

An Infant with Alagille Syndrome: A Very Rare and Early Presentation with Portal Hypertension and Variceal Bleeding

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Abstract

6 months old boy had presented with Upper gastro intestinal bleeding. Clinical examination and laboratory investigations had revealed that he had characteristic features of Alagille syndrome with cholestasis and bleeding esophageal varices. Genetic tests had confirmed the diagnosis. The child was treated conservatively but had ultimately succumbed to another episode of recurrent GI bleeding. This was a very rare early presentation of Alagille syndrome with portal hypertension and variceal bleeding.

Keywords: *Infant; Alagille Syndrome; Portal Hypertension; Variceal Bleeding*

Introduction

Alagille Syndrome is a rare genetic disorder presenting in infancy, with an incidence of about 1:70,000 babies worldwide. Although there is multi-systemic involvement, the one of the hallmark features that distinctively identifies this syndrome is intrahepatic bile duct paucity, which even when absent on presentation in the neonatal period, develops and progresses thereafter. Later on this may lead to portal hypertension and/or variceal bleeding. We present an infant with the classical features of Alagille syndrome presenting very early with portal hypertension and bleeding varices. Genetic analysis confirmed the diagnosis and the baby unfortunately had succumbed from recurrence of upper GI bleeding.

Case Report

6 months old baby boy was admitted with history of blood mixed loose stools and two episodes of hematemesis over 10 days. He had been admitted at a local nursing home where a Meckel scan was negative and the baby had been stabilized with blood and plasma transfusions for anemia and deranged coagulation profile.

There was history of consanguinity in parents and this baby born at term by Cesarean section (uneventful perinatal history) is the first child of the couple.

On admission, the baby was hemodynamically stable but had severe pallor and obvious failure to thrive (weight 3.8 kg, length 58 cm, OFC measurement 38 cm).

He had hepatosplenomegaly, a systolic murmur best heard in the left parasternal area and dysmorphic facial features (antimongoloid slant, widely spaced deep set eyes and a broad forehead) (Figure 1).



Figure 1: Characteristic facial features of Alagille syndrome-broad forehead, deep set eyes, pointed chin, elongated nose with bulbous tip.

The initial lab investigations revealed a negative sepsis screen and TORCH screen and a negative IEM panel. There was cholestatic jaundice with very high liver enzymes- GGT 1540, ALP 983, SGPT 297.Total serum bilirubin was 3.35 (54.6% direct component).

ECHO showed a 1.3 mm PDA and stenosis at the origin of left pulmonary artery (Figure 2). Sepsis screen as well as coagulation profile were normal.



Figure 2: ECHO showing Left Pulmonary artery origin stenosis.

With 3 prominent features pointing towards a possibility of Alagille syndrome (cholestatic jaundice, pulmonary artery stenosis, facial dysmorphism), the remaining investigations were directed to confirm the same.

Chest and abdominal x-ray showed multiple classical butterfly vertebrae involving the thoraco lumbar vertebrae (Figure 3).

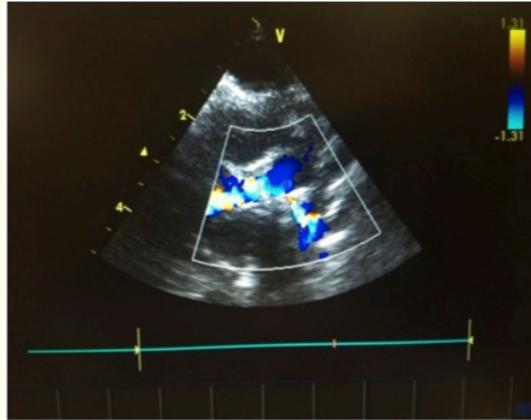


Figure 3: Classical butterfly vertebrae (thoracolumbar).

An eye exam showed bilateral posterior embryotoxon and peripheral iridocorneal adhesions.

Abdominal ultrasound confirmed the presence of hepatosplenomegaly and showed bilateral echogenic kidneys-probably early changes of renal parenchymal disease. Renal function including electrolytes was normal.

So, the baby had met all the major criteria for a clinical diagnosis of Alagille syndrome.

Genetic mutation studies revealed a heterozygous deletion of JAG1 gene. The upper GI endoscopy revealed the presence of esophageal varices. He was treated by a short course of octreotide. The parents had refused a liver biopsy to confirm the paucity of bile ducts, and regular monitoring and follow up of cardiac, renal, and pancreatic functions were advised.

He was discharged in a stable condition with multi-vitamin supplements (especially the fat soluble ones) and diets rich in medium chain triglycerides were advised. Subsequently he was lost in follow up and unfortunately succumbed from a massive recurrence of upper gastro intestinal bleeding.

Discussion and Conclusion

Alagille syndrome (arteriohepatic dysplasia) is a rare genetic disorder inherited as an autosomal dominant condition with variable expression in 50% cases, the remaining being sporadic cases. Mutations in the JAG1 (chr 20p12) and NOTCH2 (chr 1p12) genes (involved in the formation of intrahepatic biliary architecture) are implicated in giving rise to this syndrome complex.

Most babies present before 6 months of age with either neonatal jaundice (70%) or cardiac murmurs/symptoms (17%). Failure to thrive is a common association.

A definite diagnosis includes liver biopsy confirmation to show absence or marked reduction in the number of interlobular bile ducts in the portal triads, and at least 3 of the 5 major criteria for diagnosis [1]:

- 1. Cardiac involvement:** Peripheral pulmonary stenosis is most common. ASD, VSD, PDA, TOF may be present.
- 2. Hepatic involvement:** Cholestatic jaundice, hepatosplenomegaly. Coagulopathy, fat soluble vitamin deficiencies, severe pruritus and xanthomata may be present.
- 3. Eye involvement:** Posterior embryotoxon (thickened, anteriorly displaced schwalbe's line) and Axenfeld anomaly (iris attached to descemet's membrane) are most common.

- 4. Skeletal abnormalities:** Characteristic butterfly vertebrae (present in upto 70% patients). Spina bifida or limb abnormalities may occur.
- 5. Facial dysmorphism:** Broadened head, pointed chin, elongated nose with bulbous tip, deep set eyes.

These children may also have renal, pancreatic, vascular and neural involvement for which they need long term follow-up and treatment. Treatment usually involves supplementation of fat soluble vitamins, antihistamines for pruritus (which in many cases is resistant to therapy), cholestyramine for hyperlipidemia and bile acid supplements. Severe cases of hepatic dysfunction or severe portal hypertension may need liver transplant. The 20 year survival is about 75%, in cases not requiring liver transplant and about 60% in the ones that need transplant [2].

Because the syndrome has multisystemic involvement, the severity of the cardiac and renal manifestations often overshadow the usually slowly progressive liver involvement. It was considered as a "benign syndrome of intrahepatic cholestasis" [3]. Liver complications were considered to be responsible for death in only 5% of cases [4] with rare indications of liver transplantation [4]. Recent literature however suggests that the liver involvement is more severe particularly in those presenting with neonatal cholestasis. Liver failure and/or hepatocellular carcinoma is reported in children as early as 2 - 4 years [5,6].

This baby was an index case of Alagille syndrome in this family. So, the screening of other family members was advised. Such a rapid progression of his liver disease, so much so to produce significant portal hypertension and bleeding esophageal varices were very rare and unusual.

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