Alagille-Watson syndrome

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ABSTRACT

Alagille syndrome (AS) is also known as arteriohepatic dysplasia, Watson Miller syndrome, and syndromic bile duct paucity. It is rare autosomal dominant genetic syndrome with incidence of 1 in 100,000 live births. The major manifestations include paucity of interlobular bile ducts, characteristic facies, posterior embryotoxon, vertebral defects, and peripheral pulmonary stenosis. A developmentally normal 14-month-old male toddler born of a non-consanguineous marriage presented with progressive jaundice since 4 months of age and was associated with generalized pruritus, high-colored urine, and pale-colored stools. On examination, broad forehead, pointed chin, low-set eyes, xanthomas over the cheek, and posterior embryotoxon were noticed. Ultrasonography showed hepatomegaly and ectopic kidney, and blood investigations revealed anemia, conjugated hyperbilirubinemia, raised serum glutamic pyruvic transaminase, and serum glutamic oxaloacetic transaminase, with altered triglyceride and cholesterol levels. Liver biopsy revealed paucity of intrahepatic bile ducts and diagnosis of AS. The above case report stresses the need to look for any dysmorphic features in a case of neonatal cholestasis as AS, though rare, is a cause of neonatal cholestasis.

Key words: *Alagille syndrome, Neonatal cholestasis, Watson syndrome*

Alagille syndrome (AS) is also known as arteriohepatic dysplasia, Watson Miller syndrome, and syndromic bile duct paucity [1]. It is rare autosomal dominant genetic syndrome with incidence of 1 in 100,000 live births [2]. It occurs due to defects in components of the Notch signaling pathway, most commonly JAG 1 (ALGS1), in a small proportion of cases mutation in NOTCH2 (ALGS2) [3]. 60% of cases due to new mutation and 40% inherited from parents [4]. The five major manifestations include the paucity of interlobular bile ducts, characteristic facies, posterior embryotoxon, vertebral defects, and peripheral pulmonary stenosis [5].

CASE REPORT

A developmentally normal 14-month-old male toddler born of a non-consanguineous marriage presented with progressive jaundice since 4 months of age and was associated with generalized itching, high-colored urine which stains the cloth, and pale-colored stools. Similar history noted in sibling and died at the age of 13 months with bleeding manifestations. Antenatal, natal, and immediate post-natal history was non-contributory. On general examination, the child was stunted with a length of 70 cm and undernourished with a weight of 6.5 kg (both were <3rd percentiles for are according to WHO charts), and weight for length was also <3rd percentile according to WHO charts.

The general physical examination showed broad forehead, deep-set eyes, depressed nose, pointed chin, multiple raised non-itchy yellow-colored lesions over cheeks, and other body folds (Fig. 2). Mild pallor and icterus noted in the eyes, vitals were normal. On palpation of the abdomen, a firm non-tender, moderate hepatosplenomegaly was present (liver span 9 cm, soft and spleen 6 cm). Ejection systolic murmur was heard over the aortic area. Provisional diagnosis of neonatal cholestasis was made, and the child was managed with symptomatic and supportive treatment. Ophthalmologic examination with slit lamp showed posterior embryotoxon.

Investigations showed anemia (Hb: 7.5 g/dl), conjugated hyperbilirubinemia (total/direct/indirect: 32/24/8 mg/dl), raised serum glutamic pyruvic transaminase (120 IU/L), serum glutamic oxaloacetic transaminase (300 IU/L), ALP (390 IU/L), and GGT (600 IU/L). Serum triglycerides were elevated (215 mg/dl), and HBsAg and anti-hepatitis C virus antibody were negative. His chest X-ray was normal, and 2D echocardiography was normal. Skeletal survey was also normal. Abdominal ultrasound showed moderate hepatomegaly with liver parenchymal changes and crossed fused ectopia of the left kidney (Figure 3). Liver biopsy was performed and sent for histopathological examination which showed paucity of the bile ducts (Figure 1). With the above features, a diagnosis of AS was made. We could not perform genetic studies as this facility was not available. The child was managed symptomatically; however, he developed hemorrhagic manifestations and died later.

DISCUSSION

AS is the syndrome of paucity of intrahepatic bile ducts. It is probably inherited in an autosomal dominant fashion with variable

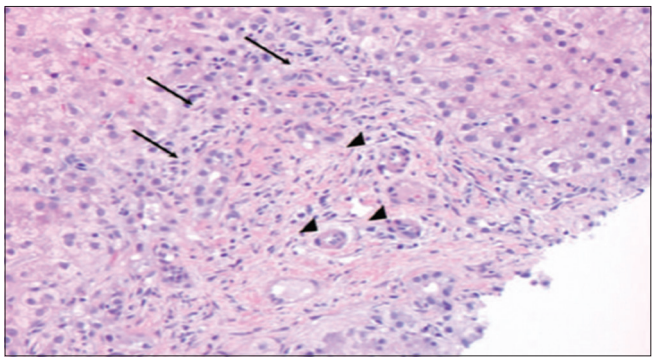

Figure 1: Liver biopsy findings (arrowheads show arteries and arrows showing lymphocytic infiltrate)

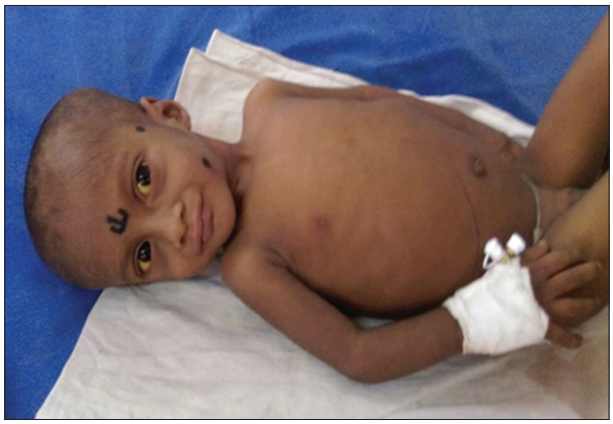

Figure 2: Child with Alagille syndrome showing characteristic facies (triangular facies, wide-spaced eyes, pointed chin, and low-set ears)

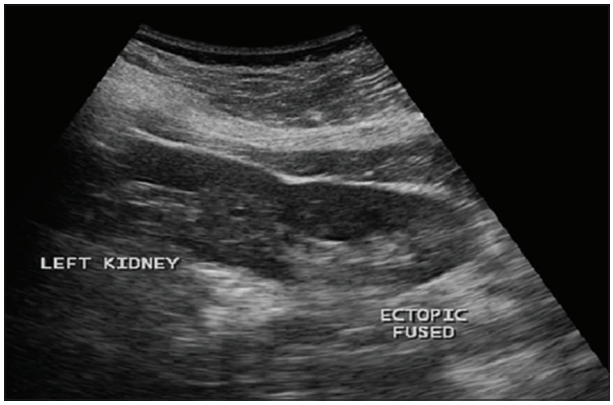

Figure 3: Ultrasonography abdomen and pelvis showing crossed fused ectopic left kidney

expression [6]. The disease is characterized by a peculiar facies, with abnormalities of the liver, heart, eye, skeleton, and kidney. Mild to moderate mental retardation may be present. Individuals commonly present before 6 months of age for either neonatal jaundice or cardiac murmurs; later, they may present with poor linear growth, with a broad forehead, pointed chin, deep-set eyes, and elongated nose with a bulbous tip. Hepatic disease is the key factor in AS, and the long-standing cholestasis and resultant hypercholesterolemia cause cutaneous manifestations of jaundice, pruritus, and widespread xanthomata [5].

Emerick et al. conducted a study on 92 patients with AS, showed paucity of interlobular bile ducts in 85%, cholestasis in 96%, cardiac murmurs in 97%, butterfly vertebra in 51%, posterior embryotoxon in the eye in 78%, and characteristic facies in 96% of the cases [7]. In a study by Shendge et al., case had three of the five major features of the syndrome with no vertebral or ophthalmologic defects. This form of "partial" or "incomplete" AS has also been reported in the Indian literature by Shendge et al. [8]. Nigale et al. reported an Indian girl with AS who had bilateral corneal opacity, mental retardation, typical facies, cardiac murmur, xanthomatosis, and cholestatic jaundice [9]. In our case, the child was having 3 out of five major characteristic features including the paucity of interlobular bile ducts, characteristic facies, and posterior embryotoxon along with minor features such as renal anomalies and xanthomas.

Long-term prognosis of AS is uncertain. Surgical treatment of choice is liver transplantation. Rapid resolution of widespread xanthomata has been reported in AS following orthotopic liver transplant [6]. Pruritus, often recalcitrant to medical therapy, has been reported to improve with cholestyramine (12-15 g/day) [2]. The estimated 20-year survival rates are 80% for those not requiring liver transplant and 60% for those requiring it [7]. The common factors affecting mortality are congenital heart disease, hepatic cirrhosis, intracranial bleeding, and renal abnormalities [10,11].

CONCLUSION

The above case report stresses the need to look for any dysmorphic features in a case of neonatal cholestasis as AS, though rare, is a cause of neonatal cholestasis.

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