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Case Report

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Syndromic paucity of bile ducts Alagille syndrome: A case report

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Abstract

Alagille syndrome is an uncommon genetic disorder with autosomal dominant inheritance characterized by chronic cholestasis and paucity of interlobular bile ducts. The condition has been reported only as isolated cases in India. We report a case of 2-month baby with cholestasis who was diagnosed with syndromic Alagille. There are two recognized forms of the disease: the syndromic type linked to other congenital defects and the no syndromic type that has no other anomalies found at birth. We describe the case and discuss its clinical and histopathological features. Additionally, we explore the various etiologist included in the differential diagnosis of bile duct paucity. This case emphasizes the significance of prompt identification and treatment of Alagille syndrome, contributing to the sparse literature on this uncommon condition.

Abbreviations: BA: Biliary Atresia; ALGS: Alagille Syndrome; TOF: Tetralogy of Ballot; DORV: Double Outlet; AAT: Alpha-1-antitrypsin; AATD: Alpha-1-antitrypsin Deficiency; GD: Gaucher Disease; NPD: Niemann-Pick Disease; CF: Cystic Fibrosis; ERCP: Endoscopic Retrograde Cholangiopancreatography; MRCP: Magnetic Resonance Cholangiopancreatography; PFIC: Progressive Familial Intrahepatic cholestasis.

Introduction

Alagille Syndrome (ALGS) is an uncommon genetic condition that can affect multiple organ systems of the body such as the liver, heart, skeleton, eyes and kidneys. The specific symptoms, organ system involvement and severity of Alagille syndrome can differ widely between individuals, even among family members. Certain individuals might experience mild variations of the disorder, while others could face more severe cases [3]. Typical symptoms that frequently appear within the initial three months of life consists of cholestasis, jaundice, Inadequate weight gain and growth along with intense itching (pruritus). Other symptoms consist of heart murmurs, congenital heart abnormalities, variations in the vertebrae (spine), thickening of the corneal ring in the eye (posterior embryotoxic) and unique facial characteristics. The majority of individuals with Alagille syndrome possess alterations (mutations or variants) in a single copy of the JAG1 gene. Variants in the NOTCH2 gene are found in a small proportion (2%) of patients. These variants may be inherited in an autosomal dominant manner, however in approximately 50% of cases, the variant arises as a new (de novo) mutation in the individual. Alagille syndrome was first described by Alagille Watson and Miller. They established the possible dominant inheritance and its variable expression. The incidence is between 1 in 30,000 and 1 in 45,000 with no gender predilection [5]. The clinical diagnostic criteria include intralobular bile duct paucity identified on liver biopsy, along with at least three out of five major clinical features, with genetic analysis serving as the confirmatory diagnosis.

1. Cholestasis (pruritus, xanthomas, hepatocellular carcinoma).

2. Cardiac disease with pulmonary stenosis (TOF/DORV/ASD/VSD).

3. Skeletal defects - classical butterfly shaped thoracic vertebra, with other abnormalities such as a pointed anterior process of C1, spina bifida occulta, fusion of adjacent vertebra, hemi vertebra and the absence of the 12th rib.

4. Eye- posterior embryotoxon (90%), optic disc drusen, and widespread hypopigmentation of fundus.

5. Typical facial features- triangular face with deep set eyes, pointed chin, moderate hypertelorism and prominent forehead.

Case report

A 2 month old baby, born of a non-consaguineous marriage, immunized for age presented with yellowish discoloration of skin for 2 days and poor weight gain. On admission, vitals stable. He had sick looking appearance and also mild pallor and icterus. Head to foot examination shows facial dysmorphism, prominent nose tip, large posteriorly rotated ears, progeroid facies, dry skin, sparse hair and eyebrows, wide anterior fontanelle, seborrheic dermatitis, grade II marasmus.

Anthropometry: Height was 55 cm (z score -2 to -3 SD), weight 2.8 kg (z score <-3 SD) and head circumference 40 cm (<3 SD). The biochemical parameters of the patient along with corresponding reference ranges for the laboratory are described in Table 1. Neonatal cholestasis was the provisional diagnosis, and the child received symptomatic and supportive care. Stool had a pale colour; Ultrasonography abdomen revealed no abnormalities. TORCH profile and viral markers were negative. Technetium -99 m scan deferred by the parents. Liver biopsy done and tissue stained with haematoxylin and eosin showed linear core of liver tissue with hepatocytes showing ballooning degeneration and feathery degeneration and spotty necrosis (Figure 1). Canalicular cholestasis noted. Portal tracts are not visible. Immunohistochemistry revealed only one duct (Figure 2). Histopathological diagnosis given as intrahepatic cholestasis with paucity of bile ducts. Possibilities given are Progressive familial intrahepatic cholestasis and Alagille nonsyndromic. Genetic study and extensive workup done followed by liver biopsy. Genetic study showed JAG1 gene mutation (Figure 3). An X-ray of spine showed butterfly-like vertebrae (Figure 4). Two-dimensional echocardiography showed small patent ductus arteriosus. Ophthalmologic examination was non-contributory. Dermatology consultation done in view of ichthyosis.

Our patient was finally diagnosed as having the syndromic Alagille. Because along with bile duct paucity, he had cholestatic jaundice, and the typical facial and vertebral appearance, patent ductus arteriosus (4 out of 5 features and liver biopsy suggest Alagille syndrome). He was treated with ursodeoxycholic acid, vitamin D3, calcium, vitamin A solution and multivitamins. Referred to paediatric gastroenterology Department for further management.

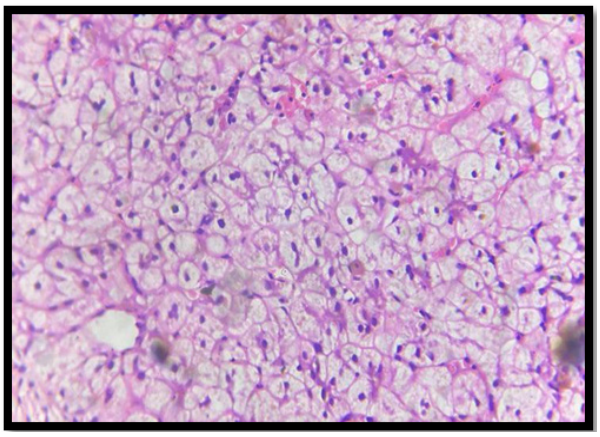

Figure 1: Liver histology findings of the patient.

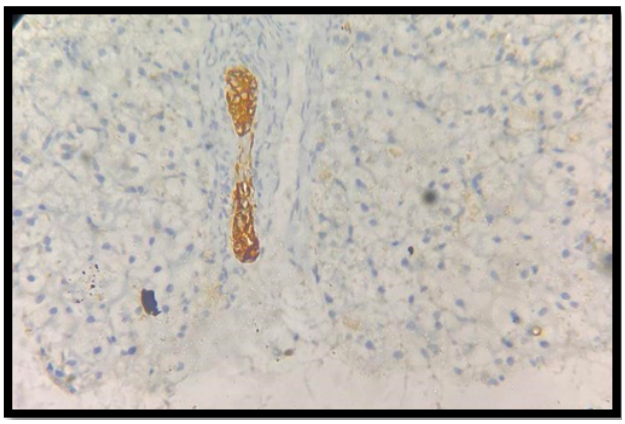

Figure 2: Cytokeratin 19 staining highlights bile duct Only single bile duct seen in whole section.

SNV(s)/INDELS

Gene[a] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[b]
JAG1 (-) (ENST00000254958.10)	Exon 25	c.3194dup (p.Thr1066AsnfsTer43)	Heterozygous	Alagille syndrome 1 (OMIM#118450)	Autosomal dominant	Likely Pathogenic (PVS1, PM2)

Figure 3: Genetic study showed JAG1 gene mutation.

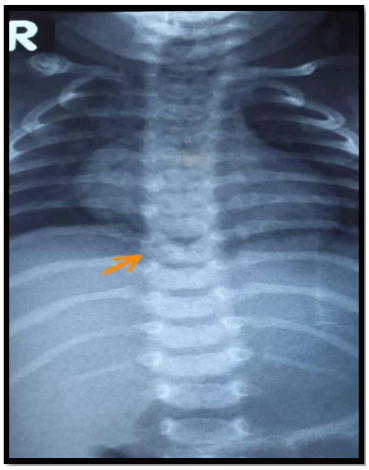

Figure 4: X-ray spine shows butterfly shaped vertebrae.

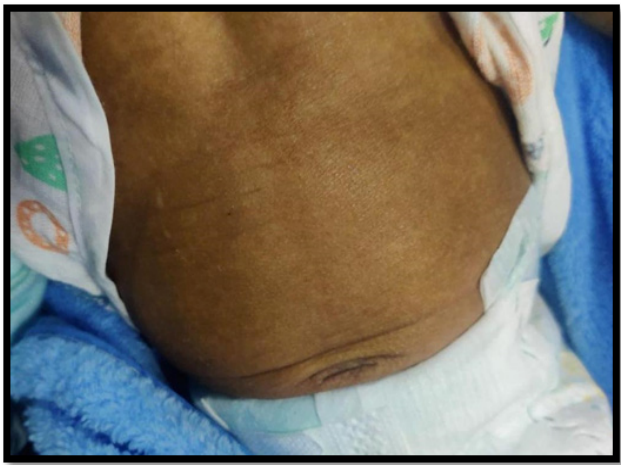

Figure 5: Abdomen shows mild distension and icterus.

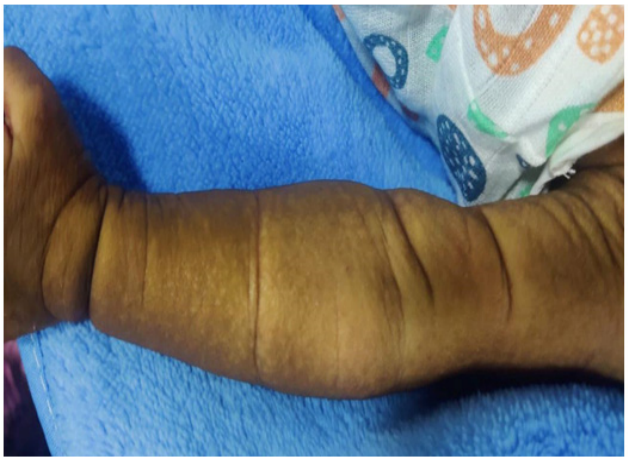

Figure 6: Showing skin changes.

Table 1: Laboratory Parameters of the patient along with corresponding reference ranges.

Parameters	Values in the patient	Normal reference range	Inference
Hemoglobin(g/dL)	8	9.4 – 13.0	Decreased
PCV(%)	24	28- 42	Decreased
TLC (cells/cu.mm)	19520	5000-15000	Increased
PLT (cells/mcL)	5.6	2-5	Increased
Serum urea (mg/dL)	14	5-18	Normal
Serum creatinine (mg/dL)	0.4	0.10-0.36	Normal
Serum total bilirubin (mg/dL)	9.6	0.05-0.68	Increased
Serum direct bilirubin (mg/dL)	5.8	0.05-0.30	Increased
Serum AST (U/L)	436	20-67	Increased
Serum ALT (U/L)	376	5-33	Increased
Serum ALP (U/L)	371	134-518	Normal
Serum GGT (U/L)	151	8-127	Increased
Serum Protein (g/dL)	5.7	4.7-6.7	Normal
Serum Albumin (g/dL)	4.1	2.8-4.7	Normal
Serum Ferritin (ng/mL)	>1000	14-647	Increased
Urine reducing substance, bile salt, bile pigment	Negative		

TLC: Total Leukocyte Count; PCV: Packed Cell Volume; PLT: Platelet Count; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; GGT: Gamma Glutamyl transferases.

Discussion

Alagille Syndrome is a rare autosomal dominant genetic disorder characterized by abnormalities in the liver,eyes, heart, skeleton and a distinct facial appearance. ALGS results from mutations in either the JAG1 or NOTCH2 genes [1]. In our case, the patient exhibited three of the major features of the syndrome but lacked ophthalmic features. He had cholestatic jaundice, distinct facial features characteristic of ALGS, butterfly-shaped vertebrae and histologic study confirmed bile duct paucity. Genetic study identified a heterozygous single base pair duplication in exon 25 of the JAG1 gene, causing a frameshift and premature truncation of the protein 43 amino acids downstream to codon 1066. There has been a case report of Alagille syndrome occuring in a 14 month old male toddler. In a study by Shendge et al; partial or incomplete ALGS has been reported in the Indian literature. Emerick et al. conducted a study on 92 patients with ALGS, showed paucity of interlobular bile ducts in 85%, cholestasis in 96%, cardiac murmurs in 97%, butterfly vertebrae in 51%, posterior embryotoxic in the eye in 78%, and characteristic facies in 96% of the cases. Bile duct paucity is characterized by a bile duct to hepatic artery ratio of less than 0.5 in an adequate liver biopsy specimen, which should contain at least 10 portal tracts [2]. The differential diagnosis for bile duct paucity, when other clinical signs of ALGS are absent, is extensive and primarily encompasses congenital infections, metabolic disorders such as cystic fibrosis, Neimann-Pick disease and alpha-1 antitrypsin deficiency, as well as progressive familial intrahepatic cholestasis (PFIC). Congenitally acquired pathogens commonly include toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis. In cases of toxoplasmosis, cranial imaging is performed on neonates to evaluate for focal brain lesions or hydrocephalus. Cytomegalovirus has been identified as the most prevalent congenital viral infection. Cranial CT imaging can reveal a variety of brain abnormalities such as periventricular leukomalacia, cystic abnormalities, periventricular calcifications and ventriculomegaly. Neonatal herpes simplex virus (HSV) infection may present as bilateral, diffuse pneumonitis on chest X-ray, indicative of primary HSV pneumonia. In our case, the TORCH profile was negative, thereby ruling out congenital infections.

Additionally neonatal excretion of conjugated bilirubin is compromised in several metabolic disorders, including galactosemia, tyrosinemia, lipid metabolism disorders (such as Niemann-Pick disease and Gaucher disease), Caroli's disease, alpha-1-antitrypsin deficiency, neonatal hemochromatosis, and

cystic fibrosis. Galactosemia is a metabolic disorder affecting carbohydrate processing, leading to neonatal cholestasis due to a deficiency in galactose-1-uridyl transferase. Infants with this condition typically exhibit mixed hyperbilirubinemia following the introduction of galactose-containing feedings. Diagnosis is indicated by the detection of reducing substances in the urine and is confirmed through an assay measuring galactose-1-phosphate uridylic transferase activity in erythrocytes, leukocytes, or liver. Disorders of lipid metabolism, including Gaucher disease (GD) and Niemann-Pick disease (NPD) may also manifest with cholestasis. GD is an inborn error of metabolism that disrupts the recycling of cellular glycolipids, leading to the accumulation of glucocerebroside and related compounds within lysosomes, affecting the visceral organs, bone marrow, and skeletal system in all patients. Caroli's disease is a hereditary condition characterized by the segmental and multifocal enlargement of the large intrahepatic bile ducts. The diagnosis is confirmed through imaging techniques that reveal bile duct ectasia and abnormal, cystic expansion of the large proximal intrahepatic bile ducts, while the common bile duct remains unaffected. These characteristics can be detected using ultrasound, ERCP, and MRCP. Alpha-1-antitrypsin deficiency (AATD) may lead to neonatal cholestasis. AAT functions as an antiprotease and serves as the natural inhibitor of serine proteases released by activated neutrophils. In newborns, other clinical manifestations include hepatomegaly with elevated aminotransferase levels, as well as early signs of moderate to severe liver disease characterized by ascites and bleeding diathesis. The diagnosis primarily relies on spirometery to assess pulmonary function; however, it has been proposed that a chest CT scan could reveal reduced lung density in certain cases of AAT deficiency. Cystic fibrosis (CF) is the most prevalent lethal autosomal recessive disorder, occurring in approximately 1 in every 2000 to 3000 live births. The condition is characterized by persistent lung infections, pancreatic insufficiency, and increased sweat chloride levels. Nevertheless, many patients exhibit mild or atypical symptoms such as neonatal cholestasis. CT is the current "gold standard" for assessment of lung morphology. Radiological observations include linear atelectasis, dilated and thickened airways, and irregular peripheral opacities that could indicate the presence of mucopurulent plugs. Furthermore, ERCP can be used to assess biliary patency. In cystic fibrosis patients, ERCP typically reveals multiple irregular filling defects throughout the biliary system, indicative of thickened bile, mucus and stones. While cystic fibrosis can lead to meconium ileus and respiratory issues; these symptoms were not in our case. Biliary atresia and choledochal cysts two conditions that can cause obstructive neonatal cholestasis. The most frequent cause of neonatal jaundice for which surgery is recommended is biliary atresia, a progressive, idiopathic, destructive disease of the extrahepatic biliary tree that manifests as biliary obstruction during the neonatal period [2]. BA exhibits its distinctive cholangiogram and histology findings. Inflammation, portal tract fibrosis, cholestasis, and bile duct proliferation are commonly observed in the histology. The extrahepatic bile ducts have lost their patency, as shown by the cholangiogram [2]. Known as the gallbladder ghost triad (GB <19 mm, irregular contour, incomplete irregular mucosa), the gallbladder is typically absent or irregular in shape on ultrasound examination in infants with BA. One uncommon but curable cause of conjugated hyperbilirubinemia is choledochal cysts. They represent congenital cystic dilatations of the biliary tree. Ultrasonography can typically detect diffuse enlargement of the common bile duct in the majority of affected infants.

Progressive familial intrahepatic cholestasis (PFIC) is a diverse set of disorders marked by impaired secretion of bile acids or other bile constituents, typically manifesting in infancy or childhood, and linked to growth retardation and progressive liver disease. A definitive diagnosis can only be established through genetic testing. Individuals with PFIC may exhibit symptoms such as hearing loss, pancreatic insufficiency, gallstones and diarrhea,and the condition often has a familial pattern.

Conclusion

Alagille syndrome is a rare and intricate genetic condition marked by paucity of bile ducts, cardiac defects, ocular abnormalities, skeletal abnormalities and facial dysmorphism. The genetic cause lies in mutations of the JAG-1 or NOTCH-2 genes. The symptoms and severity can differ significantly among those affected. The prognosis varies, with some individuals experiencing mild symptoms while others may face severe complications. This specific syndromic type of bile duct deficiency has been rarely reported in Indian literature so far. Because these patients usually have multi-system involvement, they may be evaluated by multiple clinical subspecialties and therefore it is necessary that all clinicians should be aware of this disorder. Early diagnosis and timely referral to the appropriate specialities and poor outcome can be prevented.

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