Clinical Case Reports

CASE REPORT

Williams syndrome presenting with findings consistent with Alagille syndrome

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Key Clinical Message

Conjugated hyperbilirubinemia, posterior embryotoxon, and vertebral anomalies are not features of William syndrome (WS). We herein report a preterm infant who presented with features suggestive of Alagille syndrome, but microarray showed findings consistent with WS. This further extends the phenotype of WS and emphasizes the need for microarray analysis.

Keywords

Introduction

Williams syndrome (WS) (Online Mendelian Inheritance in Man [OMIM] # 194050) is a genetic condition characterized by distinct facial appearance, typical cardiovascular anomalies (supravalvular aortic/pulmonic stenosis, peripheral pulmonary stenosis, and hypertension), hypercalcemia, and a characteristic neurodevelopmental and behavioral profile. It is a contiguous gene disorder with a deletion at 7q11.23, a segment that contains 26–28 genes [1].

Alagille syndrome (AS) (OMIM # 118450) is a condition caused by mutation in the *Jagged 1* or *NOTCH 2* genes. AS consists of liver dysfunction (cholestatic jaundice due paucity of bile ducts), cardiac abnormalities (dysplastic pulmonary valve and peripheral pulmonic stenosis), spine anomalies (butterfly vertebrae), eye abnormalities (posterior embryotoxon), characteristic facial features, renal abnormalities (dysplasia and renal artery stenosis), and rarely arteritis.

We herein report a preterm infant with clinical features suggestive of AS but have microarray analysis consistent with WS. To the best of our knowledge, this, very unusual association, have been reported only on three occasions in the past [2–4] and further extend the phenotype of WS in the neonate rather than being a coincidental finding.

Case Report

The patient was born to a 48-year-old G3P0A2L0 mother and a 52-year-old father, both of Caribbean descent. The father was healthy and the mother had high blood pressure. The pregnancy was complicated with maternal hypertension treated with labetalol, severe symmetrical intrauterine growth retardation (IUGR), agenesis of the corpus callosum (ACC), and fetal echocardiography showing mildly dysplastic pulmonary valve. Delivery was at 35.6 weeks gestation, by emergency cesarean section

Figure 1. Clinical photograph showing depressed nasal bridge and prominent forehead.

for IUGR and a transverse lie. The baby boy had severe respiratory distress with APGAR scores of 1 and 6 at 1 and 5 min, respectively, required cardiopulmonary resuscitation.

His birth weight was 1020 g, head circumference of 27 cm, and length of 34 cm, all substantially below the third centile. Investigation done to delineate the etiology of the IUGR included chromosome analysis (46,XY), TORCH screen and urine for virology, which were all normal. His initial eye examination was normal and head ultrasound confirmed ACC. He received a dose of surfactant and was ventilated for 2 days. His initial examination showed a large anterior fontanel, depressed nasal bridge, bilateral epicanthic folds, full lips (Fig. 1), and hypospadias with chordee. Echocardiography showed pulmonary artery valve dysplasia and stenosis and stenosis of both pulmonary arteries. He had unconjugated jaundice on day one of life with serum bilirubin level of 122 mmol/L, which was treated with phototherapy (his and mother's blood group were O positive, direct antibody test (DAT) was negative, G6PD and galactosemia screen were normal). He was stable for 2 weeks and then developed abdominal distension, bloody stools suggestive of necrotizing enterocolitis (NEC), and acholic stools with conjugated hyperbilirubinemia and transaminitis. Investigation to delineate the etiology of the hyperbilirubinemia including TORCH screen, virology, metabolic workup, and liver ultrasound were unremarkable except for elevated Thyroid stimulating hormone (TSH). The possibility of primary hypothyroid was entertained and the baby was treated successfully with thyroxin. He was noted to have systolic hypertension on a few occasions that was treated with hydralazine. His abdominal ultrasound, renal dopplers, and urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels were normal.

In view of his facial dysmorphism, IUGR, conjugated hyperbilirubinemia and pulmonary stenosis, AS was suspected. Brain magnetic resonance imaging (MRI) showed hypoplasia of the corpus callosum with all segments present and narrowing of the foramen magnum with no signal abnormalities of the spinal cord.

Eye examination showed posterior embryotoxon. This made the diagnosis of AS more likely. Liver biopsy performed at 65 days of age (corrected age [CA] 44 weeks) showed evidence of cholestasis with no evidence of biliary atresia or paucity of bile ducts. He was started on ursodeoxycholic acid. The gamma-glutamyltransferase (GGT) remained very high (peak value-2000) with normalization of the conjugated bilirubin and other liver enzymes (peak conjugated bilirubin – 100, alanine transaminases (ALT)-
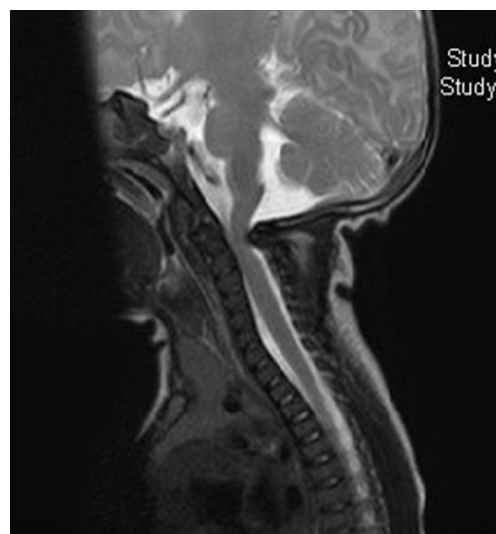

Figure 2. MRI spine – narrowing of cervical canal.

Figure 3. Abdominal ultrasound showing narrowing of the abdominal aorta above the bifurcation.

250, aspartate aminotransferase (AST)-350, alkaline phosphatase (ALP) > 800).

Repeat MRI showed indentation of the dorsal aspect of the spinal cord with T2 signal changes suggestive of injury of the spinal cord (Fig. 2). Vertebral CT scan showed malalignment at the craniocervical junction with narrowing of cervical canal at the level of C1. Neurosurgeons recommended C spine precautions (avoidance of flexion and extension of neck and care with handling). A repeat abdominal ultrasound showed normal renal Dopplers but narrowing of the lower part of the abdominal aorta (just above the bifurcation) with minimal thickening of the aortic wall suggestive of arteritis (Fig. 3). He also developed bilateral inguinal hernia that was repaired before discharge.

DNA analysis of Jagged1 gene, associated with AS, showed no detectable mutation. Microarray analysis showed a 7q11.23 deletion [7q11.23(72,323,639-73,779,626)X1] consistent with WS.

At 50 weeks of age, his calcium was slightly elevated (3.1 and 2.9) on a few occasions. His weight gain remained poor despite high caloric feeds with all growth parameters being substantially below the third centile. He was discharged at 18 weeks post term on home oxygen.

Discussion

WS is a complex multisystem disorder with considerable phenotypic variability caused by the extent of the deletion of more than two dozen genes in the WS chromosome region (7q11.23) and their interaction with other genes outside that region [1]. Almost all the cases result from the de novo deletion as in our case. The initial diagnosis of this syndrome is made by clinical evaluation, usually during mid-childhood when the features, cognitive profile, and cardiac findings become more apparent with age. Fluorescence in situ hybridization (FISH) is particularly helpful in making the diagnosis in infancy by detecting the typical submicroscopic deletion at 7q11.23 [13].

Cholestatic jaundice and posterior embryotoxon are not known features of WS. Our patient presented mainly with IUGR, peripheral pulmonary stenosis, and cholestatic jaundice which are the common findings in AS (Fig. 4). Our suspicion became stronger with the development of posterior embryotoxon. AS is associated with group of ocular findings with no serious functional problems, the most common being posterior embryotoxon seen in 95% of the patients [7]. Posterior embryotoxon has never been reported in association with WS. Facial dysmorphism can be subtle early in life and may lead to difficulty in diagnosis in both syndromes [1–3]. All these features pointed toward the diagnosis of AS; however, our patient did not have typical butterfly vertebrae, which are more easily recognized in older children [5,6]. Our patient was preterm and was only 15 weeks post term when he was transferred to the pediatric ward. In our case, there was narrowing of the cervical canal at the level of C1, which was attributed to the dysplastic C1 arch in view of absence of ossification of the anterior arch and incomplete ossification of the posterior arch of the atlas. Vertebral anomalies are not typically associated with WS.

Vascular anomalies are also recognized in both syndromes. It is one of the major causes of morbidity and mortality in AS. Renovascular hypertension and coarctation of abdominal aorta being one of them. The common cause of hypertension in these patients has been attributed to the involvement of the renal vasculature [9, 10, 15,16]. Arterial narrowing due to thickening of the vascular smooth muscle is also well known in WS and can be isolated or occur simultaneously anywhere [1]. The stenosis of the thoracic aorta and middle aortic syndrome has been described as an important feature of WS. Middle aortic syndrome is characterized by narrowing of abdominal aorta and sometimes including the renal and visceral branches leading to hypertension and claudication [11, 12]. Our patient had narrowing of the abdominal aorta which has been reported in the literature as coarctation of the abdominal aorta or stenosis of the thoracic aorta. Abdominal ultrasound did not reveal any involvement of the renal vasculature and the cause of occasional hypertension remained undetermined in our case and resolved.

Growth retardation is also one of the recognized features in both the syndromes [5]. Our patient had severe IUGR prenatally and the weight gain remained a major struggle.

The findings on liver biopsy done at 44 weeks of CA were not suggestive of AS. Characteristic finding of pau-

Current Case	Alagille Syndrome	Williams Syndrome
Cholestatic Jaundice • Bilirubin level returned to normal before discharge. • GGT remained high. • Liver biopsy –not suggestive of Alagille syndrome.	• Found in 91% of patients . • Improve with time. • The high GGT may persist for many years. • Paucity of bile ducts is an evolving feature- repeated biopsies overtime are useful.	• Not a known feature.
Dysmorphic features	• Subtle early in life.	• Subtle early in life.
IUGR/Failure to thrive	• Well known.	• Well known.
Heat Disease • Peripheral Pulmonic Stenosis.	• Typical finding.	• Supravalvular aortic stenosis in 70%. • Pulmonic stenosis also well known.
Eye anomalies • Posterior Embryotoxon	• In 88%.	• Not a Known Feature.
Vascular Anomalies • Narrowing of the abdominal aorta just above the bifurcation.	• Major causes of morbidity and mortality in Alagille Syndrome. • Coarctation of the abdominal aorta and renovascular hypertension.	• Arterial narrowing due to thickening of the vascular smooth muscle is a well-known complication. • Stenosis of the thoracic aorta and middle aortic syndrome.
Vertebral Anomalies • Dysplastic C1 arch.	• Butterfly vertebrae seen in 66% of patients.	• Not a known feature.
Occasional hypercalcemia • 2 episodes asymptomatic hypercalcemia.	• Not known.	• Well known. • 5-50% of the patients may have one or more episode of mild hypercalcemia.

Figure 4. Comparison with William and Alagille syndrome.

city of bile duct is an evolving feature, thus repeated biopsies overtime are useful for evaluation of this condition. The jaundice level does improve with time but may recur with any intercurrent illness; GGT may also persist for many years [8]. In our patient, jaundice had returned to normal before he was discharged. Our patient had pulmonary stenosis, although in 70% of the case with WS have supravalvular aortic stenosis [1].

Hypercalcemia has been reported in 5–50% of the patients with WS. This is generally mild but can be moderate to severe particularly during the infancy. Our patient did have a few episodes of asymptomatic hypercalcemia. In AS, mutation is identified in up to 70% of the cases and this figure increases to greater than 90% with sequential screening approach [14]. Genetic testing in our case failed to reveal any mutation consistent with the AS, however, microarray analysis revealed a deletion at 7q11.23. Parental FISH analysis showed that the patient's deletion was de novo.

To the best of our knowledge, there have been three case reports of infants with query AS who on microarray analysis were found to have WS [2–4].

All three cases had hepatic disease and biliary hypoplasia was noted in one [2]. Abdominal ultrasound showed absent left portal and hepatic vein in the other [3]. One patient also had absent corpus callosum, butterfly vertebrae and later died of sepsis. His autopsy did not reveal paucity of bile ducts seen in AS [3]. All the three infants were mildly dysmorphic, growth retarded, and had pulmonary artery stenosis. One infant also had mildly hypoplastic aortic isthmus [4]. They were clinically diagnosed as AS but microarray analysis revealed deletion at 7q11.23. One of the infants was diagnosed at 10 months of age when the features of WS (hypercalcemia, facial features, and hypertension) became more apparent [2]. Two of the cases had ACC and IUGR. Since WS is a contiguous gene disorder, these cases may shed light on the specific gene/genes at 7q11.23 that cause these clinical manifestations in some of the cases with WS.

Conclusion

WS is a rare genetic neurodevelopmental disorder with a characteristic physical and behavioral phenotype. It is

usually diagnosed in childhood based on the typical facial features, hypercalcemia, and the typical cardiac abnormalities. The other neurodevelopmental and behavioral findings may become apparent at a later age. There may be some overlap of clinical features of this syndrome with AS especially pulmonary stenosis, vascular anomalies, and growth retardation but conjugated hyperbilirubinemia, posterior embryotoxon, and vertebral anomalies are not the typical feature of William syndrome. Our patient highlights the need to perform array Comparative genomic hybridization (CGH) in newborns with features questioning AS since the two conditions have different prognosis and follow-up guidelines. These findings extend the recognized phenotype of WS and emphasize the overlap between Alagille and WS in some cases.

Conflict of Interest

None declared.

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