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Varying Clinical Presentation of Williams Syndrome: A Case Series

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ABSTRACT Williams syndrome (OMIM 194050) is a rare multisystem genetic disorder with an incidence of 1/ 75000 which usually occurs sporadically caused by the deletion of 26 contiguous genes, including elastin (ELN) (OMIM 130160) on chromosome 7q11.23. The researchers present here three cases of Williams syndrome with cardiac anomalies and varying clinical presentation. In this paper the researchers suggest a defined protocol with more attention while evaluating cardiac anomalies in childhood period, especially when the patient has facial dysmorphism or developmental delay.

INTRODUCTION

Williams syndrome (OMIM 194050) (WS), also known as Williams-Beurens syndrome (WBS), is rare (1:75,000 live births) multisystem genetic disorder and is characterized by typical facial dysmorphisms, congenital heart defects, mental retardation and a characteristic cognitive profile. In addition, infantile hypercalcemia, hoarse voice, hyperacusis, endocrine abnormalities, growth deficiency, orthopaedic problems and renal abnormalities may also be associated (Gray et al. 2013). WS is considered a segmental aneusomy due to a hemizygous deletion of a contiguous gene at the long arm of chromosome 7 (7q11.23) (Stromme et al. 2002). Most individuals with WS (99%) have a 1.5 mega base deletion in 7q11.23 encompassing the elastin gene (*ELN*) and 26-28 other genes (Kozel et al. 2014) all of which is detectable by fluorescent in situ hybridization (FISH) (Wiliams and Lind 2012). Diagnosis of WS is made by clinical evaluation, usually during infancy, when they have distinctive facial appearance including broad brow, periorbital fullness, a stellate/lacy iris pattern, strabismus, short nose, full nasal tip, depressed nasal bridge, long philtrum, full lips, wide mouth, and prominent earlobes (Kotzot et al. 1995). The FISH test is useful for confirming the diagnosis because the broad phenotypic spectrum hinders the making of a diagnosis, especially in the first year of life (Sugayama et al. 2007). In this paper, the researchers discuss 3 patients with WS who presented to them with cardiac anomalies and varying clinical features. The aim of the paper is to provide an in-depth description of the clinical features of WS and to emphasis the multidisciplinary approach needed in the management.

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CASE PRESENTATION

Patient 1

A 10-month-old girl child born to non-consanguineous young couple with maternal age 25 years and paternal age 31 years. There was no significant medical or family history of note. The infant was born full term uneventful pregnancy by caesarean section. The birth weight was 2.55 kg with no perinatal issues. There was history of mild motor delay. Clinical examination revealed overfriendly active child with facial dysmorphisms. This included broad forehead, periorbital fullness, full cheek, short upturned nose and protruding lips. The proband also had feeding difficulties leading to failure to thrive, including gastroesophageal (G-E) reflux, disordered suck and swallow, and vomiting. In view of a systolic heart murmur, echocardiogram was done which revealed a mild supravalvular aortic stenosis (SVAS).

Patient 2

A 3-year-old girl child born to non-consanguineous young couple with maternal age 26

years and paternal age 31 years. There was no significant medical or family history of note. The infant was born full term normal delivery. The birth weight was 2.49 kg with no perinatal issues. There was history of mild motor delay. Clinical examination revealed overfriendly active child with facial dysmorphisms. This included broad forehead, short upturned nose and protruding lips. The proband also had failure to thrive, temperamental abnormality. Echocardiogram was done which revealed a large ventricular septal defect (VSD), bilateral peripheral pulmonary artery stenosis, mild SVAS. She underwent surgical correction, VSD closure, pericardial patch of peripheral pulmonary arteries, Doty's repair of SVAS with good result.

Patient 3

A 1-year-old girl child born to non-consanguineous couple with maternal age 34 years and paternal age 37 years. There was a history of primary infertility for the past 10 years. The infant was born via in vitro fertilization (IVF) and full term lower segment caesarean section delivery. The birth weight was 2.5 kg. There was history of mild motor delay. Clinical examination revealed overfriendly active child with facial dysmorphisms. This included broad forehead, periorbital fullness, full cheek, short upturned nose and protruding lips. The proband also had feeding difficulties leading to failure to thrive, including gastroesophageal (G-E) reflux, disordered suck and swallow, and vomiting. Echocardiogram was done which revealed severe coarctation of aorta in neonatal period. She underwent surgical repair of coarctation which showed marked aortic wall thickening with thick leather like consistency. She developed recoarctation after 10 months. After a transcatheter balloon angioplasty of aortic recoarctation, she developed an iliac hematoma with blood loss and succumbed after the procedure.

All the three patients with a triad of dysmorphic facies (Fig. 1a), cognitive disorder and characteristic congenital heart defect; a diagnosis of WS was made clinically. FISH was performed on metaphase chromosomes for these patient using LSI WS (Elastin Gene) region probe localized to 7q11.23 from Vysis Inc., USA. The result of FISH showed the red signal only on one of the chromosome 7 at 7q11.23 region in all the metaphases analysed suggesting deletion of *ELN* gene (FISH positive WS) (Fig. 1b).

METHODOLOGY

The blood samples were collected from the affected individuals (2-5 ml each). Phytohemagglutinins (PHA) stimulated 72 hours whole blood cultures were set up to obtain metaphases using standard techniques. FISH was carried out using LSI Williams syndrome (Elastin gene – 7q11.23) region probe (Vysis Inc., USA) by co-denaturation of the probe with the test samples at 72^0C for 5 minutes, followed by overnight hybridization at 37^0C. After washing as per the manufacturer's protocol, the slides were mounted in the counter stain DAPI (4',6-diamidino-2-phenylindole) and observed under a Zeiss fluorescent microscope. The images were captured and processed with metasystems isis software.

Fig. 1. (a) Facial features of Williams syndrome patients
(b) The fluorescence hybridization in situ (FISH) method shows the deletion of 7q11.23 in our patients

DISCUSSION

The most significant cause of morbidity and mortality in WS is the cardiovascular disease. SVAS is present in ~70 percent and requires surgical correction in ~30 percent, usually before age 5 years (Collins et al. 2010). Most patients with SVAS are diagnosed during evaluation of an asymptomatic heart murmur (Frank and Jacobe 2011). Jones and colleagues evaluated 19 patients with WS and found five with pulmonary stenosis, two with VSD, two with atrial septal defect, one with valvar aortic stenosis and nine with extra cardiac defects (that is, other than SVAS). The first patient had mild SVAS and there were no signs of cardiac hypertrophy or heart failure; thus surgery was not necessary. Second patient was diagnosed to have large VSD, bilateral peripheral pulmonary artery stenosis, mild SVAS had surgical fenestrated VSD patch closure, branch pulmonary artery pericardial patch repair with DOTY's repair of SVAS. Third patient had neonatal coarctation and arch hypoplasia with diffuse narrowing of descending aorta. She underwent surgical correction of coarctation followed by balloon angioplasty for recoarctation. Her surgical findings were markedly thickened aortic wall. No aortic biopsies were done. Although balloon dilation (Jacob et al. 1993) and stent treatment (Lezo et al. 2004) of SVAS have been reported, the close proximity to the aortic valve and coronary artery orifices are significant obstacles, and currently operation is the treatment of choice.

The WS phenotype is characterized by short stature, craniofacial abnormalities (Tassabehji et al. 2005) with a characteristic dysmorphic face, abnormalities affecting different systems such as the cardiovascular system (vascular stenosis), the musculoskeletal or endocrine systems, and frequent infantile hypercalcaemia leading to nephrocalcinosis (Gut and Kutilek 2011). In addition, feeding problems and sleeping disturbances have been reported in individuals with WS (Mason et al. 2011; Parlak et al. 2014).

WS arises when there is a genomic microdeletion at human chromosome 7q11.23 which is subject to numerous genomic rearrangements, including deletions, inversions, and duplications (Scherer and Osborne 2006). The deletion arises on either the maternally or the paternally inherited chromosome 7 and is sporadic (for example, de novo) in virtually all cases (Koolen et al. 2012). Due to the facts, parents were advised to undergo both cytogenetic analysis and FISH testing. The result found was normal and hence, at genetic counselling they were reassured about the low recurrence risk for subsequent pregnancy.

CONCLUSION

Currently, diagnostic testing for the deletion may be accomplished by fluorescent in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MPLA), chromosome microarray or complete ELN exon sequencing. The clinical and echocardiographic diagnosis in patients who have WS is of the utmost importance, because this is a degenerative and progressive illness. In addition interventions may help children with WS to achieve their full potential.

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