrated that pathologic species of a-synuclein could spread from the gut muscles to the brain through connections of the vagus nerve. These mice also showed neuropsychiatric symptoms, including anxiety, depression, olfactory dysfunction, and spatial learning and memory abnormalities. They also assessed another group of animals that were submitted to an injection of a-synuclein and vagotomy. The authors observed that no transmission of pathologic α-synuclein occurred in these animals, which were also free of the cardinal symptoms of PD[82].

Several studies have been published exploring the gut microbiome in PD (Table 5). However, the need for well-designed clinical studies exploring the role of the gut microbiome in PD in the clinical setting is still lacking.

Gut microbiota alterations in neuropsychiatric diseases

Autism Spectrum Disorder

Clinical observations indicate that patients with Autism Spectrum Disorder (ASD) have GI disturbances that include diarrhea, constipation, and abdominal pain[83]. Likewise, a growing number of studies have shown that patients with ASD have an altered gut microbiota composition compared to neurotypical individuals[84]. Moreover, GI disturbances strongly correlate with the severity of ASD symptoms, and GI disturbances are markedly associated with GI dysbiosis[83,84]. Therefore, it has been suggested that gut microbiota alterations may contribute to the pathogenesis of ASD(69). Although several studies have shown that adult rodents prenatally exposed to VPA, a model for ASD, exhibit gut dysbiosis[85,86], there is a lack of evidence of a causal link between abnormal microbiota and ASD-like behaviors.

Schizophrenia

Patients with schizophrenia commonly have GI disturbances, such as constipation and GI hypomotility and inflammation[87,88]. A growing body of evidence indicates that altered gut microbiota may account for the GI disturbances and the severity of symptoms in schizophrenia patients suggesting a key role of the gut microbiota in promoting the pathogenesis of schizophrenia. Interestingly, this suggestion has been recently proved by Zheng and colleagues. In this study, the authors found that the gut microbiota from patients with schizophrenia induced behavioral alterations and modulated brain excitability when transferred to mice[89]. Other studies have also suggested that GI disturbances and gut microbiota alterations in schizophrenia may be related to the use of antipsychotic medication[90]. However, gut microbiota seems to be altered in patients even before medication[91]. Hence, to better understand the gut microbiota alterations in schizophrenia, experimental validation of clinical findings seems necessary. Furthermore, animal models of schizophrenia reinforce the clinical data showing that gut dysbiosis may be implicated in schizophrenia, mainly pointing to alterations in the *Firmicutes* phylum bacteria.

ANXIETY AND DEPRESSION DISORDERS

Preclinical studies have shown that the intestinal microbiome seems to play a crucial role in the pathophysiology of both neuropsychiatric disorders. Also, fecal microbiota from patients diagnosed with anxiety and depression induce behavioral and physiological features of these disorders when transplanted to microbiota-deficient animals, including anhedonia, anxiety-like behaviors, and altered tryptophan metabolism[92-94].

Park and colleagues showed that anxiety- and depression-like behaviors induced by olfactory bulbectomy (OBx) are related to colonic motility alterations and gut microbiota composition changes. In addition, the expression of hypothalamic corticotropin-hormone (CRH) was elevated in OBx mice, suggesting that GI disturbances and gut dysbiosis may be due to the recruitment of the hypothalamic-pituitary-adrenal axis[95,96]. Murakami et al. analyzed the gut microbiota composition of fecal samples from Wistar rats submitted to maternal separation when neonates. This early-life stressor leads to anxiety- and depression-like behaviors in adulthood. The authors found that maternal separation induced a specific reduction in *Bifidobacterium*, *Bacteroidetes*, and *Prevotella* genera[97]. Li et al. analyzed the gut microbiota of fecal samples from mice submitted to the chronic unpredictable mild stress (CUMS) model. They found that the gut microbiota of CUMS-treated mice exhibits drastic alterations in microbiota composition, including an increased α-diversity and changes in the abundance of specific microbial phyla, such as Verrucomicrobia and Proteobacteria. At the genus level, animals exposed to CUMS exhibit an increased abundance in *Helicobacter*, *Turicibacter*, *Parasutterella*, *Alistipes*, *Odoribacter*, and *Akkermansia*, but a decrease in *Barnesiella*, *Bifidobacterium*, *Lactobacillus*, and *Olsenella*[98].

FUTURE DIRECTIONS

Reports using cutting-edge technologies such as metagenomics and metabolomics are changing some of the established paradigms regarding the physiopathological mechanisms behind neuropsychiatric diseases. Using the potential of microbial profiles as biomarkers of neurological and mental health disorders may maximize the efficacy of existing therapies. Current challenges remain in establishing causation rather than association and translating basic science studies into clinical practice with the potential of targeting the microbiome for therapeutic purposes.

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HISTORICAL NOTES

Seventy years since the invention of the averaging technique in Neurophysiology: Tribute to George Duncan Dawson

70 anos da invenção da técnica de promediação na Neurofisiologia: Tributo a George Duncan Dawson

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ABSTRACT

In 1951, the physiologist George Duncan Dawson presented his work with the averaging of the signal in the evoked potentials (EPs), opening a new stage in the development of clinical neurophysiology. The authors present aspects of Professor Dawson's biography and a review of his work on the EPs and, mainly, the article reveals the new technique in detail that would allow the growth of the clinical application of the visual, auditory, and somatosensory EPs.

Keywords: Evoked Potentials; Neurology; Neurophysiology; Evoked Potentials, Somatosensory.

RESUMO

Em 1951 o fisiologista George Duncan Dawson apresentou seu trabalho com a promediação de sinal nos potenciais evocados, abrindo uma nova etapa no desenvolvimento da neurofisiologia clínica. Os autores apresentam aspectos da biografia do professor Dawson e uma revisão de seus trabalhos sobre os potenciais evocados, principalmente do artigo que mostrava a nova técnica, que viria a permitir o crescimento da aplicação clínica dos potenciais evocados visual, auditivo e somatossensitivo.

Palavras-chave: Potenciais Evocados; Neurologia; Neurofisiologia; Potenciais Somatossensoriais Evocados.

The initial description of the evoked potential (EP) by Richard Caton in 1875 was when he observed on the galvanometer fluctuations in the electrical activity of the monkey's exposed cortex in response to the stimulation of his lips and the light shone in one eye, and it took more than half a century, due to the lack of adequate equipment to record these evoked responses, even the pioneering work of the English physiologist George Duncan Dawson[1].

EPs recorded on the human's scalp were difficult to extract due to the high voltage of the cortical oscillating electroencephalogram noise, among other causes. Recording of EP is a noninvasive method for investigating brain activity. This tool corresponds to voltage fluctuations blocked by time derived from the continuous electroencephalography (EEG) signal in response to a specific peripheral sensor[2].

Dawson demonstrated that electrical stimulation of a peripheral nerve in human produces brain responses[3], and the analysis of these responses at the time, distally stimulating the median or ulnar nerves, they generated a low amplitude action potential[4], making their study difficult, a problem that was solved with the summation technique he developed.

In 1947, George Dawson blocked the stimulation of the median nerve for scanning his oscilloscope. Pairs of electrodes placed on the human's scalp, overlying the parietal lobes, captured responses of repetitions of electrical stimuli of the median nerves which were amplified and displayed on a

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storage oscilloscope screen. Multiple Dawson's photographs overlapping somatosensory evoked responses showed a first positive peak of latency at 28 ms[3] (Figure 1). Cerebral action potentials evoked by stimulation of somatic nerves may be detected on the human's scalp by superimposing many records. In 1970, Jewett and Williston used Dawson's averaging technique to record the minute auditory response of electrodes on the human's scalp[1].

On May 19, 1951, at the Physiological Society in Cambridge, Dawson demonstrated his equipment built with his assistant Jack Pitman, using a bench of 25 condensers and a moving paper camera motor[5,6]. In 1954, Dawson improved the equipment by developing the electromechanical signal mediator (EMSM), a motorized rotary switch that powers each individual scalp response blocked by a single median nerve stimulus in the time of 1 of the 62 capacitors every 0.1 s. The EMSM discharged each capacitor in series into an amplifier connected to a storage oscilloscope[7].

Dawson's contribution to the advancement of EP registration was the solution he found to solve the signal-to-noise problem in obtaining EP. For that, it established the method of the first sum and average, that is, the responses evoked at each repetition of the stimuli were displayed on an oscilloscope and superimposed on a photographic film. Thus, brain activity blocked by time resulted in overexposure in part of the film, while random activity exposed the entire film only slightly. This method of photographic film over the trace, therefore, made it possible to suppress unrelated spontaneous potentials, extracting the phases of significantly low amplitude response evoked by stimulation[5].

Due to the impact of his work, George Duncan Dawson is considered the father of EP studies and from then on, EP became an independent field of neurophysiology. The averaging method was subsequently improved to bring the current computerized digital averaging methods that allow multiple responses to be averaged, and the old galvanometers were progressively replaced by highly sensitive amplifiers.

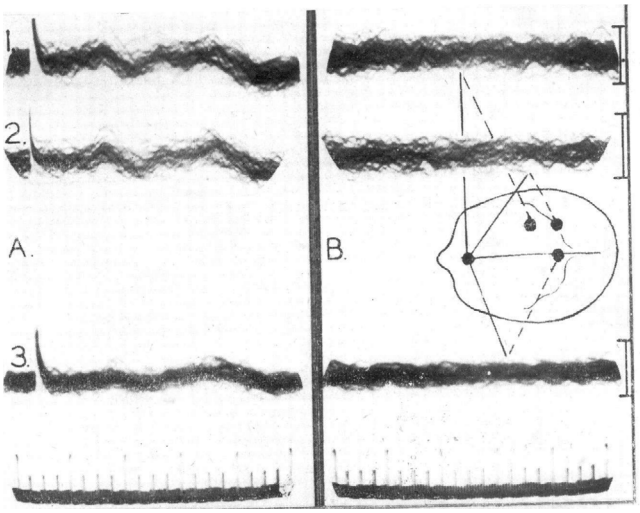

Figure 1. Dawson photograph of the superimposed responses to 50 successive stimulations of the ulnar nerve at the wrist (with permission of BMJ Publishing Group Ltd., License Number: 5061900358457).

GEORGE DUNCAN DAWSON

George Duncan Dawson (Figure 2) was born in Manchester in 1912, and his father was a pathologist at the Manchester Royal Infirmary. Dawson was educated at Repton and Manchester University, graduating in medicine in 1936, 3 years before he completed his master's degree in research on nerve action potentials. In 1938, at the Manchester Royal Infirmary, he helped set up Professor Sir Geoffrey Jefferson's EEG laboratory, later dedicated to the study of brain electrical activity in patients with epilepsy at the David Lewis Colony in Sandlebridge, Cheshire[6]. Together with Gray Walter, he published two articles considered classic in EEG.[8,9] Although Dawson was really interested in the potential of EEG as a scientific tool, he had already investigated a special group of epileptics in whom myoclonic reflexes were associated with large isolated waves in the EEG.

In 1944, Dawson was part of the Medical Research Council Unit of the National Hospital for Nervous Diseases, Queen Square, under the guidance of Professor Carmichael, where he developed techniques to identify small electroencephalographic signals against background noise while studying patients with epilepsy. At that time, he studied a patient

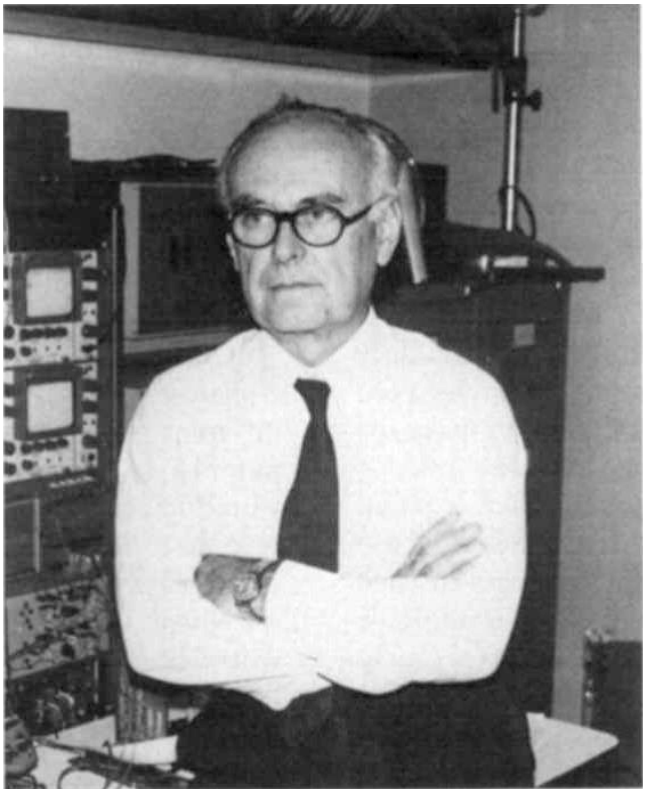

Figure 2. George Duncan Dawson[7].

with myoclonic seizures that could be caused by light electrical stimuli applied to a peripheral device nerve. The resulting cortical waves were large enough (50 μV) to be captured with the naked eye, from the spontaneous EEG background on the oscilloscope[10]. It was the first description of the potential giants.

Dawson became the head of the Department of Clinical Neurophysiology at the London Institute of Psychiatry in 1961, was named the Second Professor of Physiology at University College London in 1966, where he remained until his retirement, and continued his research work on epilepsy in the Lingfield Epileptic Colony, developing the computer-based methods to evaluate treatments with antiepileptic drugs. Dawson died on November 13, 1983, and his work endures as a milestone in the development of Clinical Neurophysiology[6].

In conclusion, Professor Dawson was an emeritus professor of Physiology at University College London. The signal averaging technique, originally described by Dawson, has been improved with the development of computerized processing. The technique now applies a stimulus repeatedly, records the evoked response in the corresponding area of the brain, and mathematically calculates the average change in the number of stimuli and responses.

Dawson's contribution to Neurophysiology deserved recognition for the highest order, including a Nobel Prize, a task that Franklin F. Offner was trying to promote at the time of his death. However, the researcher's modesty prevented him from taking any action designed to bring him greater fame, "it would be the furthest thing from your mind, and it was totally foreign to his nature"[7].

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https://doi.org/10.1590/0004-282X-ANP-2021-0163

The falling teacup: a curious stroke case

A queda de uma chávena: um caso interessante de acidente vascular cerebral

Augusto RACHÃO[1], Tiago GERALDES[1], Cláudia GUARDA[1]

A 63-year-old man presented with sudden-onset right index finger weakness that made him drop his morning teacup. He could not fully extend, adduct, and abduct his finger (Figure 1). A brain magnetic resonance imaging revealed a minor acute ischemic lesion on the left precentral cortex, in the hand knob (HK) area (Figure 2), of undetermined etiology.

HK infarctions are uncommon, often cardioembolic, and can present with different patterns of isolated hand weakness[1]. This case illustrates the rare involvement of a single finger following HK stroke and strengthens the existence of finger somatotopy in human motor cortex[1,2]. This observation helps clarifying motor cortex anatomy and clinical correlations, further detailing the Penfield's homunculus[3], its first proposed somatotopic organization.

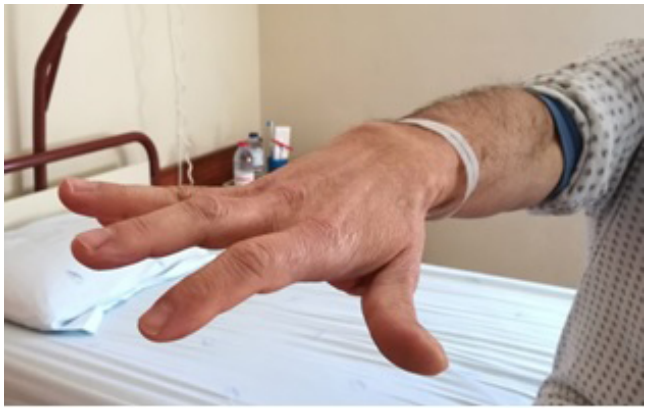
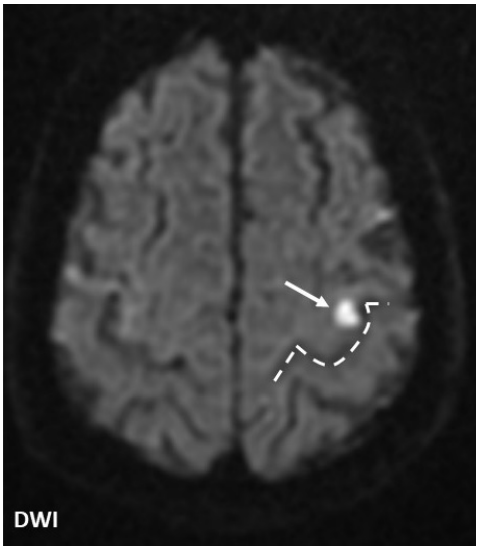


Figure 1. Photograph of the involved hand, evidencing a tendency toward the flexion of the right index finger, since the patient could not fully extend, adduct, and abduct it.



DWI: diffusion weighted imaging.

Figure 2. Brain magnetic resonance imaging (axial section) displaying an acute infarction (white arrow) in the hand knob territory, presenting as an inverted omega (dashed line).

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Conflict of interest: There is no conflict of interest to declare.

Authors' contributions: AR: approached the patient, conceptualized the work, wrote the original draft, and revised the final draft; TG: approached the patient and revised the final draft; CG: oversaw the work, approached the patient, and revised the final draft.

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Brain abscess and hereditary hemorrhagic telangiectasia

Abscesso cerebral e telangiectasia hemorrágica hereditária

Leonardo Furtado FREITAS[1], Márcio Luís DUARTE[2], Eduardo Carvalho MIRANDA[3]

A 58-year-old woman presented speech impairment, mental confusion, and left hemiparesis after being found unconscious. Brain magnetic resonance imaging (MRI) showed pyogenic abscess and multiple vascular malformations in the cerebral hemispheres (Figures 1 and 2), resulting in suspicion of Rendu-Osler-Weber disease, i.e., hereditary hemorrhagic telangiectasia (HHT). Chest computed tomography (CT) revealed pulmonary arteriovenous malformation. Ectoscopy detected multiple telangiectasia in the lips,

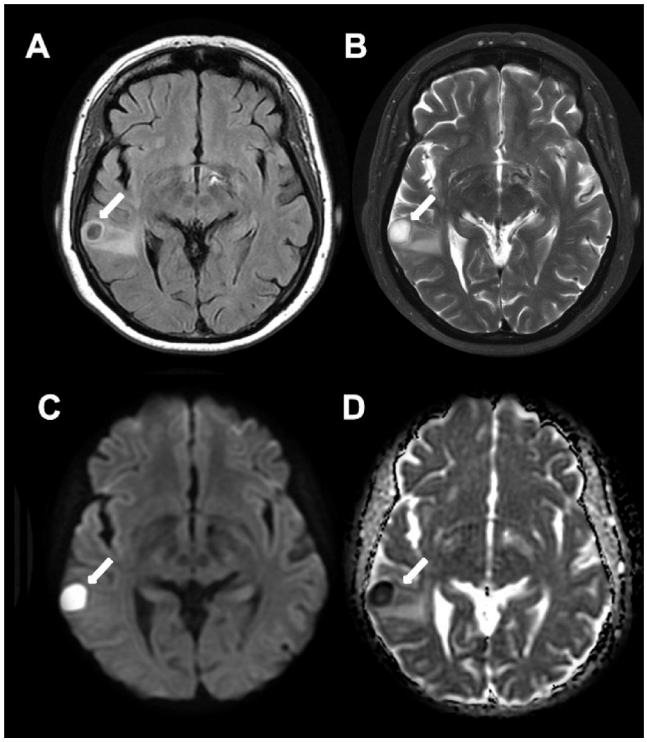

Figure 1. Brain MRI in axial FLAIR (A), T2-weighted (B), B1000 diffusion (C), and ADC map (D). A pyogenic abscess surrounded by vasogenic edema (arrows) in the right superior temporal gyrus is detected.

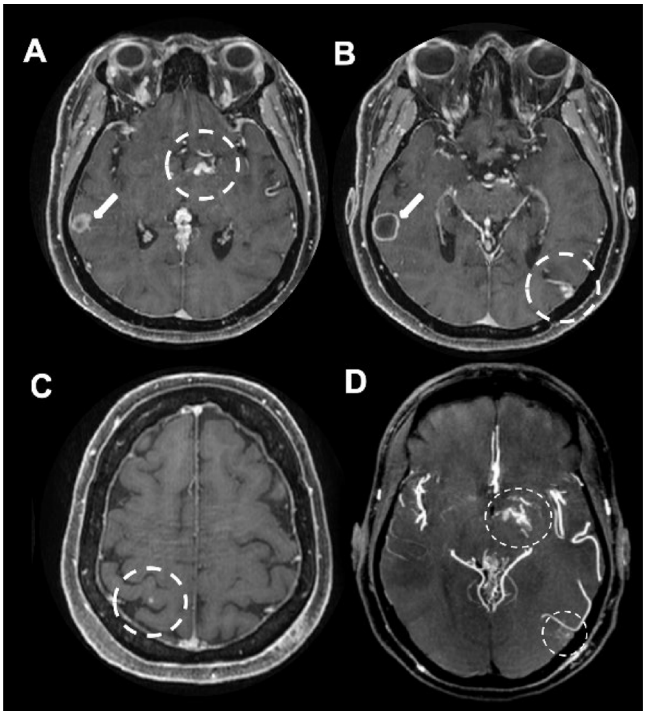

Figure 2. Brain MRI in axial, post-gadolinium volumetric T1 (A to C) and MIP (D) sequences. A pyogenic abscess surrounded by vasogenic edema (arrows) in the right superior temporal gyrus is detected (arrows in A and B). Dashed circles of images A to D highlight multiple tiny vascular malformations in both cerebral hemispheres (capillary malformations and microMAVs), more conspicuous in the MIP sequence.

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Correspondence: Leonardo Furtado Freitas; Email: drleonardofurtado@gmail.com.
Conflict of interest: There is no conflict of interest to declare.
Authors' contributions: LFF, MLD: manuscript composition; ECM: manuscript review.
Received on September 19, 2021; Received in its final form on October 20, 2021; Received in its final form on October 21, 2021.

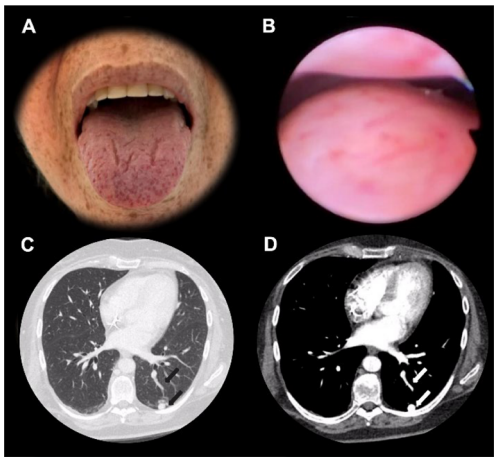

Figure 3. Face ectoscopy (A) and rhinoscopy exam (B); CT of the chest in the lung (C) and soft tissue (D) windows. Other systemic changes in the spectrum of the syndrome: multiple tiny cutaneous telangiectasia on the face, tongue, and labial mucosa (A), as well as on the nasal mucosa (B) and pulmonary vascular malformation compatible with arteriovenous malformation (AVM) (arrows on C and D).

tongue, face, and nasosinusal mucosa (Figure 3). HHT is a rare systemic fibrovascular dysplasia (prevalence rate: 1:50000–100000)[1], and brain abscess is an acute and easily forgotten complication that occurs in 1% of patients with considerable mortality, i.e., death rate of 40%[2].

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Keppra® levetiracetam

NOVO
KEPPRA XR™
levetiracetam

O PRIMEIRO.[1]
O ÚNICO.*

O ÚNICO LEVETIRACETAM DISPONÍVEL EM AMPLA GAMA DE OPÇÕES TERAPÊUTICAS.[2,3]

M.S. 1.2361.0083.007-1
M.S. 1.2361.0083.004-7
M.S. 1.2361.0083.005-5
M.S. 1.2361.0093.001-7
M.S. 1.2361.0093.002-5

CONFIANÇA:
mais de 20 anos de experiência clínica[4]

COMODIDADE:
ampla gama de apresentações[2,3]

ADESÃO:
apresentação XR **(1X ao dia).[2]**

*Único no Brasil.

Referências bibliográficas: 1. Diário Oficial da União. Nº 61, segunda-feira, 30 de março de 2020. RESOLUÇÃO-RE Nº 871 **2.** Bula de Keppra XR™. **3.** Bula de Keppra®. **4.** Shonvon, S. D. et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia.* 2000 Sep; 41(9):1179-86.

Keppra XR (levetiracetam). **Apresentações:** comprimidos revestidos de liberação prolongada de 500 mg ou 750 mg em embalagens com 60 comprimidos. **Indicações: é indicado como monoterapia** para o tratamento de crises focais/parciais em pacientes a partir dos 16 anos com epilepsia. **Keppra XR** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais em pacientes com idade superior a 12 anos, com epilepsia refratária; crises mioclônicas em adultos, adolescentes e crianças com idade superior a 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos, adolescentes e crianças com mais de 12 anos de idade, com epilepsia idiopática generalizada. **Contraindicações:** hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra XR** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno. **Keppra XR** é um medicamento e durante seu uso, recomenda-se precaução nos pacientes que executam tarefas especializadas, como condução de veículos ou utilização de máquinas. **Interações Medicamentosas** (vide bula completa do produto): Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. **Reações Adversas:** para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia:** A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais em pacientes a partir dos 16 anos com epilepsia, é de 500 mg ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 1000 mg ao dia, após duas semanas. A dose máxima é de 3000 mg ao dia. Nos casos de terapia adjuvante, para adultos e adolescentes acima de 12 anos e com mais de 50 kg, a dose terapêutica inicial é de 1000 mg ao dia. Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 3000 mg ao dia. Ainda nos casos de terapia adjuvante, para adolescentes (dos 12 aos 17 anos) com peso inferior a 50 kg a dose terapêutica inicial é de 20 mg/kg ao dia, a dose pode ser aumentada até 60 mg/kg ao dia. A alteração das doses não deve exceder aumentos ou reduções de 20 mg/kg ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. Além disso, as concentrações disponíveis de **Keppra XR** não são apropriadas para o tratamento inicial em crianças com menos de 25 kg, para pacientes incapazes de deglutir comprimidos ou para administração de doses menores que 500 mg. Em todas estas situações deve ser utilizada a solução oral de **Keppra. USO ADULTO E PEDIÁTRICO ACIMA DE 12 ANOS. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** Para maiores informações, consulte a bula completa do produto. (0302040014 R4 Rev. Março 2021). www.ucb-biopharma.com.br. **Reg. MS - 1.2361.0083. Levetiracetam (lista C1 Port. 344/98).**

Keppra® (levetiracetam). **Apresentação**: comprimidos revestidos de 250 mg em embalagens com 30 ou 60 comprimidos ou comprimidos de 750 mg também em embalagens com 30 ou 60 comprimidos. **Indicações:** é indicado como monoterapia para o tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. **Keppra®** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais com ou sem generalização secundária em adultos, adolescentes e crianças com idade superior a 6 anos, com epilepsia; crises mioclônicas em adultos, adolescentes e crianças com idade superior a 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos, adolescentes e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra®** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno. **Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas (vide bula completa do produto):* Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas:* para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia**. A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica de 500 mg duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg duas vezes ao dia. Nos casos de terapia adjuvante, para crianças (dos 6 aos 11 anos) e adolescentes com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. A forma farmacêutica comprimido revestido não é adaptada para bebês e crianças com menos de 6 anos. **Keppra®** solução oral é a forma farmacêutica ideal para uso nesta população. **USO ADULTO E PEDIÁTRICO ACIMA DE 06 ANOS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** Para maiores informações, consulte a bula completa do produto. (0302040013 R26 Rev. Junho/2021). www.ucbbiopharma.com.br. **Reg. MS - 1.2361.0083. Levetiracetam (lista C1 Port. 344/98).**

Keppra® (levetiracetam). **Apresentação**: Frasco de vidro âmbar contendo 150 mL de solução oral (100 mg/mL), acompanhado de uma seringa de 3 mL para administração. **Indicações:** é indicado como monoterapia para o tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. **Keppra®** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais em adultos, crianças e bebês a partir de 1 mês de idade, com epilepsia; crises mioclônicas em adultos e adolescentes a partir dos 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra®** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno. **Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas (vide bula completa do produto):* Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas:* para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia**: A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg (2,5 mL) duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 500 mg (5 mL) duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg (15 mL) duas vezes ao dia. Nos casos de terapia adjuvante, para adultos e crianças acima de 12 anos e com peso igual ou superior a 50 kg, a dose terapêutica inicial é de 500 mg/duas vezes ao dia (5 mL/duas vezes ao dia). Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 1500 mg/duas vezes ao dia (15 mL/duas vezes ao dia). Ainda nos casos de terapia adjuvante, para adolescentes, crianças e bebês a partir dos 6 meses com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg (0,3mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. Nos casos de terapia adjuvante para bebês com mais de 1 mês e menos de 6 meses de idade a dose terapêutica inicial é de 7mg/kg (0,07 mL/kg) duas vezes ao dia, a dose pode ser aumentada para um máximo de 21 mg/kg (0,21 mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 7 mg/kg (0,07 mL/kg) duas vezes ao dia a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A solução oral é a forma farmacêutica ideal para uso em bebês. **USO ADULTO E PEDIÁTRICO ACIMA DE 01 MÊS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** Para maiores informações, consulte a bula completa do produto. (0302040021 R22 Rev. Março/2021). www.ucb-biopharma.com.br. **Reg. MS - 1.2361.0083. Levetiracetam (lista C1 Port 344/98).**

CONTRAINDICAÇÃO: HIPERSENSIBILIDADE AO PRINCÍPIO ATIVO OU A OUTROS DERIVADOS DA PIRROLIDONA OU A QUALQUER UM DOS EXCIPIENTES. **INTERAÇÃO MEDICAMENTOSA:** FORAM OBSERVADOS RELATOS ISOLADOS DE DIMINUIÇÃO DE EFICÁCIA QUANDO O LAXANTE OSMÓTICO MACROGOL FOI ADMINISTRADO CONCOMITANTEMENTE A LEVETIRACETAM ORAL. ASSIM, A ADMINISTRAÇÃO ORAL DE MACROGOL NÃO DEVE SER REALIZADA DENTRO DE 1 HORA (ANTES OU APÓS) DA ADMINISTRAÇÃO DE LEVETIRACETAM.

BR-P-KP-EPI-2100055- Dezembro/2021- Material de uso exclusivo da classe médica.

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