CASE REPORT

# Alagille Syndrome Mimicking Biliary Atresia

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## ABSTRACT

The clinical presentation of jaundice, dark urine, persistently acholic stools, hepatosplenomegaly and a rudimentary, non-contractile gall bladder on ultrasound in an infant raises a suspicion of biliary atresia (BA). However, Alagille syndrome (AGS) may clinically, radiologically and histopathologically mimic BA and should be suspected in infants with other extrahepatic features.

We report a 2.5-month old girl with an initial suspicion of BA who was eventually found to have AGS. We highlight the clinical, biochemical and radiological features that helps one in differentiating between these two conditions.

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**Key words:** Alagille Syndrome, Biliary Atresia, Jaundice

## INTRODUCTION

The clinical presentation of jaundice, dark urine, acholic stools and rudimentary gall bladder (GB) on ultrasound in an infant raises the possibility of biliary atresia (BA). However, Alagille syndrome (AGS), a multisystem disorder with a prevalence of 1:30-50000 may have a similar presentation and its clinical and laboratory manifestations may show a considerable overlap with BA. (1) There have been reports in the past where children with AGS have been initially diagnosed as BA and have even inadvertently undergone a Kasai procedure, which has led to poor outcomes. (2)

We present a 2.5-month old female in whom the diagnostic dilemma between AGS and BA was eventually sorted by genetic analysis. We highlight the clinical, biochemical and radiological features that helps one in differentiating between these two conditions.

## CASE REPORT

A 2.5-month old female child presented with jaundice, dark urine and acholic stools since birth. She was the first born to non-consanguineous parents. She'd undergone an ultrasound a few days prior to presentation which showed a small GB raising the possibility of BA.

On examination her weight was 3.5 kg (-2 to -3 SD) and she had icterus. The liver was palpable 4 cm below the right costal margin with a soft consistency. An ejection systolic murmur at pulmonary area was audible. Investigations showed total bilirubin/ direct -12.4/8.4 mg/dL, AST/ALT-262/188IU/L, gamma glutamyl transpeptidase-1380 IU/L. Ultrasound abdomen showed a rudimentary gall bladder (~ 9mm) with absent common bile duct and raised echogenicity of both kidneys. (Fig 1a,b) A HIDA scan was performed which was non-excretory at 24 hours. To evaluate for the murmur an echocardiogram was performed which demonstrated a left pulmonary artery origin stenosis.

Though BA continued to be the most important differential, the possibility of AGS was also considered at this point because of the renal findings on ultrasound and the echocardiogram findings. We re-visited the facial features of the child and found that the child had a broad forehead and pointed chin giving it a triangular appearance (Fig 2) Ophthalmological evaluation and dorsal spine x-ray were normal. Lipid profile showed cholesterol-326 mg/dL (elevated), triglycerides-471mg/dL (elevated), HDL-27mg/dL, LDL-209mg/dL (elevated). Liver biopsy showed features of moderate portal inflammation with intrahepatic cholestasis and interface hepatitis. There was no paucity of bile ducts.

To sort out the diagnostic dilemma genetic testing for AGS was performed, which showed heterozygous c.439+1G>A (5'splice site) variant in intron 3 of JAG1 gene confirming the diagnosis of AGS

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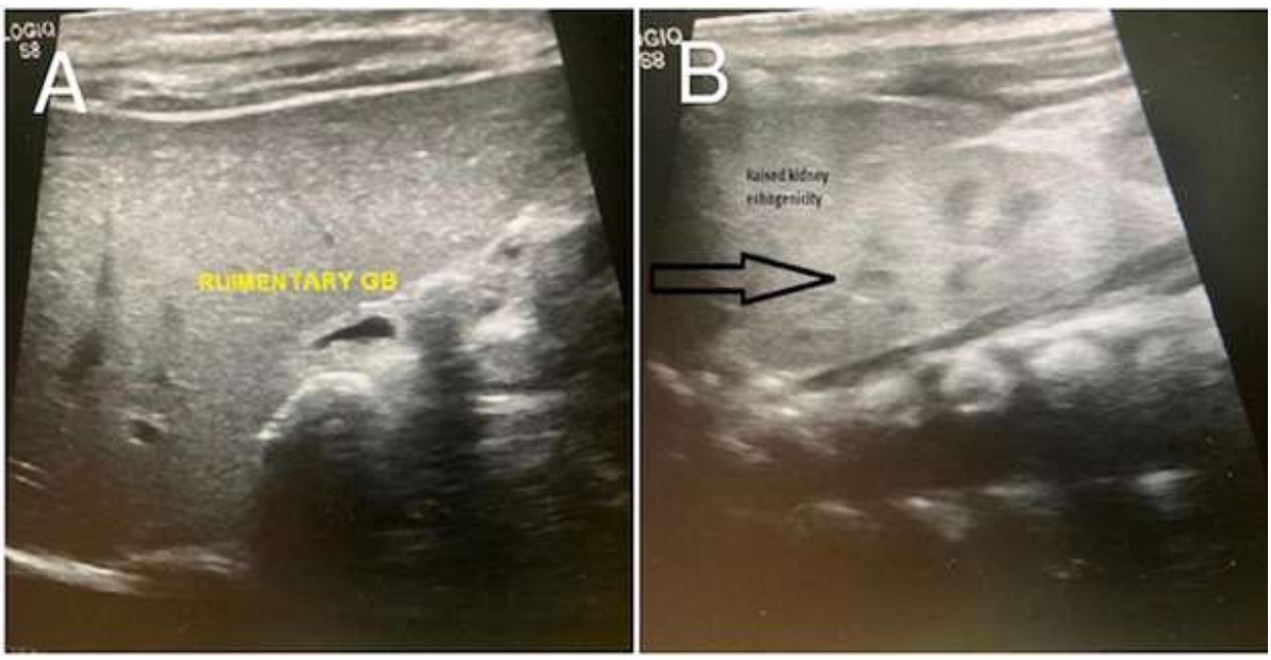


**Fig. 1a** Ultrasound image of the rudimentary gall bladder

**Fig 1b.** Ultrasound image showing increased echogenicity of the kidney

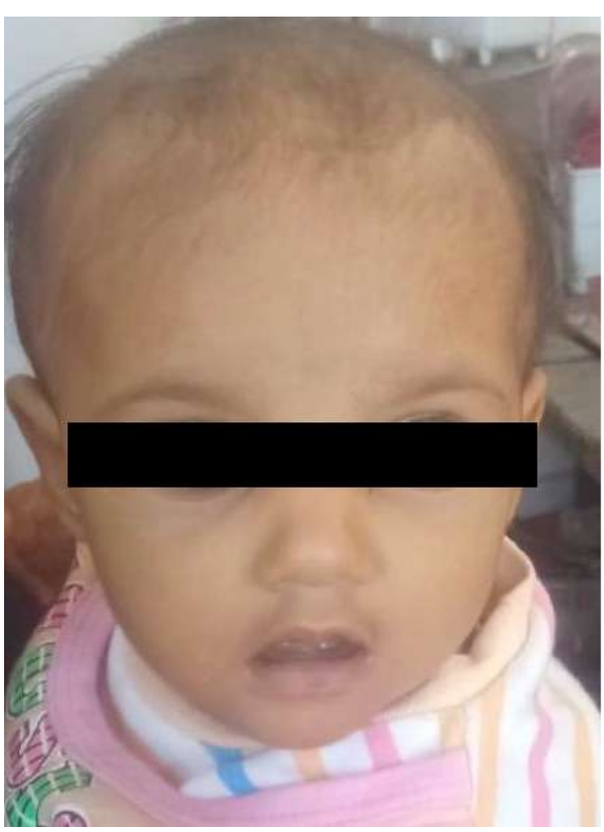

**Fig 2.** Alagille Facies

## DISCUSSION

On initial presentation we suspected BA in our child, which was further supported by the presence of a rudimentary, non-contractile GB on ultrasound. However, this finding can be seen in AGS too. Cho et al. evaluated the ultrasound findings of 75 children with BA and compared it with children with AGS (n=23). They found that a small GB may be seen in both AGS (57%) and BA (79%). They found that the presence of a triangular Cord Sign [TCS, 41% (BA) vs 0% (AGS)] and hypertrophied hepatic artery [HA,83% (BA) vs 13% (AGS)] helps in differentiating between these conditions. (3) Han et al. also evaluated the USG findings of AGS (n=7) and BA (n=55) and found that small GB was found in both [86% (AGS) vs 81% (BA)] and that apart from TCS and HA enlargement that helped in differentiating between them, the presence of features of portal hypertension were seen more commonly in BA. (4) This study also evaluated the role of a MRCP and found that non-visualization of the extrahepatic biliary tree did not differ between AGS and BA. (4) In AGS it is speculated to be absent because of insufficient bile secretion due to bile duct paucity.

A HIDA scan is often not useful in differentiating between these conditions as ~60% patients with AGS do not show radiotracer excretion even after 24 hours. A liver biopsy in infants <6 months may also often not be helpful as instead of a paucity of bile ducts one may even find features of ductal proliferation. (1)

The misdiagnosis of AGS as BA has important connotations as the treatment of BA is Kasai Portoenterostomy which worsens outcomes in AGS. Fujishiro et al. carried out a systematic review [6 studies (394 AGS patients)] and found that liver transplantation (odds ratio:6.46) and mortality (odds ratio:15.05) were significantly higher in AGS patients who underwent a Kasai than in those who did not. (2)

An intra-operative cholangiogram may help in solving this diagnostic dilemma however in AGS there may be non-visualisation of the common hepatic duct or confluence masquerading as BA. (4) Eventually it is testing for JAG1 (or rarely NOTCH2) mutation that gives one a confirmatory diagnosis as seen in our patient.

So when should one think of AGS in a child with cholestasis and pale stools and evaluate accordingly? Firstly,

in the presence of extrahepatic findings including - cardiac (> 90%, primarily involving the pulmonary arteries), skeletal (butterfly vertebrae – 33-87%), ophthalmologic (posterior embryotoxon – 56-88%), vascular, renal and facial abnormalities (70-100%). (1,4) It should be remembered that even in BA, ~10% [biliary atresia splenic malformation (BASM)] may have associated congenital heart diseases (CHD) and their presence alone should not deviate one from the diagnosis of BA. Renal abnormalities include dysplasia, glomerular mesangiolipidosis and renal tubular acidosis. Mesangiolipidosis may be seen as hyperechogenic kidneys on the ultrasound as seen in our child. The facial features include a prominent forehead, hypertelorism, flat nasal bridge, bulbous tipped nose, prominent ears and a pointed chin giving a triangular appearance. The triangular shape becomes less marked with age. (1,4)

Secondly, a relatively "soft" liver on clinical examination as seen in our case in a child with suspected BA (especially if ~2-3 months old) should prompt one to consider a different diagnosis as there is rapidly progressive liver fibrosis in BA giving the liver a "firm" feel.

Thirdly, looking at the lipid profile maybe helpful. Bojanovski et al reported that cholesterol levels are far higher in children with AGS than BA. (5)

To conclude, one should keep the possibility of AGS at the back of one's mind when evaluating a child with suspected BA as it may clinically, radiologically and histopathologically mimic BA. When in a dilemma, early molecular diagnostics could be considered in selected cases with overlapping features of AGS and BA.

## Further Reading:

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