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Case Report

Wolf-Hirschhorn Syndrome: A Rare Genetic Defect

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Abstract

We report the first documented paediatric case of Wolf-Hirschhorn syndrome, a rare genetic chromosomal abnormality, in a small island developing country in the Eastern Caribbean, Barbados. Although there are documented case reports on Wolf-Hirschhorn syndrome worldwide, few studies have described the condition in patients of Afro-Caribbean descent and from resource-limited countries.

This case highlights the importance of access to specialized investigations to aid in patient diagnosis and management. Many cases with complex neuro-genetic conditions often go undiagnosed in resource-limited countries due to the lack of access to genetic testing. In order to provide comprehensive medical care to children with Wolf-Hirschhorn syndrome, and other genetic disorders, it is imperative to have timely confirmation of diagnosis. This allows for comprehensive management of the disorder, considering the natural history of the disease, its progression and prognosis.

This case is presented with the purpose of increasing clinical knowledge of the condition in resource-limited countries.

Keywords: *Greek Helmet Facies; Wolf-Hirschhorn; 4p Deletion; Resource-Limited Countries*

Introduction

We report the first documented paediatric case of Wolf-Hirschhorn Syndrome, a rare genetic chromosomal abnormality, in a small island developing country in the Eastern Caribbean, Barbados.

Case Report

This now 3-year-old Afro-Caribbean girl was diagnosed with Wolf-Hirschhorn Syndrome at 17 months of age after evaluation of subtle dysmorphic features, developmental delay, and uncontrolled epilepsy. There was no significant family history of epilepsy, cardiac disease or chromosomal abnormalities.

Past medical history

The patient was delivered via spontaneous vertex delivery to a 24-year-old G2P1 mother at 39+5 weeks gestation. Labour was induced as there were concerns about intra-uterine growth restriction from approximately 37 weeks. There was no previous history of intrauterine infections and no congenital anomalies were detected on a 2nd trimester ultrasound scan at 20 weeks. The labour and delivery were uneventful. Apgar scores awarded were 9 (1 min) and 9 (5 mins). The patient was symmetrically small for gestational age with parameters as follows: weight 2140g (< 10th centile), length 45.4 cm (10th centile), occipito-frontal circumference 31.5 cm (10th centile). There was a wide anterior fontanelle with splayed sagittal suture. The postnatal period was uneventful and the patient was discharged home on day 2 of life after breastfeeding was established. TORCH infection screen was negative and thyroid function tests were normal.

At 8 months of age, the patient presented to the Queen Elizabeth Hospital in Barbados with a history of fever and erythema noted to the umbilicus from the day of presentation. Prior to presenting to hospital, she had focal seizures of the left upper limb which became generalized and lasted more than one hour. The seizure was aborted with IV diazepam on arrival. She subsequently had a generalized tonic-clonic seizure 20 minutes later requiring another dose of IV benzodiazepines. She received a loading dose of Phenytoin at 20 mg/kg and commenced on maintenance at 5 mg/kg/day. On assessment in the emergency room, the patient was ill-appearing and lethargic. She was tachycardic with an unrecordable blood pressure and required a 20 ml/kg fluid bolus. Her umbilicus was erythematous with a central punctum which spontaneously ruptured and pus was expressed.

The child showed subtle dysmorphic features (Figure 1) including buphthalmos, hypertelorism, frontal bossing, high anterior hair line, and a short frenulum. The motor examination showed truncal ataxia with mild hypotonia. There was a grade 2/6 systolic murmur heard throughout the entire precordium without evidence of heart failure. The patient was admitted to the paediatric intensive care unit (PICU) with status epilepticus and septic shock (fluid responsive) due to an umbilical abscess.

Figure 1: *The above pictures of the patient showing the subtle dysmorphic features including buphthalmos, hypertelorism, frontal bossing, high anterior hair line, and a short frenulum (Pictures were provided by the patient's mother after written consent obtained).*

Blood, urine, and cerebrospinal fluid cultures were all sterile. Umbilical wound swab yielded a growth of coagulase negative *Staphylococcus*. She completed a course of IV antibiotics. An echocardiogram was done which revealed a large secundum atrial septal defect (ASD)

with moderate pulmonary stenosis. A non-contrast CT brain and electroencephalogram were normal. An abdominal ultrasound scan revealed ectopia of left kidney. On completion of the antibiotic course, she was discharged home on maintenance phenytoin.

At 9 months of age, she was noted to have gross motor developmental delay and failure to thrive so she was referred to the dietitian and physiotherapy was commenced. A comprehensive step one screening panel inclusive of acylcarnitine profile, amino acid profile, G6PD DNA analysis, 17-alphahydroxyprogesterone, immunoreactive trypsinogen, biotinidase, haemoglobinopathies, TSH, uridyltransferase and total galactose were within normal limits for the patient.

She re-presented to hospital at 12 and 13 months of age with recurrent status epilepticus. Anti-seizure medication was changed to valproic acid. MRI brain revealed widespread cerebral white matter signal abnormalities. At 14 months of age, she developed congestive cardiac failure and was commenced on furosemide.

At 17 months of age, she was referred to an international cardiac centre and had surgical patch closure of the atrial septal defect. Chromosomal microarray was performed at that time and revealed a 9.8 Mb loss of 4p16.3.1 (68, 345-9, 768, 141) x1 and 1.85 Mb gain of 4p16.1p15.33, 590 kb gain of 4p15.33 and 262 kb gain of 4p15.33. These results suggested a complex rearrangement of the 4p region with the loss of 4p16.1p15.33 being diagnostic of Wolf-Hirschhorn syndrome. Parental microarray studies were recommended to determine if this was familial or *de novo* in origin.

At last follow-up, the patient's seizures were controlled on valproic acid. Following cardiac surgery, she gained weight to the 50th centile on WHS-specific growth charts.

Discussion

The prevalence of Wolf-Hirschhorn Syndrome (WHS), first described in 1961 by Americans Herbert L. Cooper and Kurt Hirschhorn, is estimated at 1:50,000 births with a 2:1 female predominance [1]. Due to misdiagnosis or underdiagnosis of this rare condition, this prevalence may be an underestimate [2].

WHS occurs due to deletion of contiguous genetic material near the distal end of the short (p) arm of chromosome 4. The size of the deletion is variable with larger deletions having a greater incidence of severe intellectual disability and physical abnormalities compared to smaller deletions [3-5]. For example, loss of the NSD2 gene is associated with many of the characteristic features of Wolf-Hirschhorn syndrome, including the typical facial features and developmental delay while deletion of the LETM1 gene appears to be associated with seizures in some patients or other abnormal electrical activity in the brain [6] and loss of the MSX1 gene may be responsible for the dental abnormalities and cleft lip or palate that also occur with this syndrome.

Approximately 90% of cases occur because of *de novo* mutations in early embryonic development and are not inherited. We were unable to perform parental microarray studies to determine if our patient's case was familial or *de novo* in origin however, there was no known family history. Approximately 50% of affected individuals have a *de novo* deletion of 4p16 and about 40 - 45% have an unbalanced translocation with a deletion and partial trisomy on another chromosome arm.

WHS is characterized by craniofacial features consisting of the "Greek warrior helmet" appearance of the nose, microcephaly, high anterior hairline with prominent glabella, hypertelorism, high-arched eyebrows, short philtrum, downturned corners of the mouth, micrognathia and ear anomalies. Affected individuals have intrauterine growth deficiency followed by postnatal growth retardation. All patients with WHS have developmental delay and intellectual disability of varying degrees.

Epilepsy constitutes a major medical challenge during the first years of life and seizures occur in up to 90% of children with WHS. In a study conducted by Battaglia., *et al*. in 2008 [7], epilepsy occurred in 81 patients (93%) within the first 3 years of life. Of those patients,

74% had generalized tonic–clonic seizures, which was the only seizure pattern. Varying other seizure types were described inclusive of tonic spasms, complex partial seizures and clonic seizures. Distinctive electroencephalographic (EEG) abnormalities were observed in 73 out of 81 (90%). EEG abnormalities included frequent, ill-defined, high-amplitude, sharp element-spike/wave complexes at 2-to 3.5-Hz, usually diffuse, occurring in long bursts, and activated by slow wave sleep; and frequent high-amplitude, spikes, poly spikes/wave complexes at 4- to 6-Hz, over the posterior third of the head, often only seen with the eyes closed [1]. Epilepsy was well controlled mainly with valproate and phenobarbitone and improved with age in all patients with WHS [7].

WHS is also associated with other congenital anomalies including skeletal anomalies, heart defects, urinary tract anomalies, structural brain abnormalities. Brain magnetic resonance imaging (MRI) studies are the preferred imaging modality and studies have reported various abnormalities including multifocal white matter hyperintensity areas as also demonstrated in our case. As seen in the literature, other MRI abnormalities can include thinning of the corpus callosum and agenesis of the corpus callosum agenesis was observed [1].

Cardiac manifestations are seen in up to 50% of the cases and are usually not complex. The congenital cardiac defects include atrial septal defects, most frequently, followed by pulmonary stenosis, ventricular septal defect, patent ductus arteriosus, aortic insufficiency and tetralogy of Fallot [5].

The clinical phenotype and the craniofacial features are characteristic of WHS; however, there may be overlap with other genetic syndromes such as Seckel, CHARGE, and Smith-Lemli-Opitz syndromes [7].

The diagnosis is made on chromosomal analysis such as chromosomal microarray, conventional cytogenetic analysis, or fluorescence in situ hybridization (FISH) when there is a heterozygous deletion on chromosome 4p16.3 of the WHS critical region (WHSCR) [6]. The pattern of inheritance depends on the mechanism of the origin of the deletion.

Management is supportive and focused on addressing the specific manifestations associated with WHS [7,8]. Frequently, a diagnosis of WHS is associated with fetal demise or infant death within the first year of life. Individuals who live past the first year of life, have developmental and growth delays. Following diagnosis, measurement on appropriate WHS-specific growth charts is important as well as developmental surveillance, EEG monitoring, evaluation for feeding difficulties and other associated anomalies as previously mentioned.

Conclusion

The patient described in this report displayed craniofacial features and sequelae typical of Wolf-Hirschhorn syndrome. Partly due to the unavailability of chromosomal analysis in Barbados, diagnosis was delayed, as is often the case in previously reported cases. This highlights the need for increased access to genetic testing in resource limited settings globally. Significant progress has been made in the understanding of WHS since the chromosome 4p deletion was first described but management of patients with WHS is still largely supportive involving many specialties.

Children with WHS face many challenges, physically and developmentally and both doctors and caregivers have to make difficult care decisions. Accurate diagnosis allows for genotype-specific anticipatory guidance and recommendations to families of individuals with WHS [6]. In recent years guidelines for routine health supervision in the primary care setting have been proposed for children with various syndromes including WHS. With further genetic work being done, there is a possibility for development of targeted molecular treatments in the future [9].

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