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Wolf-Hirschhorn syndrome a series of 18 patients: Their clinical characteristics, cytogenetic and molecular findings

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Abstract

Objective: Wolf–Hirschhorn syndrome (WHS) (#194190) is a well-defined microdeletion syndrome characterized by typical facial findings, prenatal and postnatal growth retardation, hypotonia, microcephaly, intellectual disability, and seizures. Clinical findings vary depending on the size of the deletion. *WHSC1*, *WHSC2*, *LETM1*, *CPLX1*, *CTBP1*, *PIGG*, and *FGFRL1* were responsible for the clinical findings. The objective of this study was to describe the clinical, cytogenetic, and molecular characteristics of patients diagnosed with WHS and to contribute to the existing literature by presenting our data. *Methods:* This study retrospectively presents the clinical, cytogenetic, and molecular findings of 18 patients. *Results:* All the patients had typical facial findings, growth retardation, microcephaly, hypotonia, and intellectual disability. Seizures were present in all patients, except for two. Moreover, 16 patients had thin corpus callosum on cranial magnetic resonance imaging. The diagnosis was confirmed by chromosomal analysis, fluorescence in situ hybridization, and microarray analysis.
Conclusion: Confirmation of the diagnosis is important for increasing clinical awareness, appropriate follow-up, of patients and genetic counseling.

Keywords: Seizure, microcephaly, intellectual disability, hypotonia

INTRODUCTION

Wolf–Hirschhorn syndrome (WHS) (#194190) is a rare syndrome resulting from deletion of the short arm of chromosome 4. The WHS critical region (WHSCR) is localized within band 4p16.3. Clinical findings have been associated with the *WHSC1* (WHS candidate 1) (*NSD2*), *WHSC2* (*NELF-A*), *LETM1* (leucine zipper/ EFhandcontaining transmembrane protein 1), *CPLX1* (complexin-1), *CTBP1* (C-terminal binding protein), *PIGG* (phosphatidylinositol glycan anchor biosynthesis class G), and *FGFRL1* (fibroblast growth factor receptor-like 1) genes.[1,2,3] The size of the deletion varies between 2 and 30 megabases (Mb).[3,4] The clinical manifestations of WHS vary according to deletion size. The distinctive facial features of WHS, which include a high forehead, prominent glabella, hypertelorism, high-arched eyebrows, a broad and depressed nasal bridge extending to the forehead, microretrognathia, a short philtrum, and downturned corners of the mouth, collectively referred to as the "*Greek* warrior *helmet*" appearance, are particularly notable. The most notable clinical features include prenatal and postnatal growth retardation, hypotonia, microcephaly, seizures, and intellectual disability. Furthermore, ocular findings, hearing loss, cardiac abnormalities, skeletal abnormalities, and recurrent infections may also be observed.[2,5,6]

This study investigated 18 patients diagnosed with WHS exhibiting typical facial features that were confirmed by cytogenetic and molecular

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tests. The objective of this study was to describe the clinical, cytogenetic, and molecular characteristics of patients diagnosed with WHS, to determine the relationship between the clinical findings and the deletion size, and to contribute to the existing literature by presenting our data.

METHODS

The typical facial features and clinical findings of the 18 patients who underwent genetic testing at Ankara Bilkent City Hospital were evaluated by the Department of Pediatric Genetics. A retrospective analysis was conducted on patients who had presented to the hospital over the past five years, with a focus on patients aged between 0 and 18 years. The patients underwent a series of diagnostic procedures, including cranial magnetic resonance imaging (MRI), electroencephalography (EEG), echocardiography, auditory testing, and abdominal ultrasound (USG). The diagnosis was confirmed by chromosomal analysis, fluorescence in situ hybridization (FISH), and microarray analysis. Chromosomal analysis was conducted using peripheral blood lymphocytes, in accordance with standard protocols, and the G-bands using the Giemsa (GTG)-banding technique was employed to prepare the sample for analysis at 550-band resolution. In FISH analysis, the Cytocell FISH probe specific to the Wolf–Hirschhorn locus was employed. Microarray analysis was performed using Illumina Infinium CytoSNP 850 K and AffymetrixCytoscan 315 K analysis. This study was approved by the Ethical Review Committee (number E2-24-6158). Written informed consent for genetic testing was obtained from the legal guardians of all patients.

RESULTS

A total of 18 patients, comprising 10 males and eight females were included in the study. The mean age of the patients was 6 (range: 1–16) years, and the mean age at diagnosis was 3 months to 2 years. Seven patients presented with infantile hypotonia, five with seizures, five with dysmorphic facial appearance, and one with atypical genitalia. 13 patients exhibited intrauterine growth retardation (IUGR), with a range of –5.7 to –1.4 SDs. All patients exhibited typical facial features (Figure 1a-c, e-h). Of the patients, eight had ear anomalies, one had macroglossia, one had cleft lip, one had cleft palate, six had undescended testes, four had hypospadias, one had atypical genitalia, and four had inguinal hernia. The patients exhibited a range of head circumferences (–3.7 to –7.8 SDs), body weights (–2 to –8.6 SDs), and heights (–0.1 to –5.7 SDs). All the patients exhibited hypotonia and delayed neuromuscular development. Two patients could walk with support, and five patients could walk independently; they started walking when they were 3–5 years old. With regard to speech,12 patients lacked the capacity to produce words or sentences. Six patients began to form single words at the ages of 2 to 6 years; among these, three also began to make sentences between the ages of 5 and 6 years. 16 patients (89%) experienced seizures. 13 patients (72%) had epileptic activity on EEG, and two patients (11%) had cerebral dysfunction (Figure 2c). When considering nutrition, 15 patients received oral nutrition, while three patients received percutaneous endoscopic gastrostomy (PEG) feeding. Three patients exhibited symptoms of gastroesophageal reflux disease (GERD), while two underwent Nissen fundoplication surgery. 12 patients had cardiac anomalies, five had renal pathology, and one had malrotation. Nine patients had ophthalmological anomalies, and two patients had hearing loss. On cranial MRI, 16 of the 18 patients exhibited the presence of a thin corpus callosum (Figure 1d). Chromosome analyses revealed deletions in nine patients (Figure 2a). FISH analysis was performed on seven patients, which revealed that these patients exhibited a deletion. Microarray analysis was performed in 9 of the 18 patients and revealed the presence of a deletion at the 4p16.3 locus (Figure 2b). A summary of the clinical, radiological, and molecular findings of patients is presented in Tables 1 and 2.

DISCUSSION

WHS is a well-defined microdeletion syndrome characterized by typical facial findings, prenatal and postnatal growth retardation, hypotonia, microcephaly, intellectual disability, seizures, ocular and auditory findings, cardiac findings, and genitourinary anomalies. These anomalies occur as a result of deletion of the terminal region of the short arm of chromosome 4.[2,5] WHS was first described by Cooper and Hirschhorn in 1961 and subsequently confirmed by Wolf et al. in 1965.[6] It occurs at a frequency of 1/20,000–50,000 births. To date, more than 300 patients with WHS have been reported in the literature.[7,8] The male-to-female ratio is 2:1.[2] In contrast to previous studies, the current investigation

Figure 1. **(a)** Patient 3, **(b)** Patient 5, and **(c)** Patient 11 with deletions < 5 Mb in the 4p16.3 region
(e) Patient 6, **(f)** Patient 8, **(g)** Patient 1, and **(h)** Patient 2 with deletions ≥ 5 Mb in the 4p16.3 region
Common craniofacial findings include hypertelorism, high forehead, prominent glabella, high-arched eyebrows, a broad and flat nasal bridge, microretrognathia, a short philtrum, and downturned corners of the mouth
(d) Thin corpus callosum on cranial MRI

did not identify a predisposition with regard to sex among the patients, as the ratio of males to females was 10:8.

In the majority of cases (>75%), a distinctive facial appearance is associated with WHS. Herein, it was observed that all the patients exhibited a typical facial appearance associated with WHS (Figure 1a-c, e-h). The clinical findings in the literature include IUGR in 80% of patients, postnatal growth retardation in 100%, microcephaly in 90%, genitourinary anomalies in 50%, and hypotonia in 90%.[7] In the present study, all the patients exhibited postnatal growth retardation, microcephaly, hypotonia, and cognitive impairment. A total of 72% of the patients exhibited IUGR and 44% genitourinary anomalies. In patients with WHS, seizures are observed in approximately 90–100% of patients and EEG abnormalities in 80–90% of patients. In the current cohort, it was also found that 89% of the patients had seizures, 83% had abnormalities on their EEGs (Figure 2c).[9] In the present study, the age at onset of the first seizure ranged from 17 days to 3 years. Moreover, 31% of the cases manifested within the first 6-month period, 44% between 6- to 12-month and 25% beyond the 12-month mark. In 38% of the cases, the patients' seizure symptoms regressed. Levetiracetam is a highly efficacious antiepileptic medication frequently used in the treatment of WHS.[10] A total of 81% of patients were found to be using levetiracetam.

The results of studies in the literature indicate that renal anomalies were observed in 30% of patients, while cardiac anomalies were observed in 50% of patients. Moreover, ocular abnormalities were observed to be between 25% and 50%, whereas hearing loss was between 25% and 50%.[7,10] The findings of the present study are in alignment with those reported in the literature, with 27% of patients exhibiting renal anomalies and 66% demonstrating cardiac anomalies, 50% had ocular abnormalities, 11% had hearing loss. The most common cranial MRI finding is a thin corpus callosum that can be observed in up to 80%–100% of patients.[10] In the current study, 89% of patients exhibited a thin corpus callosum (Figure 1d). One of the most striking clinical features of WHS is the marked impairment of verbal fluency.[11] A significant proportion of patients (> 75%) exhibit cognitive impairment.[7,10] The findings revealed that all the patients exhibited cognitive impairment.

The diagnosis of WHS is based on clinical

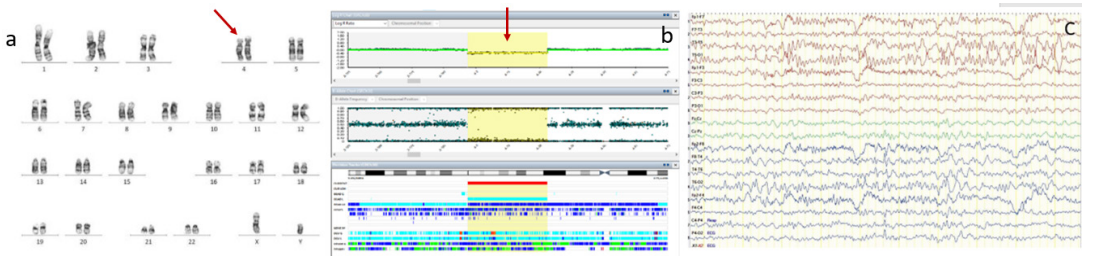

Figure 2. **a** Chromosome analysis of Patient 13 showed del(4)(p15)
b Microarray analysis of Patient 1 showed a 29-Mb deletion in the 4p15–p16 region
c EEG of Patient 16 showed epileptic discharges in the bilateral frontotemporal regions

examination, and cytogenetic and molecular analyses. The definitive diagnosis of WHS is made by identifying the deletion within the 4p16.3 region. Deletions exceeding 5 Mb can be identified through karyotyping, whereas smaller deletions necessitate the use of FISH, multiplex ligation-dependent probe amplification (MLPA), and microarray analysis. Karyotyping can identify approximately 50–60% of deletions. The present study found that chromosomal analysis had a deletion in nine patients (Figure 2a). FISH and MLPA can detect more than 95% of deletions.[2] Herein, we confirmed that FISH analysis had a 100% detection rate. Microarray analysis is the gold standard test for determining the size of deletions, identifying the underlying genetic content, and forecasting future treatment options, predicting prognosis.[4] It outperforms FISH and chromosomal analysis in all these areas.[12] Furthermore, the current study revealed that all patients who underwent microarray analysis exhibited a deletion within locus 4p16.3 (Figure 2b).

Deletion size is a significant factor in determining the clinical presentation. As the size of the deletion increased, the number of genes within it also increased, resulting in a more pronounced clinical manifestation. Determination of the size of the deletion in an individual provides the opportunity to make a more accurate prognosis.[2,4,12-14] In the present study, microarray analysis of nine patients revealed a range of deletion sizes between 2.1 and 29 Mb. To determine the relationship between clinical findings and deletion size in patients in whom microarray analysis could not be performed, patients with normal chromosomal analysis were considered to have a ≤5 Mb deletion, and patients with deletions in chromosomal analysis were considered to have a >5 Mb deletion. Regardless of deletion size, all patients exhibited typical facial features, pronounced growth retardation, hypotonia, and cognitive impairment. The present study indicated that IUGR, gait and speech disorders were more pronounced in patients with deletions greater than 5 Mb. Regarding other findings, we did not detect significant differences between microdeletions and large deletions. This phenomenon can be explained by the presence of a critical region that determines the characteristics of the syndrome or, alternatively, by the limited number of participants.

The prognosis of WHS varies depending on deletion size, seizure, and major congenital anomalies. In addition to pharmacological treatment, patients are offered a range of supportive therapies, including speech therapy, physical therapy, and seizure treatment. The WHS exhibits a high mortality rate, with 30% of deaths occurring within the first 2 years of life. The most prevalent complications leading to mortality are hypoxia, respiratory tract infections, congenital heart disease, and other congenital abnormalities.[4] The results of previous studies indicate that there is a statistically significant correlation between the degree of deletion and the risk of mortality.[7] In the present study, the mortality rate was 11%. One patient died at 1 year of age due to sepsis, a complication of measles. Unfortunately, it was not possible to obtain the medical records of other patients.

In conclusion, WHS is a well-defined microdeletion syndrome characterized by typical facial features, prenatal and postnatal growth retardation, hypotonia, microcephaly, intellectual disability, and seizures. Clinical findings vary depending on the deletion size. Determination of the deletion size allows for better prediction of prognosis, which emphasizes the importance

Table 1: Clinical, radiological, cytogenetic, and molecular findings of the patients and comparison with the literature

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Present study	Previous reports*
Current age (Year)	2	6	11	11	1	6	7	3	5	16	8	5 Die at	7	11	1 Die at	6	2	1		
Gender	F	M	M	F	M	F	F	M	F	F	M	M	M	M	F	M	M	F	F/M 8/10	F/M 2/1
Consanguinity	-	+	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	16%	
IUGR	+	+	-	+	+	+	+	+	-	-	-	+	+	-	+	+	+	+	72%	80%
HC(SDS)	-5	-3	-4	-3	-6	-4	-3	-7	-5	-5	-4	-7	-6	-5	-7	-4	-5	-4		
Weight (SDS)	-4	-5	-2	-4	-5	-6	-3	-6	-5	-2	-4	-5	-5	-8	-3	-5	-5	-4		
Height (SDS)	0	-2	-2	-3	-5	-4	-5	-4	-4	-3	-3	-3	0	-5	-2	-3	-5	-3		
Typical facial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	>75%
Microcephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	90%
Hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	90%
İntellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	>75%
Growth retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	>75%
Motor retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100%	>75%
Gait ability	-	-	+ Support	-	-	+ Support	+	-	+	+	+	-	-	-	-	+	-	-	38%	45%
Speech	-	-	-	-	-	-	+ Sentence	-	+ Word	+ Sentence	+ Sentence	-	-	-	-	+ Word	+ Word	-	33%	
Seizure	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	89%	90-100%
EEG abnormality	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	83%	80-90%
Cardiac abnormality	-	+ ASD, LVH	+ ASD	+ ASD	+ PDA	-	-	+ ASD, LVH	-	+ ASD	-	+ ASD, VSD	-	+ ASD	+ ASD	+ ASD, AS	+ ASD	+ ASD Transverse arcus hypoplasia	66%	50%
Renal abnormality	+ HN	-	-	+ HN,VUR	+ CKD	-	-	-		-	-	-	+ HN,VUR, PV	-	-	-	-	+ HN	27%	30%
Ophthalmo-logical abnormality	-	-	+ Esotropia Nystagmus	+ Esotropia	-	-	+ Astigmatism	+ CVI	+ CVI	+ Esotropia	-	-	+ Esotropia, CVI	+ Leucoma	-	+ DSR	-	-	50%	25-50%
Hearing loss	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	11%	25-50%

Table 1: (continued)

Thin corpus callosum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	89%	80-100%
Chromosomal analysis	Del 4p15	Del 4p16	46,XY	46,XX	46,XY	Del 4p16	46,XX	Del 4p16	46,XX	46,XX	46,XY	Del 4p15	Del 4p15	46,XY	46,XX	Del 4p16	Del 4p16	Del 4p16	50%	50-60%
FISH	N/A	WH-SCRx1	WHSCRX1	WH-SCRX1	N/A	N/A	WHSCRX1	N/A	N/A	WH-SCRx1	N/A	N/A	N/A	WH-SCRx1	WH-SCRx1	N/A	N/A	N/A	100%	>95%
Microarray deletion size	4p15 p16 (29 Mb)	N/A	N/A	N/A	4p16.3 (2.1 Mb) 19p13.3dup (1.8 Mb)	4p16.3 p16.1 (7.9 Mb) MSX1	N/A	4p16.3 p16.1 (7.2 Mb)	4p16.3 (2.6 Mb)	N/A	4p16.3 (3.3 Mb)	N/A	N/A	N/A	N/A	4p16.3 (8.5 Mb)	4p16.3 p16.1 (9.4 Mb) 8p23.3 dup (6.8 Mb)	4p16.3 p16.1 (6.8 Mb)	100%	100%
Parental Chromosomal Analysis	N/A	Father inv(4)	N/A	N/A	Normal	Normal	Normal	Normal	N/A	N/A	Normal	N/A	N/A	Mother t(4,20)	N/A	N/A	Normal	Normal	22%	20%

***2,7,9,16**

Abbreviations: IUGR intrauterine growth retardation, HC Head Circumference, N/A not assessed,ASD atrial septum defect, VSD ventricular septum defect, LVH left ventricular hypertrophy, PDA patent ductus arteriosus, AS aortic valve stenosis, HN hydronephrosis, CKD chronic kidney disease, VUR vescico ureteral reflux, PUV posterior urethral valves,CVI: cortical visual impairment, DSR lacrimal duct obstruction, Del deletion, Dup duplication, WHSCR WHS critical region, Mb megabase, inv inversion, FISH fluorescence in situ hybridization.

Table 2: Comparison of deletion size with clinical and radiologic findings in our study

Deletion Size	>5 MB (n:9)	≤5 MB (n:9)
IUGR	100%	44%
Seizure	89%	89%
EEG abnormality	89%	77%
Cardiac abnormality	67%	67%
Abdominal USG abnormality	33%	22%
Thin corpus callosum	78%	100%
Ocular abnormality	33%	66%
Gait ability	22%	55%
Speech	22%	44%

of microarray analysis. Confirmation of the diagnosis is important for increasing clinical awareness, appropriate patient follow-up, and genetic counseling. Therefore, parental chromosomal analysis should be performed to prevent recurrence.

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DISCLOSURE

Ethics: This study was approved by the ethical review committee of Ankara Bilkent City Hospital (number E2-24-6158). Written informed consent was obtained from the patient's family for the clinical examination and molecular analysis.
Data availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest: None

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