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Case Report

Unmasking Alagille Syndrome in Adulthood- A Complete Clinical Portrait of a Rare Syndrome

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Abstract

Alagille syndrome (ALGS) is a rare autosomal dominant multisystem disorder characterized by marked phenotypic variability, and the diagnosis is sometimes very challenging. We describe a 26-year-old man who presented with progressive jaundice, pruritus, and weight loss over three months, with a history of similar episodes in early childhood. He had previously been diagnosed with atrial septal defect with severe pulmonary stenosis, myopia, and hypothyroidism. After a thorough Clinical examination which revealed icterus, pedal edema, stigmata of chronic liver disease, and characteristic facial dysmorphism with café-au-lait spots, a possibility of Alagille syndrome was considered. Laboratory evaluation showed cholestatic liver dysfunction and pancytopenia. Whole-exome sequencing identified a likely pathogenic JAG1 variant, and liver biopsy confirmed bile duct paucity. This case highlights the diagnostic challenges of ALGS and underscores the importance of meticulous clinical evaluation and comprehensive longitudinal history-taking, as multiple healthcare encounters preceded the correct diagnosis as far as this patient is concerned.

Keywords

Alagille Syndrome, JAG1, Bile Duct Paucity, Chronic Liver Disease, Congenital Heart Disease

1. Introduction

Alagille syndrome (ALGS) is a genetically heterogeneous, autosomal dominant disorder with multisystem involvement and an estimated incidence of 1 in 30,000 live births [1]. It is also known as arteriohepatic dysplasia. ALGS results from mutations in the JAG1 gene (98%) or NOTCH2 gene (2%), both of which play roles in the Notch signaling pathway [2]. ALGS was initially described as a hepatic disorder, but many patients with genetic mutations do not show overt liver disease.

Diagnosis is typically based on the presence of at least three of five major clinical features: butterfly vertebrae, congenital cardiac defects (most commonly involving the pulmonary arteries), posterior embryotoxon, cholestasis with bile duct paucity, and characteristic facial features, with vascular and renal anomalies also reported [3]. The hallmark hepatic feature is bile duct paucity, leading to cholestasis [4].

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2. Diagnostic Criteria

Traditional diagnostic criteria for ALGS include histological evidence of bile duct paucity and three of the following features:

2.1. Cholestasis

Cholestasis often presents in infancy, with jaundice, pruritus, xanthomas, and failure to thrive due to fat malabsorption. Liver biopsy may show early ductal proliferation but typically reveals bile duct paucity, with an interlobular bile duct-to-portal tract ratio <0.4 [5]. Approximately 15% of patients progress to chronic liver disease and may require liver transplantation [6].

2.2. Posterior Embryotoxon (Ocular Anomaly)

Posterior embryotoxon is present in 78–89% of patients. Other findings include Axenfeld- Rieger anomaly (corectopia, polycoria), optic disc drusen, and retinal pigment changes [7].

2.3. Characteristic Facial Features

Broad and Prominent forehead, frontal bossing, prominent or large ears, deep-set eyes, hypertelorism, pointed chin and straight or bulbous nose giving a characteristic inverted triangular shaped face. These traits are strongly associated with JAG1 mutations [8].

2.4. Cardiac Defects

Cardiac anomalies are seen in up to 97% of ALGS patients. Pulmonary artery stenosis (branch or peripheral) is most common. Complex defects like Tetralogy of Fallot, aortic coarctation, and septal defects (Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD)) are also reported.

2.5. Skeletal Anomalies

Butterfly vertebrae, due to midline clefting of thoracic vertebral bodies, are seen in 33–93% of cases [9]. Other skeletal features may include tapering phalanges and supernumerary flexion creases [10]. Fractures may occur due to metabolic bone disease [11].

2.6. Expanded Criteria

Include renal and vascular anomalies. Vascular abnormalities include intracranial hemorrhage, renovascular anomalies, and middle aortic syndrome. [12] Renal anomalies such as small echogenic kidneys, cysts, renal artery stenosis, and renal tubular acidosis occur in up to 39% of patients. Patients' may be having short stature because of immunodeficiency, repeated infections, inherent bone problems (50–90%), poor growth linked to cholestasis, or a serious heart defect.

Diagnosis can be established clinically or genetically. Liver biopsy is not mandatory if genetic confirmation (JAG1/NOTCH2 mutation) is available.

2.7. Genetics of ALGS

98% of cases are caused by mutations in JAG1 and 2% are caused by mutations in NOTCH2. There are no genotype-phenotype associations between the location of the mutation within the gene or the particular types of JAG1 pathogenic variants with the clinical symptoms of ALGS [13]. ALGS with JAG1 Mutation almost always exhibits the characteristic facial traits [11].

3. Case Presentation

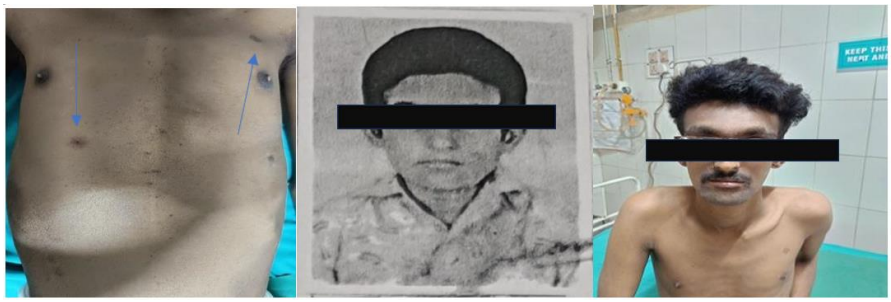


Figure 1. *Multiple café au lait spots, Facial dysmorphism with gradual change in his shape of face from 15 years to 26 years.*

A 26-year-old man presented with jaundice, dark urine, and pruritus for three months duration. He had experienced similar episodes at 3 months and 18 months of age, with persistent mild pruritus since childhood. He had no history of gastrointestinal bleeding or ascites.

Past medical history included myopia (diagnosed in 2010), congenital heart disease (ASD with severe pulmonary stenosis), balloon pulmonary valvotomy (2012), and ASD device

closure (2016). He was diagnosed with hypothyroidism in 2014. There was no family history of similar illness. His siblings were healthy.

On examination, he was pale, icteric, and had bilateral pedal edema. BMI was 17.6 kg/m². Stigmata of chronic cholestasis and chronic liver disease included scratch marks, shiny nails, and spider nevi. He also had multiple café au lait spots over the trunk. (Figure 1). Hepatosplenomegaly was present; cardiac auscultation revealed a systolic murmur. Facial features were consistent with ALGS. There was gradual change in his shape of face from 15 years to 26 years to give the current characteristic facial dysmorphism.

4. Investigations

CBC showed pancytopenia.

LFT: Cholestatic pattern.

Viral and autoimmune markers were negative.

Serum ceruloplasmin and ferritin were normal.

Peripheral smear: Macrocytic RBCs with target cells.

Ophthalmology evaluation: Posterior embryotoxon, high myopia, epiretinal membrane (Figure 2).

Skeletal X-ray: Butterfly vertebrae (T9, T10) (Figure 3).

Cardiology: Echo showed mild pulmonary stenosis and no residual ASD shunt.

USG: Coarse liver, small echogenic right kidney.

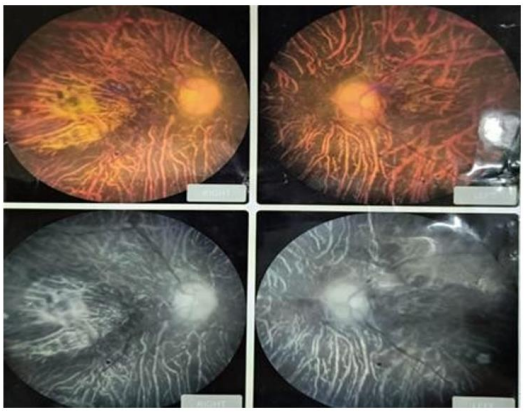
MRCP: Chronic liver disease with portal hypertension.

CECT: Segmental liver atrophy with hypertrophy of segment IV.

Upper GI Endoscopy: Grade III esophageal varices.

Liver biopsy: Bile duct paucity, cholestasis, cirrhosis.

Whole Exome Sequencing: Identified a heterozygous likely pathogenic 5′ splice-site variant c.2458+1G>A in intron 20 of the JAG1 gene (chr20p12.2), aberrant mRNA splicing and functional loss of the Jagged 1 protein consistent with autosomal dominant Alagille syndrome due to JAG1 haploinsufficiency.



Right eye Left eye-Myopic fundus

Figure 2. *Right eye epiretinal membrane with macula, chorioretinal dystrophy and myopic fundus.*

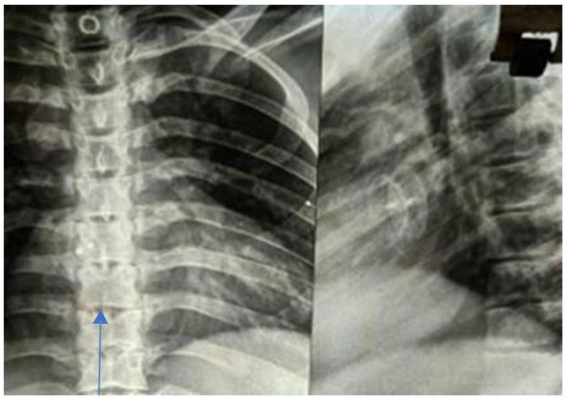


Figure 3. *Xray Thoracic spine -AP view showing butterfly vertebrae (T9, T10) and Lateral view showing ASD closure device.*

5. Discussion

This patient had all seven recognized clinical features of Alagille Syndrome: cholestasis, cardiac, ocular, skeletal, renal, vascular abnormalities, and facial dysmorphism. Genetic testing confirmed a pathogenic JAG1 mutation, establishing the diagnosis.

Differentials such as PFIC, autoimmune hepatitis, primary sclerosing cholangitis, and congenital hepatic fibrosis were ruled out based on clinical, histological, and serological findings. Unique findings in this case were café au lait spots and hypothyroidism, not commonly described in ALGS.

Management of ALGS is multidisciplinary. Medical therapy for pruritus includes ursodeoxycholic acid, rifampin, cholestyramine, and naltrexone. In refractory cases, surgical biliary diversion may be considered [14]. Liver transplantation remains the definitive option for progressive liver disease. Cardiac anomalies must also be managed early, as they are a major cause of early mortality. The 5-year survival rate after liver transplantation for ALGS is 80%, and 90% of those afflicted experience some catch-up growth [15]. Genetic counselling is an important component in the management of inherited disorders. The patient was counselled regarding the autosomal dominant inheritance pattern of Alagille syndrome, the possibility of variable clinical expression, the risk of transmission to offspring, and the need for clinical evaluation and genetic testing of family members.

6. Conclusion

Alagille syndrome is a multi-system disorder with highly variable presentation. Genetic testing plays a key role in diagnosis, especially when liver biopsy is not feasible. This case highlights that this rare disorder can remain unrecognized until adulthood due to its heterogenous manifestations. A high index of suspicion with a meticulous history and examination is crucial for timely diagnosis. Increased awareness among clinicians may help prevent diagnostic delays and improve

outcome. Multidisciplinary care is essential for optimal outcomes.

Abbreviations

ALGS	Alagille Syndrome
ASD	Atrial Septal Defect
VSD	Ventricular Septal Defect
CBC	Complete Blood Count
LFT	Liver Function Test
RBC	Red Blood Cells
USG	Ultrasonography
MRCP	Magnetic Resonance Cholangiopancreatography
CECT	Contrast Enhanced Computed Tomography
PFIC	Progressive Familial Intrahepatic Cholestasis

Conflicts of Interest

The authors declare no conflicts of interest.

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