TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

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MORE THAN JUST JAUNDICE: A MULTISYSTEMIC CASE OF ALAGILLE SYNDROME

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Abstract

Background: Alagille syndrome is a rare autosomal dominant multisystem disorder characterized by cholestasis, cardiac anomalies, skeletal defects, renal involvement, and distinctive facial features. **Case Report:** "We present the case of a 3-year and 4-month-old female, second born to degree consanguineous parents, who was referred with swelling and pain in the left cheek secondary to a dento-alveolar abscess. She had a history of generalized pruritus, persistent jaundice since infancy, and recurrent respiratory infections requiring admissions. Antenatal history was unremarkable apart from maternal hypothyroidism. The child was born late preterm with intrauterine growth restriction, required brief NICU admission, and exhibited developmental milestones appropriate for age. Clinical examination revealed severe malnutrition, pallor, icterus, grade III clubbing, coarse facies, xanthomas, and dental caries. Cardiovascular examination identified an ejection systolic murmur area. Laboratory tests showed anemia, thrombocytosis, hyponatremia, and elevated gamma-glutamyl transferase and alkaline phosphatase, billirubin (direct and indirect). Imaging studies revealed small kidneys, mild to moderate pulmonary stenosis, and a butterfly vertebra at T6. Based on the constellation of features, a diagnosis of Alagille syndrome was made clinically. **Conclusion:** This case highlights the importance of a detailed systemic evaluation in pediatric patients presenting with cholestasis, cardiac anomalies, skeletal defects, and failure to thrive. Comprehensive clinical assessment remains crucial for the diagnosis of Alagille syndrome, especially in settings where genetic testing is limited. Early recognition and multidisciplinary management are essential to optimize outcomes in affected children.

Keywords: Alagille syndrome, cholestasis, pulmonary stenosis, butterfly vertebra, consanguinity, failure to thrive.

INTRODUCTION

Alagille syndrome is a complex, multisystem disorder with an autosomal dominant inheritance pattern, primarily caused by mutations in the JAG1 gene and, less commonly, the NOTCH2 gene.(1, 2) It is characterized by abnormalities involving the liver, heart, skeleton, kidneys, and eyes, along with distinctive facial features. The estimated incidence of Alagille syndrome is approximately 1 in 30,000 to 50,000 live births, although underdiagnosis is likely due to its wide phenotypic variability.(3) Liver involvement, manifesting as cholestasis due to bile duct paucity, is often the initial clinical presentation and may progress to cirrhosis or end-stage liver disease.(4) Cardiac anomalies, particularly peripheral pulmonary stenosis, are present in the majority of patients and represent a significant contributor to morbidity.(5) Additional features include skeletal anomalies like butterfly vertebrae, renal abnormalities such as renal hypoplasia or dysfunction, ocular anomalies like posterior embryotoxon, and characteristic facial dysmorphism including a prominent forehead, deep-set eyes, and a broad nasal bridge.(6)

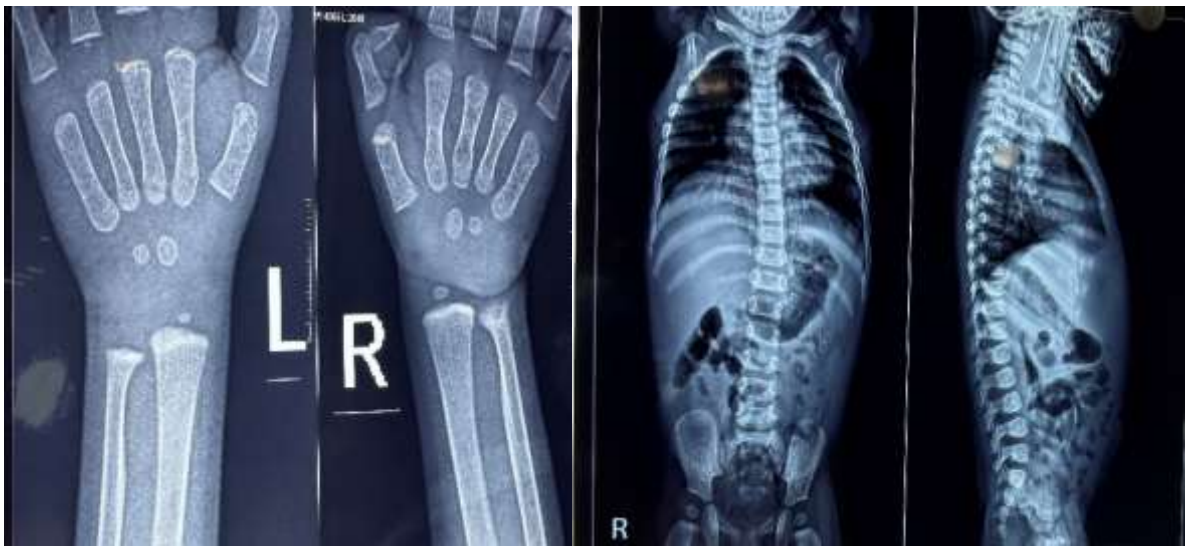
The diagnosis of Alagille syndrome is traditionally clinical, based on the presence of characteristic features in at least three organ systems, although molecular genetic testing has become the gold standard for confirmation.(7) Given the multisystem involvement and considerable variability in expression, a high index of suspicion is crucial

for early recognition, particularly in cases with consanguinity, as seen in some populations. In this case report from the Department of Pediatrics, Saveetha Institute of Medical and Technical Sciences, Tamil Nadu, India, we describe a 3-year, 4-month-old female child presenting with typical features of Alagille syndrome.

Case report

A 3-year and 4-month-old female child was brought by her father, a reliable informant, with complaints of swelling and pain on the left side of the cheek for the past one day, along with generalized itching all over the body for the past one year. The child was referred from a dental hospital for management of left cheek cellulitis secondary to dento-alveolar abscess. The antenatal history was unremarkable with spontaneous conception. The mother had received appropriate antenatal care including iron-folic acid (IFA) supplements and tetanus toxoid (Td) vaccine, and there was no history of gestational diabetes or hypertension. However, the mother had hypothyroidism, managed with tablet Thyronorm 50 mcg. Antenatal scans were normal. The child was delivered at 36 weeks of gestation (late preterm) with intrauterine growth restriction (IUGR), weighing 1.9 kg at birth, and cried immediately after delivery.

Postnatally, she required NICU admission for one day. She was exclusively breastfed for six months, following which complementary feeding was introduced, though occasional faulty practices such as the use of gripe water were reported. A history of neonatal polycythemia was present, although supporting documentation was unavailable. At six months of age, following an episode of respiratory infection, echocardiography revealed mild pulmonary stenosis. At eight months, the child developed generalized pruritus and jaundice. Investigations at that time showed abnormal liver function tests: serum total bilirubin was elevated to 3.36 mg/dL, direct bilirubin to 1.26 mg/dL, with elevated transaminases. Ultrasonography of the abdomen showed that both kidneys were small for age (right kidney 5.0 × 2.4 cm; left kidney 5.2 × 2.4 cm), with maintained corticomedullary differentiation and no pelvicalyceal dilatation; normal liver size (7.6 cm) and echotexture; and a partially distended gallbladder with normal wall thickness and no calculi. Pancreas and spleen (5.8 cm) appeared normal. A repeat echocardiogram at ten months of age demonstrated mild to moderate pulmonary stenosis with maximum velocity 3.2 m/s, intact atrial and ventricular septa, confluent pulmonary arteries, normal inflow tracts, normal aortic valve, and no evidence of coarctation. An X-ray of the vertebral column revealed a butterfly-shaped T6 vertebra and cardiomegaly. Bone age assessment by X-ray of both wrists showed ossification of the capitate and hamate bones with minimal ossification at the base of the 4th phalanx, corresponding approximately to a bone age of 16 months (appropriate with chronological age).



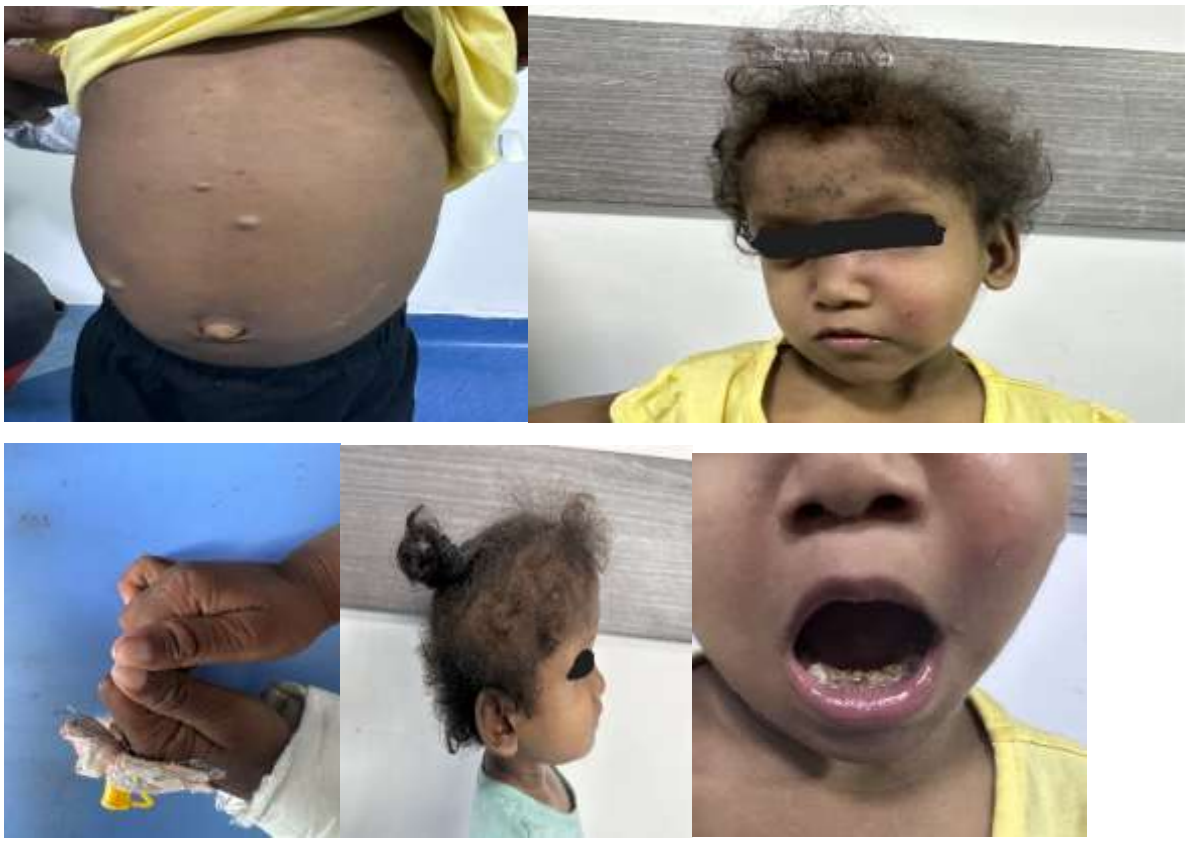
Figures 1 & 2 : Bone age assessment by X-ray of both wrist and X-ray of the vertebral column revealed a butterfly-shaped T6 vertebra

Laboratory investigations performed recently showed anemia (hemoglobin 11 g/dL), a raised total leukocyte count (14,230 cells/cumm), and significant thrombocytosis (platelet count 5.72 lakhs/cumm). The peripheral smear examination showed normocytic, normochromic red cells with reactive lymphocytosis. Renal profile revealed a low BUN of 14 mg/dL, low serum creatinine of 0.2 mg/dL, hyponatremia with a sodium level of 131 mmol/L, potassium 3.9 mmol/L, chloride 100 mmol/L, and bicarbonate 21 mmol/L. Liver function tests showed SGOT 14

IU/L, SGPT 6.7 IU/L, markedly elevated alkaline phosphatase of 431 IU/L, low total protein of 4.8 g/dL, albumin 2.8 g/dL, and a reversed albumin to globulin ratio of 0.8. Gamma-glutamyl transferase (GGT) was significantly raised at 492 U/L. Urine uric acid was within normal limits at 2.8 mg/dL. Thyroid function tests revealed TSH 3.14 µIU/mL and Free T4 1.01 ng/dL, which were within the normal range. Coagulation study was within normal range.

Developmentally, the child achieved age-appropriate milestones. Gross motor development included riding a tricycle, fine motor skills included drawing circles, social milestones included sharing toys, and language development included asking questions and forming 2–3 word sentences. She had normal bladder and bowel habits and was immunized up to date as per the National Immunization Schedule. The child was the second offspring of a third-degree consanguineous marriage; the elder sibling was developmentally normal. Over the past two years, the child had recurrent episodes of respiratory tract infections, approximately one episode every three months, managed conservatively with oral antibiotics. She also had persistent dry, itchy skin, yellowish discoloration of the skin and urine, but no history of vomiting, abdominal pain, fever, or clay-colored stools. Homeopathy medications taken for one month seemed to have worsened the jaundice.

On examination, the child was afebrile with a temperature of 98.5°F, respiratory rate of 22 breaths per minute, SpO_2 of 98% on room air, and heart rate of 115 bpm. Capillary refill time was less than 3 seconds. Anthropometric measurements revealed severe malnutrition with weight 9.4 kg, height 77 cm, and MUAC 12 cm (all below -3 SD for age). Head circumference was 43 cm, and the weight-for-height ratio was between 0 and -1 SD. Head-to-toe examination revealed pallor, icterus, and grade III clubbing. Deep-seated eyes, yellowish discoloration of skin and sclera, swelling and redness over the left cheek indicating cellulitis, and multiple dark pigmented spots on the forehead were observed. Hair was brown, friable, and undernourished. Nails were discolored. The skin was dry, rough, and patchy. Dental caries were noted along with multiple nodules and pustules over the abdomen and axillary regions. Dysmorphic facial features including a broad nasal bridge and coarse facies were present. Xanthomas were observed over the skin. Cardiovascular examination revealed an ejection systolic murmur heard best at the left second intercostal space. Respiratory system examination revealed bilateral air entry with bilateral wheeze and conducted sounds. The abdomen was soft, and the liver was palpable 3 cm below the right costal margin. The neurological examination was normal with a GCS of 15/15 and no focal neurological deficits.



Figures 3,4,5,6 & 7: Clinical examination findings of the child

Thus, based on history, clinical findings, imaging studies, and laboratory reports, the child was diagnosed with left cheek cellulitis secondary to dental caries, cholestatic jaundice, failure to thrive, mild to moderate pulmonary stenosis, lower respiratory tract infection, anemia, short stature, chronic malnutrition, and Alagille syndrome.

DISCUSSION

Alagille syndrome is a multisystem genetic disorder characterized by abnormalities in the liver, heart, skeleton, eyes, kidneys, and facial morphology. The estimated incidence is approximately 1 in 30,000 to 50,000 live births.(3) The classical diagnostic criteria include intrahepatic bile duct paucity leading to chronic cholestasis, cardiac defects (most commonly peripheral pulmonary stenosis), skeletal anomalies (such as butterfly vertebrae), ocular abnormalities (notably posterior embryotoxon), and distinct facial features.(8) This case report presents a comprehensive clinical picture that aligns well with the diagnosis of Alagille syndrome.

The patient, a 3-year 4-month-old female, demonstrated many hallmarks of Alagille syndrome. The presence of persistent cholestatic jaundice since infancy, along with markedly elevated serum GGT and alkaline phosphatase levels, supports hepatobiliary involvement typical of Alagille syndrome.(9) Cholestasis in Alagille syndrome results from a paucity of intrahepatic bile ducts, although a liver biopsy was not performed in this case due to the clear clinical and imaging findings. Cardiovascular involvement is present in approximately 90% of Alagille syndrome patients, with pulmonary artery stenosis being the most common defect.(6, 10) Moore et al. (2022) noted that involvement of the right ventricular outflow tract (RVOT) is the most common, with peripheral and central branch pulmonary arterial stenoses occurring in up to 60%.(11) Our patient had mild to moderate pulmonary stenosis, detected early in infancy and confirmed by echocardiography, consistent with the cardiac spectrum of Alagille syndrome.

Skeletal anomalies, particularly butterfly vertebrae, are another hallmark, seen in approximately 50-70% of cases.(8, 12) In this child, a butterfly vertebra was identified at the T6 level on spine radiography, reinforcing the diagnosis. Skeletal findings are often asymptomatic but serve as important radiologic clues to Alagille syndrome diagnosis.(13) Renal abnormalities, including renal hypoplasia and functional deficits, occur in up to 40% of affected individuals.(14, 15) Our patient had small kidneys on ultrasonography with preserved corticomedullary differentiation but without evidence of pelvicalyceal dilatation, suggesting congenital hypoplasia. Facial dysmorphism is characteristic and includes deep-set eyes, a broad nasal bridge, a prominent forehead, and a pointed chin.(3) These features were evident on clinical examination of our patient. The presence of xanthomas on the skin, resulting from persistent cholestasis and associated hyperlipidemia, further corroborates the chronicity of liver dysfunction.(7)

Growth failure is common in Alagille syndrome, with both weight and height typically falling below normal centiles due to a combination of chronic illness, poor nutrient absorption, and increased metabolic demand.(16) Our patient exhibited severe malnutrition with anthropometric measurements falling below -3 standard deviations, reflecting chronic undernutrition and failure to thrive. The recurrent respiratory tract infections in this patient might be explained by immunological dysfunction associated with Alagille syndrome or secondary effects of malnutrition and chronic disease. Respiratory complications have been reported less frequently but can be part of the broader clinical burden.(17)

Importantly, the consanguinity in the parents' marriage could have contributed to the homozygosity of a pathogenic variant in the JAG1 gene, which is implicated in more than 90% of Alagille syndrome cases.(18) Mutations in NOTCH2 account for a minority of cases.(1) Genetic testing for JAG1 or NOTCH2 mutations would confirm the diagnosis and should be considered, although clinical diagnosis remains valid given the characteristic manifestations observed. Management of Alagille syndrome is multidisciplinary and supportive, aiming to address individual organ involvement. Nutritional rehabilitation with a high-calorie, high-protein diet supplemented with fat-soluble vitamins (A, D, E, K) is critical.(3, 9) Ursodeoxycholic acid may help enhance bile flow and alleviate pruritus. Input from Cardiology for pulmonary stenosis and regular follow-up of liver and renal function are essential." Additionally, early dental care is crucial in such patients given the poor dental hygiene noted in our case, which predisposed her to dento-alveolar abscess and subsequent cellulitis.

CONCLUSION

This case highlights the classical presentation and multisystem involvement characteristic of Alagille syndrome, a rare genetic disorder with significant morbidity if unrecognized. The patient demonstrated key features including cholestatic jaundice, cardiac defects, skeletal anomalies, facial dysmorphism, renal abnormalities, and growth failure, which together led to the clinical diagnosis even in the absence of genetic confirmation. Early identification and comprehensive multidisciplinary management are critical in improving outcomes and quality of life in affected children. This case further underscores the importance of maintaining a high index of suspicion for syndromic diagnoses in children presenting with persistent cholestasis, congenital heart disease, and failure to thrive, especially in the context of consanguineous parentage. Timely referral for genetic counseling, appropriate nutritional support, proactive management of organ-specific complications, and regular follow-up are essential components of optimal care in Alagille syndrome.

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