Clinical Vignette

Novel Findings in a Fetus with 4p Deletion Syndrome: Case Report and Review of Literature

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Abstract

The 4p deletion syndrome, also known as Wolf -Hirschhorn Syndrome (WHS), is caused by partial deletion of the short arm of chromosome 4. The syndrome is well known and extensively described in the pediatric age groups and young adults and about 83 prenatal cases have been described to date in world literature. But literature on the fetal phenotype and genotype of WHS is limited. We are reporting here the ultrasound features, fetal autopsy, and molecular diagnosis in a fetus with WHS, in whom the diagnosis was confirmed through chromosomal microarray of the amniotic fluid sample which revealed a genomic deletion of 17.3 Mb on cytoband 4p16.3p15.32 of chromosome 4.Dilated pulmonary artery and narrow aorta noted in this fetus are novel findings not reported earlier.

Keywords: 4p deletion; fetus; genotype-phenotype correlation

Introduction

Wolf-Hirschhorn Syndrome (WHS; OMIM # 194190), caused by chromosome 4p deletion, is a well-known microdeletion syndrome. It has an incidence of 1/20,000 - 1/50,000 with a female preponderance of 2:1 (Battaglia et al., 2008). The condition was recognized by Wolf and co-workers and Hirschhorn and his group independently (Wolf et al., 1965; Hirschhorn et al.,1965).

WHS syndrome is characterized by unique facial dysmorphism referred to as the 'Greek warrior helmet' appearance (which includes broad nasal bridge, high forehead, prominent glabella, hypertelorism), severe fetal growth restriction, multiple skeletal and cardiovascular anomalies, intellectual disability, seizures, eye defects, and urogenital defects (Battaglia et al., 2001).

WHS is a contiguous gene deletion syndrome. The syndrome is caused by partial loss of the short (p) arm of chromosome 4 (4p16.3). About 55% patients with WHS have a de novo simple deletion of 4p16.3 and 40%-45% of individuals with WHS have an unbalanced translocation. These unbalanced translocations may be de novo or inherited from a parent with a balanced rearrangement.

The phenotypic severity depends upon the size of the deletion; the larger the deletion, the more severe the manifestations (Zollino et al., 2000). The severity of WHS has been classified into three types depending upon the size of the deletion: mild- less than 3.5 Mb, moderate-5 to 18 Mb, and severe- more than 22 Mb (Zollino et al., 2000). Large deletions of 22 to 25 Mb or more are characterized by severe complex features, including typical facial appearance, severe intellectual disability, severe growth delay, severe seizures, neurological abnormalities, ophthalmic abnormalities, congenital heart malformations, skeletal and renal anomalies, cleft palate and hypospadias (Zollino et al., 2000).

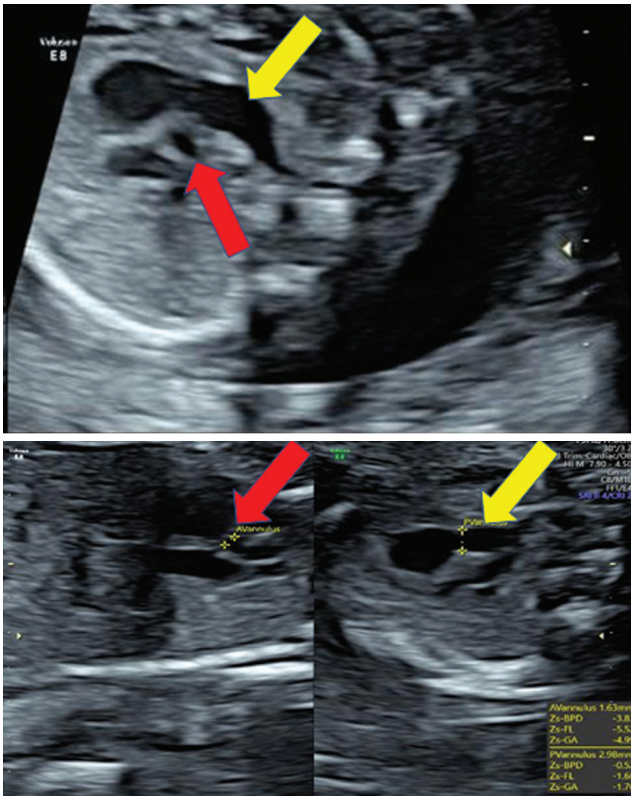
WHS critical region 1 and 2 (WHSCR1 and 2) have been identified as two critical regions for the disease. *WHSC1* and *WHSC2* genes are two candidate genes in the WHCR1 region. The *WHSC1* gene (OMIM * 602952) plays a major role in normal development and its deletion is likely to contribute to the WHS phenotype. The *WHSC2* gene (OMIM *606026) functions in mRNA processing and cell cycle. *LETM1* (OMIM 604407) is a candidate gene in WHSCR2 and is considered to be the major candidate gene for the seizure phenotype. (Zollino et al., 2008).

We report a male fetus of 20-21 weeks gestational age with 4p16.3 deletion syndrome, diagnosed by chromosomal microarray (CMA). The ultrasound and autopsy findings are described and the genotype-phenotype correlations in WHS are discussed.

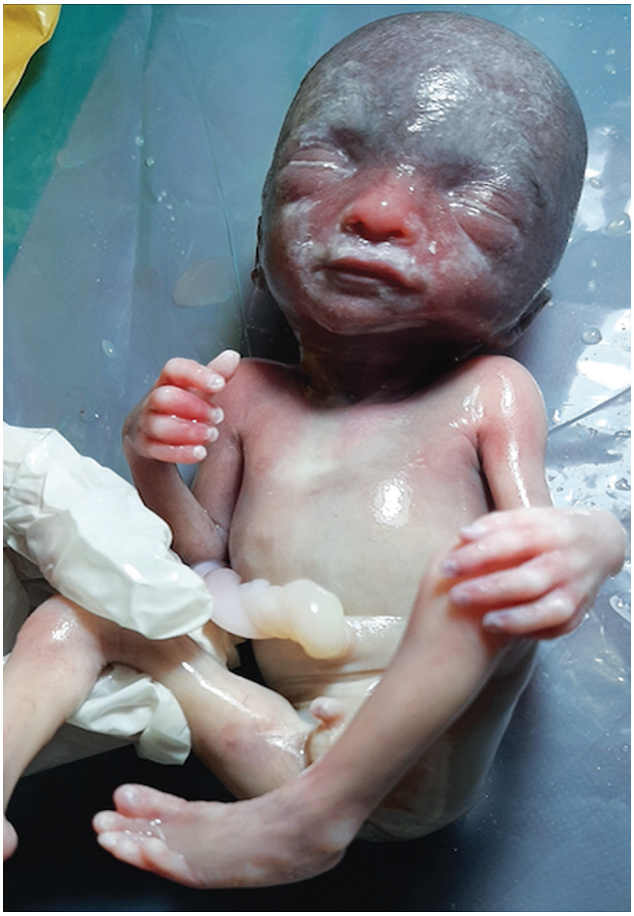
Patient details

A 33-year-old primigravida, with spontaneous conception, was referred at 19 weeks + 3 days of gestation, as her anomaly scan showed fetal growth restriction (estimated fetal weight was at 1st centile), narrow ascending aorta, and hypoplastic cerebellum (**Figure1a**). The transverse cerebellar diameter was 18 mm and was at 1st centile for

Figure 1



1a. Ultrasound of the fetus showing the narrow aorta (marked with red arrow) and dilated pulmonary artery (marked with yellow arrow)



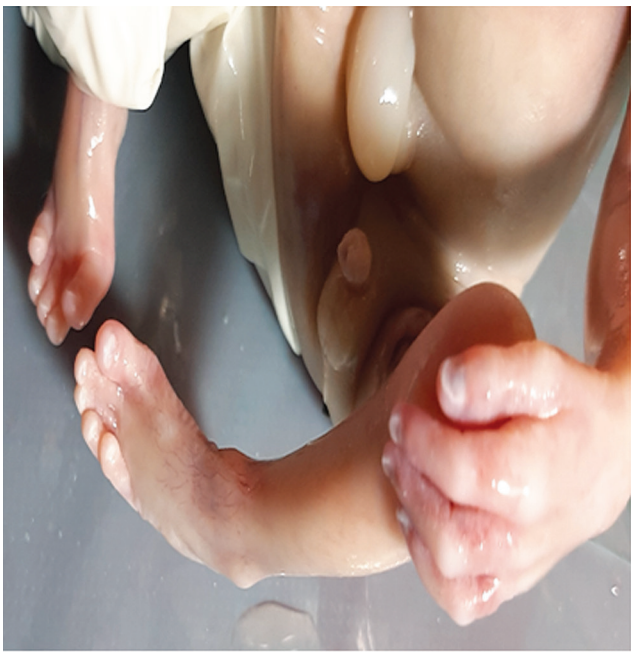
1b. Fetal autopsy showed broad nasal bridge and prominent glabella.

gestation. The aorta measured 1.63 mm at the aortic valve annulus (Z score- 4.99). The pulmonary valve annulus measured 2.98 mm (Z score -1.76) (**Figure 1a**) (Schneider et al., 2005). In addition, the dual marker test and NT (nuchal translucency) scan done earlier were normal. There was no family history of similar issues, and the couple was non-consanguineous. There was no history of fever or rash during pregnancy and no history of drug intake.

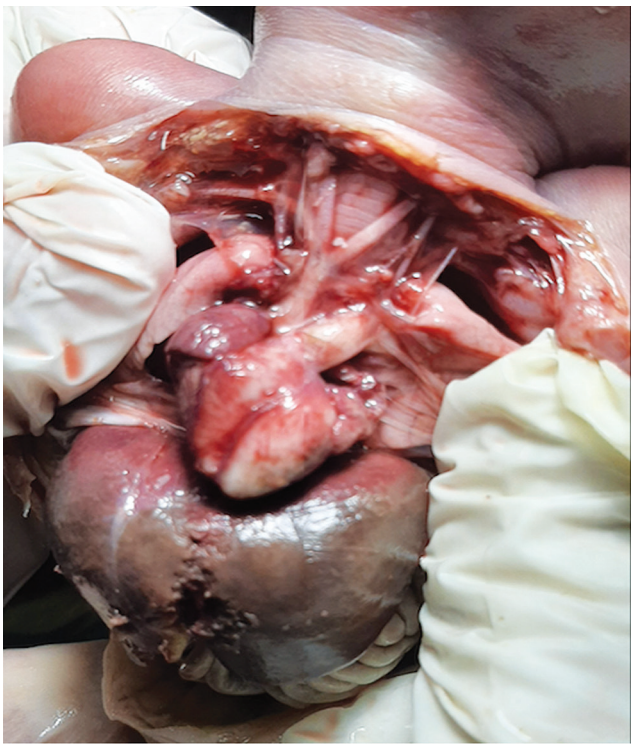
The patient was counselled about the guarded prognosis and associations with aneuploidy or copy number variation (CNV) and amniocentesis was done to check for the same. The fluorescence-in situ- hybridisation (FISH) report for five common aneuploidies (chromosomes 13, 18, 21 and sex chromosomes) in the amniotic fluid was normal.

The couple decided to terminate the pregnancy. A male fetus of weight 284 gm was delivered vaginally after medical induction and referred for fetal autopsy. Fetal autopsy revealed a male fetus corresponding to 20-21 weeks gestation with dysmorphic facies: broad nasal bridge, prominent glabella, and abnormal shape of the feet (**Figures 1b and 1c**). Internal dissection showed narrow ascending aorta compared to the pulmonary artery and hypoplastic cerebellum (**Figure1d**).

Chromosomal microarray (4x180K; Agilent Array CGH, Agilent Technologies, California, United States) of cultured amniocytes revealed a significant deletion of 17.3Mb on cytoband 4p16.3p15.32(72447_17462172)x1.



1c. Abnormal shape of the feet noted.



1d. Fetal cardiac dissection showed narrow ascending aorta and dilated pulmonary artery.

Table 1 shows various features reported on antenatal ultrasound in literature in comparison to the features we observed in this fetus (Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020).

Discussion

WHS, chromosome 4p monosomy, is a contiguous gene deletion syndrome. The unique features of 4p deletion syndrome include growth retardation, 'Greek warrior helmet' facial dysmorphism, intellectual disability, facial clefts, cardiac septal defects, corpus callosum agenesis, kidney abnormalities, feet malformations, congenital diaphragmatic hernia, increased nuchal fold thickening, and cystic hygroma.

The fetus in this study presented with mild fetal growth restriction (FGR), aortic atresia, pulmonary artery dilatation, and cerebellar hypoplasia on ultrasound. Fetal autopsy findings confirmed the same. Facial features were subtle, like prominent glabella and hypertelorism. In addition, both feet had an abnormal shape. Narrow aorta and dilated pulmonary artery are novel findings not reported in both the prenatal and postnatal series reported earlier. Xing et al. reviewed 37 cases of WHS reported in the literature along with their ten cases and reported that the standard sonographic features of WHS include intrauterine growth retardation (IUGR) (97.7%), typical facial appearance (82.9%), renal hypoplasia (36.2%), cardiac malformation (29.8%), cleft lip and palate (25.5%), cerebral abnormalities (25.5%), skeletal anomalies (21.3%) and increased nuchal translucency/nuchal fold thickness (19%) (Xing et al., 2018). In **Table 1**, we have compared about 83 fetuses reported in world literature (Simonini et al., 2022). The two most common features are FGR (fetal growth restriction) (81.92%) and typical facial anomalies (69.87%). (Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020; Simonini et al.,2022). In the fetus we report, growth was less than 1st centile, however, typical facial features were not picked up on the ultrasound and we feel that it is difficult to detect subtle facial features of this syndrome by ultrasound without high index of clinical suspicion of this syndrome.

Cardiac malformations in WHS cases have been reported with a breakpoint between 4p15.2 and 4p16.3. Only three prenatal cases with larger 4p deletions have been reported. Verloes et al. reported a fetus with 4p14 deletion with atrial septal defect (ASD), tricuspid valve hypoplasia, pulmonic valve atresia, right ventricular hypoplasia,

and aneurysmal dilation of the ascending aorta (Verloes et al.,1995). von Elten et al. reported a fetus with hypoplastic left heart syndrome (HLHS) (von Elten et al., 2013). The fetus reported by Xing et al. had a 23.4 Mb deletion at 4p15.2 and had a complex heart malformation including interruption of the aortic arch, ventricular septal defect (VSD), and pulmonary hypertension (Xing et al., 2018). Postnatal studies mainly discuss genotype- phenotype in the context of facial features, seizures, and growth delay and not based on cardiac anomalies.

In our case study, the fetus had a 17.3 Mb deletion at 4p16.3. It is a moderate size deletion, and maximum cases of this syndrome reported in literature have moderate size deletions. Patients with deletion <5 Mb cannot be picked up on routine karyotype. Chromosomal microarray has higher resolution compared to the karyotype and can detect sub-microscopic deletions upto 20 kb, and hence should be offered in all cases of fetal ultrasound anomalies and FGR.

Deletion of *WHSC1*, (abbreviated later as *NSD2* gene) (OMIM *602952), can disrupt the regulation of several genes resulting in WHS features (Meckkawy et al., 2021) De novo loss-of-function variants in *NSD2* gene were recently reported in patients with atypical WHS and in developmental delay, congenital cardiac defects and autism (Bockzeck et al., 2018). Nimura et al. hypothesized that *NSD2* gene might play a role in modulating the cardiac transcriptional network through collaboration with *NKX2.5* gene (Nimura et al., 2009).

The recurrence risk is negligible in de novo/ sporadic cases. However, in cases where WHS is due to balanced translocation in parents, recurrence risk could be 30-40% and in such cases prenatal diagnosis can be done by chorionic villus sampling or amniocentesis during pregnancy.

Conclusions

Our report highlights novel findings like narrow ascending aorta and dilated pulmonary artery associated with fetal WHS, and further such studies may provide insight into correlation between the genotype and cardiac phenotype of WHS.

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Table 1 **Summary of phenotypic features in fetuses with Wolf-Hirschhorn syndrome**
(Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020; Siminino et al., 2022)

Clinical feature	Number (%) out of 83 fetuses	Fetus in this report
Fetal growth restriction	68/83 (81.92%)	+
Facial anomalies	58/83(69.87%)	+
Microcephaly	16/83(19.27%)	-
Abdominal anomalies	10/83 (12.04%)	-
Cardiac anomalies	25/83 (30.12%)	+
Skeletal anomalies	17/83 (20.48%)	+
Cerebral anomalies	19/83 (22.89%)	-
Pulmonary malformation	12/83 (14.45%)	-
Cystic hygroma	8/83 (9.63%)	-
Increased nuchal translucency or nuchal fold thickness	18/83(21.68%)	-

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