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A Large Turkish Cohort of Williams Syndrome: The Evaluation of Facial, Cardiovascular, and Neuropsychiatric Features

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What is already known on this topic?

- *Williams syndrome (WS) is caused by a microdeletion at 7q11.23 and is characterized by a distincitive face, cardiovascular disease, and intellectual disability with a specific cognitive and behavioral profile.*

What this study adds on this topic?

- *We reported that all patients in the infantile/early childhood period had facial features such as short nose/bulbous nasal type with anteverted nares and periorbital fullness, which should be considered in the diagnosis of WS.*

ABSTRACT

Objective: Williams syndrome is caused by a microdeletion at 7q11.23 and is characterized by a distinctive face, cardiovascular disease, and intellectual disability with a specific cognitive and behavioral profile. This study aims to evaluate the clinical features and obtain important information that can guide early diagnoses and correct follow-up.

Materials and Methods: The study included 78 patients whose diagnoses were confirmed by fluorescent in situ hybridization. Facial features, anthropometric measurements, and neurocognitive, endocrine, and urinary system evaluations were obtained from the medical records, and photographs of the patients were evaluated retrospectively.

Results: The most common complaints at admission were cardiovascular disease and atypical face. The mean age at admission was 39 ± 4.8 months. The mean age of patients presenting with atypical face was 41 ± 5.6 months, while it was 11 ± 3.1 months in patients presenting with cardiovascular disease. Short nose/bulbous nasal type with anteverted nares and periorbital fullness, which are diagnostic facial features, were present in all patients in the infantile/early childhood period. 80% of the patients had cardiovascular disease; supravalvular aortic stenosis (53.8%) and peripheral pulmonary artery stenosis (41%) were the most common cardiac anomalies.Intellectual/developmental disability was present in 75.6% of the patients. Behavioral disorders including autism spectrum disorder and attention deficit hyperactivity disorder were detected in 50% of our patients. Hypersensitivity to loud and/or sudden sounds was present in all patients.

Conclusion: We highlighted that recognition of facial findings is important for early diagnosis, especially in patients without cardiovascular disease. The frequency of cardiovascular, endocrinological, renal anomalies, and intellectual disability/developmental delay was described that provide valuable information in the follow-up of patients.

Keywords: Behavioral disorders, FISH, microdeletion, Williams syndrome

INTRODUCTION

Williams syndrome (WS) (OMIM:194050) results from a microdeletion on chromosome 7q11.23 and is characterized by cardiovascular disease (CVD), distinctive face, intellectual disability, hypersocial behavior, short stature, and endocrine abnormalities.[1] The incidence is between 1:7500 and 1:25 000 live births.[2]

Although parent-to-child transmission has been reported, most cases are sporadic and caused by de novo deletions. The clinical phenotype is widely heterogeneous depending on the size of the deleted segment and the function of the genes involved.[1,3] The size

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of the deletion (1.5-1.8 MB) is similar in most individuals with WS, resulting in the loss of one copy of the 25-27 genes located in 7q11.23 region.[4] Atypical deletions may be larger or smaller than the characteristic deletion.[5] The deletion of the *ELN* (elastin) gene causes cardiovascular and connective tissue abnormalities.[3] *GTF2IRD1* and *GTF2I* deletions are associated with autism spectrum disorder, social communication skills, and neurodevelopmental retardation.[6] Visuospatial cognitive abnormalities occur in the absence of the *LIMK1* gene.[7] 75% of older children and adults have intellectual disability (IQ <70), and most of the remaining have borderline IQ (70-85) and/or neuropsychological disorders. There is also unique personality profile that includes over-friendliness, short attention span, specific non-social phobias, and anxiety. Besides, hypersensitivity to loud and/or sudden sounds (electrical machines, thunder, fireworks, etc.) is a unique finding that is described in the majority of patients during infancy and childhood whose incidence decreases during adolescence.[8-12] Typical facial characteristics include broad forehead, bitemporal narrowing, periorbital fullness, stellate iris appearance, full cheeks, short nose, long philtrum, thick upper and lower lip vermillion, and wide mouth.[1,4,13,14] Cardiovascular disease is present in 74% of the patients; the most common defect is supravalvular aortic stenosis (SVAS) followed by peripheral pulmonary stenosis (PAS).[13-15] It has been reported that 15% of patients have hypercalcemia.[16] In addition, postnatal short stature, hypothyroidism, andprecocious pubertyare other common endocrine abnormalities that are observed in patients with WS.[17,18]

The aim of this study is to examine the facial, cardiovascular, neuropsychiatric, endocrine, and other systemic features in a large cohort followed up with the diagnosis of WS and to obtain pivotal information that can guide diagnosis and follow-up.

MATERIALS AND METHODS

A total of 78 Turkish patients with the clinical diagnosis of WS, who were diagnosed and followed up in the Department of Pediatric Genetics, were included in this study. Clinical and laboratory findings, family history, anthropometric measurements, and concomitant cardiovascular, endocrine, urinary, gastroenterological, and musculoskeletal system abnormalities were recorded. Evaluation of dysmorphic findings was performed by an experienced clinical geneticist. Echocardiography was performed by an experienced pediatric cardiologist. Annual clinical evaluations including eye and hearing examinations, blood pressure measurement in both arms, urinalysis, and urine calcium/creatinine ratio were performed. In children younger than 2 years of age, the serum calcium level was evaluated every 4-6 months. Thyroid function tests were evaluated yearly until the age of 3 years and every 2 years thereafter. The weight, height, and head circumference were measured at birth, at the time of admission, and in the follow-up. Standard deviation scores (SD) of all anthropometric measurements were calculated using a national pediatric calculator loaded with national standards (https://www.ceddcozum.com). Denver-2 (in children under the age of 5) and Wechsler Intelligence Scale for Children-R (WISC-R) tests were performed to evaluate neuromotor developmental delay (DD) and intellectual disability (ID). The clinical diagnosis of the patients was confirmed by fluorescent in situ hybridization (FISH) method. All participants provided written informed consent. The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethics Committee (Number: 158705, Date: December 01, 2020).

Molecular Cytogenetic Studies

Chromosome analysis was performed on phytohemagglutinin-stimulated peripheral blood lymphocytes. The molecular cytogenetic diagnosis was confirmed by FISH method in all patients with probes specific to chromosome 7q11.23 using 1 of 3 commercial probes (D75486 probe for red and D75522 for green signal for Vysis probes; Williams-Beuren probe for red and D7Z1 for green signal for Cytocell's D7Z1 probe; Diagen's D752024 probes for red and RH10174 probes for red signal) containing the *ELN* gene. Hybridization and fixation procedures were performed according to the manufacturer's protocol. A total of 500 cells were evaluated by FISH on metaphase or interphase nuclei to exclude low-level mosaicism.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBMCorp.; Armonk, NY, USA). The numerical data were presented as mean ± standard deviation and categorical data as frequency and percentage.

RESULTS

A total of 39 patients were females (50%), and 39 (50%) were males. The mean age of fathers was 30.6 ± 5.6 years and the mothers were 26.5 ± 4.7 years. The most common complaint at admission was atypical facial findings in 38.5% of the patients, followed by congenital heart disease (30.7%) and global DD (17.9%). The distribution of initial complaints according to age groups is shown in Table 1. Other reasons for referral were growth retardation and atypical behavior. The mean age at admission was 39 ± 4.8 months in all patients; it was 41 ± 5.6 months and 11 ± 3.1 months in patients who presented with facial findings and CVD, respectively.

The main clinical and laboratory findings of our patients are given in Table 2. Typical WS facial features (100%), CVD (80.7%), ID/DD (97.4%), hypersensitivity to loud and/or sudden sound (100%), endocrine disorders (primary hypothyroidism 42.5%, subclinical hypothyroidism 21.2%; growth hormone deficiency 4.2%; puberte precox 4.2%; short stature %37.1%), urinary abnormalities (29.8%), and ocular problems (54.3%) were common findings in our patients.

Table 1. Distribution of Reasons for Admission According to Age at Diagnosis of WS Patients

	Mean Age	Frequency	Percentage (%)
Atypical facial features	41months	30/78	38.4
Cardiovascular disease	11 months	24/78	30.7
Neurodevelopmental delay	43 months	14/78	17.9
Other (growth retardation, atypical behavior, etc.)	61 months	10/78	12.8

WS, Williams syndrome.

Table 2. Clinical Findings of the Patients with Williams Syndrome

	n	%
Typical WS facial features	78/78	100
Cardiovascular disease	63/78	80.7
Intellectual/developmental disability*	**72/74**	**97.2**
<35 severe	2/74	2.7
35-50 moderate	18/74	24.3
50-70 mild	36/74	48.6
70-85 borderline	14/74	18.9
>85 normal	2/74	2.7
Behavioral/personality disorders	39/78	50
Attention deficit hyperactivity disorder	9/78	11.5
Autism spectrum disorder	8/78	10.2
Other behavioral disorders	22/78	28.2
Normal	39/78	50
Hypersensitivity to loud and/or sudden sounds	**78/78**	**100**
Endocrine disorders		
Primary hypothyroidism	20/47	42.5
Subclinical hypothyroidism	10/47	21.2
Growth hormone deficiency	2/47	4.2
Puberte precox	2/78	2.5
Short stature	29/78	37.1
Hypercalcemia	12/69	17.3
Urinary findings	20/67	29.8
Vesicoureteral reflux	4/67	5.9
Double renal collecting system	3/67	4.4
Bladder trabeculation	2/67	2.9
Bladder diverticulum	2/67	2.9
Anomalies of Kidney Rotation	2/67	2.9
Ectopic kidney	1/67	1.49
Horseshoe kidneys	1/67	1.49
Kidney agenesis	1/67	1.49
Multicystic dysplastic kidney(Nephrectomy)	1/67	1.49
Urolithiasis	3/67	4.4
Ocular findings	**25/46**	**54.3**
Strabismus	17/46	36.9
Hyperopia	3/46	6.5
Myopia	2/46	4.3
Astigmatism	2/46	4.3
Nystagmus	1/46	2.1
Stellate pattern of iris	16/78	20.5
Epilepsy	3/78	3.8
Scoliosis	3/78	3.8

*Denver II was administered to children under 5 years of age.
WS, Williams syndrome.

The distribution of facial features and its comparison to previously reported patients are described in Table 3. Short nose/bulbous nasal type with anteverted nares (86%), full cheeks (82%), and periorbital fullness (76%) were present in most of them. Long philtrum, bitemporal narrowing, and thick lips were seen in 75%, 74.5%, and 71.5% of patients, respectively. Relatively less common findings were thick vermilion of the upper and lower lips and epicanthal folds. The change in facial features in a patient during childhood and teenage periods was shown in Figure 1. Facial findings at infantile/early childhood and late childhood periods were compared, and it was observed that the typical diagnostic facial findings including short nose/bulbous nose type with anteverted nares and periorbital fullness were present in all patients at infantile/early childhood period (Figures 1A, 1B and 2A). As the children got older, the full cheeks became indistinct, but the wide eyebrows and wide mouth became more pronounced (Figure 1C and Table 4). The stellate pattern of the iris was detected in 20% of the patients (Figure 2B).

The most common CVD was SVAS in 42 patients; it was isolated in 19 patients and presented together with PAS in 21 patients (Table 5). Peripheral pulmonary stenosis was the second most common cardiac anomaly which was present in 32 patients; it was isolated in 5 patients and presented together with SVAS in 21 patients. The types and frequency of CVD found in our cohort are shown in Table 6. Fifteen patients underwent open heart surgery for cardiac anomaly; 80% of these patients had SVAS; 16.6% had PAS; and 8.3% had PDA.

Most of the patients (97.3%) had varying degree of ID/DD (Table 2). In our cohort, in physical development assessment, the mean age of head control was 5 months, supported sitting was 8.7 months, unsupported sitting was 10 months, and independent walking was 30 months. They had first words at the mean age of 29 months and made sentences with at least 2 words at 45 months. Denver-2 or WISC-R tests were performed on 74 patients. 75.6% of them had ID/DD (<IQ:70) and 18.9% had borderline IQ/DQ. Behavior/personality disorders were observed in half of our patients; 9 of these patients were diagnosed with attention deficit hyperactivity disorder (ADHD) and 8 with autism spectrum disorder. Interestingly, the behaviors such as anxiety, panic, and screaming against loud and/or sudden sounds were observed in all patients.

The patients whose birth information was available were given as follows: 58 were born at term, 12 had a history of premature birth, and 3 had a history of post-term birth. The mean birth height, weight, and head circumferences SDs were −1.01, −1.57, and −1.24, respectively. The mean SDs of height, weight, and head circumference for the patients at admission were −1.54 (37.1% were <−2SD), −1.65 (35.1% were <−2SD), and −1.99 (0.37% were <−2 SD), respectively. The mean SD of height, weight, and head circumference of boys and girls in different age groups are shown in Supplemental Table 1.

While patients with primary hypothyroidism were treated with levothyroxine, patients with subclinical hypothyroidism were monitored regularly for thyroid functions. Idiopathic hypercalcemia was detected in 17.3% of the patients.

Radiological imaging of genitourinary system was performed in 67 patients and urinary system abnormality was identified in 20The most common ocular problem in our cohort was strabismus (36.9%) which was followed by hyperopia (6.5%) and myopia (4.3%). Other medical problems in our cohort were inguinal hernia, scoliosis, and epilepsy, which were present in 13, 3, and 3 of the patients, respectively.

Table 3. Comparison of Facial Features of Our Cohort with Previous Studies

	Present Study (n = 78)	Perez Jurado et al[19] (n = 65)	Patil et al[14] (n = 27)	Kruszka et al[13] (Using Facial Analysis Technology)		
				Latin American (n = 105)	Asian (n = 24)	African (n = 8)
	%	%	%	%	%	%
Bitemporal narrowing	74.5	81.2	85	N/A	N/A	74.5
Broad eyebrow	60.2	N/A	37	63	58	60.2
Medial eyebrow flare	70.5	67	N/A	N/A	N/A	70.5
Epicanthic folds	58.5	71	52	73	63	58.5
Periorbital fullness	76	96	100	95	92	89.7
Full cheeks	82	100	88	N/A	N/A	82
Short nose/bulbous nasal type with anteverted nares	86	90	67	74	75	86
Depressed nasal bridge	73	N/A	N/A	N/A	N/A	73
Long philtrum	75	83	85	93	N/A	75
Wide mouth	64	N/A	100	91	79	64
Thick lips	71.5	97.7	N/A	N/A	78	71.5
Small jaw	70.5	N/A	85	82	N/A	70.5
Thick vermilion of the upper and lower lips	66.6	N/A	N/A	N/A	75	66.6

DISCUSSION

We presented a large cohort of WS patients who are diagnosed and followed up in a single center. The mean age of diagnosis of our patients was 39 ± 4.8 months and 74% of them diagnosed were under 5 years of age. The mean age of patients admitted due to atypical face was 41 ± 5.6, whereas it was 11 ± 3.1 months in patients with CVD. It has been reported that WS is mostly diagnosed between the ages of 3.7 and 5.3 years.[13,20,21] Cha et al[22] reported that the mean age at diagnosis of all patients was 3.2 years, while it was 1 year in patients with CVD. Similarly, Patil et al[14] reported that patients with CVD were diagnosed at the mean age of 10.9 months

The diagnosis of WS is difficult in infancy because atypical facial features are mild during this period.[23] In infancy, patients are diagnosed due to CVD and hypercalcemia rather than atypical facial features.[19] Similar to literature, facial features such as short nose/bulbous nasal type with anteverted nares, full cheeks, periorbital fullness, long philtrum, and small chin were present in most of the patients, whereas wide mouth, wide eyebrows, and epicanthal folds were less common in our cohort (Table 3). In the literature, the frequency of atypical facial features in different age and ethnic groups showed variability.[13,14,,19]Ethnicity and age at evaluation have remarkable importance in the detection of atypical facial findings.

The facial features of 12 patients who were followed up since the infantile/early childhood period were compared over their photographs (Table 4). In the literature, it has been reported that full cheeks, bitemporal narrowing, and epicanthal folds are prominent in infancy; in adolescence, depressed nasal bridge disappears and wide mouth, thick lips, and long neck become notable.[4,14] In our study, we found that while full cheeks and depressed nasal bridge become indistinct with age, bitemporal narrowing and wide eyebrows become more prominent, which is consistent with the literature. However, typical diagnostic facial features such as periorbital fullness and short nose/bulbous nasal type with anteverted nares were present in all patients in infantile/early childhood and persisted as the children grew older.

Figure 1. A patient's facial photographs from early childhood to adulthood.(A)Note the full cheeks, depressed nasal bridge, short nose/bulbous nasal type with anteverted nares, small jaw, periorbital fullness prominent in early childhood,(B)bitemporal narrowing, periorbital fullness, wide mouth in child hood,(C)anteverted nares, elongated face, long filtrum, wide mouth, long neck become notable in adolescences.

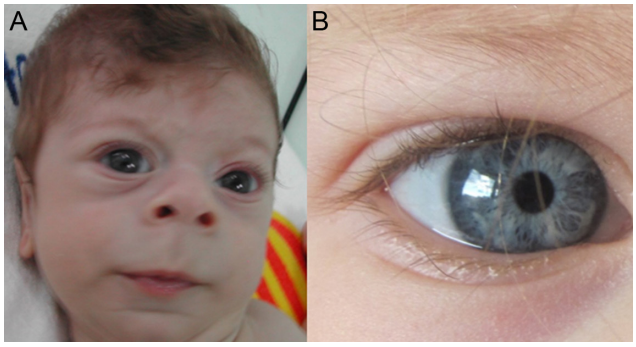

Figure 2. Facial photographs of patients with Williams syndrome.(A)Note the periorbital fullness, full cheeks, long philtrum, short nose/bulbous nasal type with anteverted nares, small jaw, depressed nasal bridge,(B) stellate pattern of iris.

The risk of CVD in patients with WS increased compared to the healthy population. Cardiovascular problems are the most important cause of morbidity and mortality in WS. The prevalence of CVD is reported at 74%-80%.[1,12,24] The frequency of SVAS has been reported in 35%-80% and PAS in 37%-61% of the WS patients in the literature[25-27] Similar to the other studies, the most common cardiac lesions in our study were SVAS (53.8%) and PAS (41%). Although SVAS and/or PAS are the most common cardiac anomalies resulting from *ELN* gene defect, many other cardiac anomalies may also accompany WS. Pham et al[28] determined the frequency of SVAS, PAS, and aortic coarctation-arch hypoplasia as 69.8%, 53.7%, and 13%, respectively, using the cardiac catheterization method. Honjo et al[29] reported the frequency of SVAS similar to the literature, while PAS (22%) and VSD (4%) were observed less frequently. Supravalvular aortic stenosis was together with other cardiac anomalies in 54.7% of our patients and PAS was the most common accompanying lesion (50%) to SVAS. Consistent with our study, coexistence of PAS and SVAS was the most frequently reported cardiac anomalies in the literature.[27,29,30] In the majority of our patients who underwent

Table 4. The Frequency of Facial Features at Different Age Groups

	Mean Age, 3.2 Years (Range: 2 Months to 5 Years)	**Mean Age, 12.3 Years (Range: 9 Years to 18 Years)**
	(n = 12) %	**(n = 12) %**
Bitemporal narrowing	66	83.3
Broad eyebrow	41.6	83.3
Medial eyebrow flare	25	58
Epicanthic folds	83.3	25
Periorbital fullness	100	75
Full cheeks	83.3	8
Short nose/bulbous nasal type with anteverted nares	100	91.6
Depressed nasal bridge	83.3	25
Long philtrum	83.3	75
Wide mouth	66	91.6
Thick lips	83.3	75
Small jaw	75	66
Thick vermilion of the upper and lower lips	33.3	66

Table 5. Distribution of Cardiovascular Disease Types in Patients

			n	**Total**
Arterial stenotic lesions	SVAS	*Isolated*	19	42
		+PAS	17	
		+PAS+VSD	3	
		+ PDA	1	
		+Persistent left superior vena cava	1	
		+PAS+CoA	1	
	PAS	*ISOLATED*	5	11
		+ASD	2	
		+PDA	1	
		+VSD	1	
		+HKMP	1	
		+VSD+PDA +Hypo Arch+CoA	1	
Septal defects	VSD	*ISOLATED*	3	5
		+Persistent left superior vena cava	1	
		+ASD+HKMP	1	
	ASD	*ISOLATED*	2	2
	Others	*MVP(2), PDA*	3	3
	Total			63

ASD, atrial septal defect; CoA, coarctation of aorta; HKMP, hypertrophic cardiomyopathy; HypoArch, aortic arch hypoplasia; MVP, mitral valve prolapse; PAS, peripheral pulmonary artery stenosis; PDA, patent ductus arteriosus; SVAS, supravalvar aortic stenosis; VSD, ventricular septal defect.

Table 6. Distribution of Frequency of Cardiovascular DiseaseTypes in Patients

	Frequency	**Percentage**
Cardiovascular disease	63/78	80.7
Stenotic arterial vascular lesions		
Supravalvar aortic stenosis	42/78	53.8
Pulmonary artery stenosis	32/78	41
Coarctation of aorta	1/78	1.28
HypoArch+CoA	1/78	1.28
Valvar disease		
Mitral valve insufficiency	14/78	17.9
Aortic valve insufficiency	12/78	15.3
Pulmonary valve stenosis	10/78	12.8
Aortic valve stenosis	4/78	5.1
Mitral valve prolapse	3/78	3.8
Septal defects		
Ventricular septal defect	10/78	12.8
Atrial septal defect	5/78	6.4
Others		
Patent ductus arteriosus	4/78	5.1
Persistent left superior vena cava	2/78	2.56
Hypertrophic cardiomyopathy	2/78	2.56

CoA, coarctation of aorta;HypoArch, aortic arch hypoplasia.

heart surgery, 80% had SVAS, and half of them operated under the age of 6 years. In the literature, SVAS is reported as the most common cause of cardiac surgery and the mean age for surgery is less than 5 years.[14,25,31] The frequency of cardiovascular anomalies other than SVAS and PAS varies depending on the age of patients and the department where the study was designed. The types of CHD in our cohort are shown in Table 6.

Most individuals with WS have mild-moderate ID/DD.[11,32] While 75.6% of our patients had intellectual disability, 18.9% of patients had borderline IQ. The mean IQ/DQ score was 52 in our cohort which was compatible with previous studies.[32,33]

Cognitive/behavioral features including autism spectrum disorders, ADHD, anxiety disorder, and specific phobias are common in WS compared to the general population.[33,34] Half of our patients had behavioral disorders. While 9 patients in this group received medical treatment for ADHD, 8 patients were followed up with the diagnosis of autism spectrum disorder. Hypersensitivity to sound has been reported in 85%-90% of patients with WS.[34-36] Similar to the literature, all of our patients had inappropriate behavior toward the sounds of electrical machines, doorbells, clapping, etc which was particularly evident in younger children.

Most patients with WS have intrauterine growth restriction.[37] In childhood and adolescence, short stature continues and the height is below the target height in 50%-60% of patients with WS.[37-39] Stature is affected by secondary factors such as nutritional deficiencies, cardiac anomalies, and also the size of the deletion. In our study, short stature was present in 37.1% of the patients at admission.

Several endocrine abnormalities have been reported in patients with WS. While primary hypothyroidism is reported in 10%-15%, subclinical hypothyroidism is reported more frequently (15%-30%) in the childhood period.[40] In our cohort, primary and subclinical hypothyroidism were detected in 42.5% and 21.2% of the patients, respectively. In addition, puberte precox was found in 2.5% and growth hormone deficiency was found in 4.2% consistent with the literature.[18,40] The higher incidence of primary hypothyroidism in our cohort was attributed to regular follow-up of the patients. Idiopathic hypercalcemia has been reported in 15%-50% of WS patients. However, actionable hypercalcemia was reported in 6% of patients.[16,41] Idiopathic hypercalcemia was detected in 17.3% of our patients. No treatment was required for the patients with hypercalcemia.

The prevalence of structural abnormalities of the urinary system in WS patients ranges from 17.7% to 51.9%.[42,43] In our study, the frequency of genitourinary anomaly was 29.8%.

Ocular problems were obtained in54.3% of the patients. Among these patients, strabismus was the most common ocular problem detected in 36.9% (17/46). Hyperopia has been also reported frequently (55%-67%) in the literature; however, it was found in 6.5% of our cohort.[44] The lower frequency of hyperopia was related to the fact that the study was conducted in the childhood age group. Iris stellate pattern was detected in 20% of our patients. Iris stellate pattern is more easily recognized in patients with light-colored eyes, and the reason for the low detection rate in our patients was thought to be the fact that most of them had brown eyes.[45]

A recent study from Turkey, which included 27 patients, found that atypical facial features were present in all patients and CVD was present in 88% of the patients similar to our study. They reported that short stature and hypothyroidism were observed less frequently when compared to our study. The differences in the frequencies of short stature, hypothyroidism, and ID/DD were attributed to the small cohort size of the reported study.[46]

In conclusion, in our cohort, the most common reasons for admission were CVD and atypical face. The mean age of admission due to facial findings was 41 ± 5.6 months, while those due to CVD were earlier at 11 ± 3.1 months. This data draw attention to the recognition of dysmorphic facial findings for diagnosis in infancy. Our study reported that all patients in the infantile/early childhood period had facial features such as short nose/bulbous nasal type with anteverted nares and periorbital fullness, which should be considered in the diagnosis of WS. The frequency of CVD was 80.7%; the most common CVDs were SVAS and PAS. Mitral and aortic valve insufficiency, stenosis, and VSD were other CVDs observed in WS. While 75.6% of the patients had DD/ID, 18.9% had borderline ID/DD and half of them had behavioral/personality disorders. The behaviors such as anxiety, panic, and screaming against loud and/or sudden sounds were observed in all patients. We suggest that this finding should be taken into account in the early diagnosis of WS. The results of our study provide important information for pediatricians that can guide the early diagnosis and follow-up by evaluating the clinical features of WS in a large cohort.

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethics Committee (no: 158705, December 01, 2020).

Informed Consent: Informed consent and permission for the publication of photos of children were obtained from all patients/parents.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. The Mean Height, Weight and Head Circumference SD of Patients According to Age and Gender

	Male			Female		
Age	**Mean Height SD (n)**	**Mean Weight SD (n)**	**Mean Head Circumference SD (n)**	**Mean Height SD (n)**	**Mean Weight SD (n)**	**Mean Head Circumference SD (n)**
3 mo	−0.97 (4)	−1.85 (4)	−2.02 (4)	−0.93 (1)	−2.31 (1)	−2.56 (1)
6 mo	−1.38 (5)	−2.04 (5)	−2.36 (5)	−2.17 (6)	−1.68 (6)	−1.48 (6)
9 mo	−1.45 (7)	−1.94 (7)	−1.78 (7)	−0.68 (3)	−1.99 (3)	−1.23 (3)
12 mo	−2.03 (9)	−1.75 (9)	−1.93 (9)	−1.55 (14)	−1.43 (14)	−2.39 (14)
24 mo	−1.28 (9)	−1.65 (9)	−1.92 (9)	−1.21 (10)	−1.33 (10)	−1.33 (10)
3 yrs	−1.85 (17)	−1.51 (17)	−1.95 (17)	−1.50 (15)	−1.47 (15)	−1.78 (15)
4 yrs	−2.65 (8)	−2.89 (8)	−2.83 (8)	−0.96 (8)	−1.27 (8)	−1.57 (8)
5 yrs	−1.48 (9)	−1.41 (9)	−1.96 (9)	−0.98 (11)	−1.07 (11)	−1.58 (11)
6 yrs	−1.50 (14)	−1.13 (14)	−1.76 (14)	−1.19 (11)	−1.26 (11)	−1.90 (11)
7 yrs	−0.92 (7)	−1.18 (7)	−2.43 (7)	−1.46 (13)	−1.72 (13)	−1.64 (13)
8 yrs	−1.08 (7)	−1.73 (7)	−2.88 (7)	−1.31 (11)	−1.00 (11)	−2.24 (11)
9 yrs	−0.77 (5)	−1.41 (5)	−2.55 (5)	−0.98 (8)	−1.03 (8)	−2.06 (8)
10 yrs	−2.12 (3)	−1.41 (3)	−3.34 (3)	−1.26 (3)	−0.97 (3)	−2.29 (3)
11 yrs	−1.14 (3)	−1.21 (3)	−1.71 (3)	−1.80 (3)	−1.43 (3)	−2.18 (3)
12 yrs	−3.01 (1)	−2.36 (1)	−3.03 (1)	−2.31 (4)	−2.53 (4)	−1.12 (4)
13 yrs	−1.14 (3)	−1.29 (3)	−2.89 (3)	−2.40 (4)	−2.85 (4)	−1.49 (4)
14–18 yrs	−1.84 (5)	−1.66 (5)	−2.42 (5)	−1.17 (12)	−2.30 (12)	−2.34 (12)

n, patient number; mo, month; SD, Standard deviation score; yrs, years.