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Editorial

Malady and Ailment - Alagille Syndrome

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Alagille syndrome emerges as a genetic disorder demonstrating vascular and biliary anomalies along with varied anatomical aberrations. Additionally designated as arteriohepatic dysplasia, the condition manifests as an aetiology inducing syndromic paucity of bile ducts. The disease manifests with an absence of intrahepatic bile ducts wherein clinical severity varies from severe neonatal cholestasis recapitulating biliary atresia to childhood intermittent jaundice. Disease progression into cirrhosis is exceptionally observed.

Alagille syndrome arises due to distinct genetic mechanisms as

- A preponderant autosomal dominant condition (ALGS1) which demonstrates genomic mutations within Jagged1 gene situated upon chromosome 20p12 which encodes a ligand for NOTCH1 and contributes towards epithelial mesenchymal interactions. Genetic penetrance is significant although genetic expression is variable wherein up to 70% subjects display contemporary genetic mutations.
- Genetic anomaly (ALGS2) is minimally encountered and is contingent to genetic mutations within gene encoding NOTCH2 situated upon chromosome 1p13. Associated renal disease is severe. Alagille syndrome delineates an incidence of ~1:30,000 live births [1,2].

Commonly, features such as abnormal inverted triangular facies, posterior embryotoxon within the eye, pulmonary stenosis, severe congenital heart disease, butterfly vertebrae or diverse vertebral arch anomalies, skeletal anomalies as short distal phalanges or clinodactyly are represented [1,2].

Hepatic parenchyma characteristically depicts progressive loss of bile ducts along with or devoid of hypoplasia of extrahepatic bile ducts, hypoplasia of gallbladder and cholelithiasis with consequent emergence of hyperbilirubinemia and pruritus. Distinction from conditions inducing cholestasis with biliary atresia may be challenging [1,2].

Hepatic manifestations are comprised of cholestasis due to paucity of biliary ducts, conjugated hyperbilirubinemia, pruritus, xanthomas and cirrhosis with consequent end stage liver disease [1,2].

Cardiac defects occur in >90% subjects and are constituted of peripheral pulmonic stenosis, tetralogy of Fallot, ventricular septal defect, atrial septal defect, aortic stenosis and coarctation of aorta [2,3].

Renal anomalies characteristically depict renal dysplasia, glomerular mesangiolipidosis and renal tubular acidosis.

Renal abnormalities as tubulointerstitial nephropathy, membranous nephropathy, mesangiolipidosis or renovascular hypertension may be encountered.

Skeletal abnormalities are comprised of butterfly vertebrae, hemivertebrae or pathological fracture of long bones.

Ophthalmologic manifestations may emerge as posterior embryotoxon with a prominent Schwalbe line [2,3].

Dysmorphic facies typically represent as prominent, broad forehead, deep-set eyes with moderate hypertelorism, prominent ears, triangular face with a pointed chin and broad nasal bridge [2,3].

Abnormalities of vasculature are frequently associated with neurovascular anomalies as aneurysms, Moyamoya syndrome, aberrations in cerebral arteries, reno-vascular abnormalities and middle aortic syndrome [2,3].

Additionally, manifestations as short stature, failure to thrive, immunodeficiency or repetitive infections may ensue. Developmental delay, delayed puberty, supernumerary flexion creases or pancreatic insufficiency may be discerned [2,3].

Upon microscopy, portal tracts appear to lack bile ducts wherein proportion of bile duct to portal tract is 0 to 0.4, in contrast to normal proportion of 0.9 to 1.8 [3,4].

Ductular reaction appears characteristically absent. Exceptionally, infants may depict a ductular reaction. Hepatocellular transformation into giant cells and deposition of copper into periportal hepatocytes may be observed. Infrequently, the disorder may progress into overt cirrhosis [3,4].

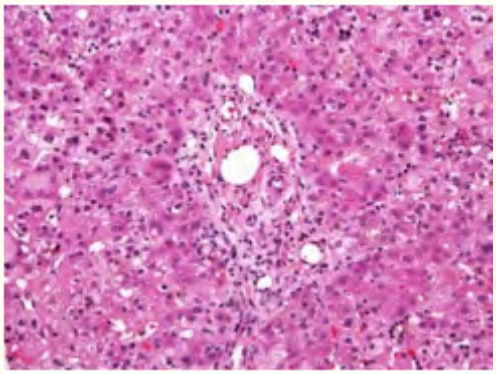

Figure 1: Alagille syndrome demonstrating paucity of bile ducts with few giant cells and copper deposition within hepatocytes. Portal fibrosis is encountered [9].

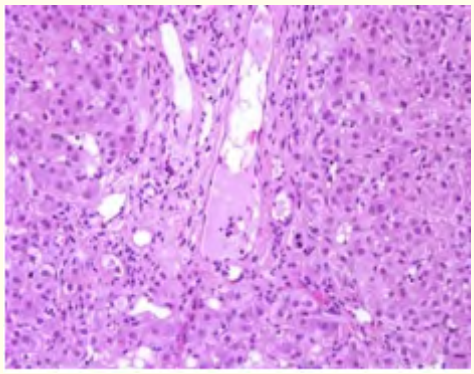

Figure 2: Alagille syndrome delineating paucity of bile ducts with few giant cells and copper deposition into hepatocytes. Inflammation and fibrosis of portal tract is observed [10].

Feature	Manifestations
Hepatic anomalies (95%)	Bile duct paucity, conjugated hyper-bilirubinemia, chronic cholestasis, pruritus, xanthoma, fat- soluble vitamin deficiency, end stage liver disease
Cardiac manifestations (90%-97%)	TOF, peripheral pulmonary stenosis
Posterior embryotoxon (78%-89%)	
Vertebral anomalies (33%-93%)	
Characteristic facies (20%-90%)	
Renal manifestations (39%)	Renal malformation and renal disease
Vascular anomalies (15%-30%)	Intracranial bleed, systemic vascular anomalies, myoamoya disease and others

Table 1: Specific and Associated Features of Alagille syndrome [3].

TOF: Tetralogy of Fallot.

Alagille syndrome requires segregation from conditions which induce cholestasis as alpha-1 antitrypsin deficiency, cystic fibrosis, childhood primary sclerosing cholangitis, mitochondrial disorders,

congenital hepatic fibrosis, liver infection as observed with congenital syphilis, congenital cytomegalovirus, congenital rubella or hepatitis B, childhood autoimmune hepatitis, hypopituitarism, graft versus host disease, Zellweger syndrome, Ivemark syndrome or Smith-Lemli-Opitz syndrome and disorder with paucity of interlobular bile ducts [4,5].

Cholestasis may occur in neonates with biliary atresia, sepsis, galactosemia, tyrosinemia, choledochal cyst or diverse extrahepatic structural anomalies. Subjects with progressive familial intrahepatic cholestasis types I and II, arthrogryposis-renal dysfunction-cholestasis syndrome, benign recurrent intrahepatic cholestasis and Norwegian cholestasis (Aagenaes syndrome) may delineate cholestasis [5,6].

Pulmonic vascular anomalies occur within Noonan syndrome, Watson syndrome, William syndrome, Down syndrome or LEOPARD syndrome. Ventricular septal defects and Tetralogy of Fallot (TOF) are commonly concurrent with chromosomal deletion 22q11.2 along with butterfly vertebrae and failure to thrive.

Posterior embryotoxon, Bannayan-Riley-Ruvalcaba syndrome and Axenfeld-Rieger syndrome may be observed.

Management of malnutrition necessitates nutritional and fat-soluble vitamin supplementation [5,6].

Supportive therapy engendering amelioration of severe pruritus and xanthoma with employment of agents decimating cholestasis as ursodeoxycholic acid, naltrexone, rifampin, colesevelam or cholestyramine appear beneficial [5,6].

Surgical manoeuvers as partial internal biliary diversion and ileal exclusion may be adopted although disease progression may not be subverted [5,6].

Although not recommended, Kasai procedure or portoenterostomy may be utilized for treating subjects with biliary atresia.

Liver transplantation may be employed for managing end-stage liver disease, a procedure associated with ~80% 5 year proportionate survival. Liver transplantation is optimally employed for treating subjects with progressive liver disease or intractable pruritus [5,6].

Disease mortality is contingent to emergence of liver disease, cardiac abnormalities and intracranial bleeding. Although life expectancy extends into adulthood, enhanced possible occurrence of hepatic failure and hepatocellular carcinoma may ensue [7,8].

Prognostic outcomes and overall mortality of Alagille syndrome are contingent to organ involvement and disease severity. Severe cardiac or hepatic disease may induce preliminary mortality whereas vascular conditions engender delayed mortality [7,8].

Cardiac, renal and vascular anomalies are managed pertaining to associated clinical symptoms. Screening guidelines for neurovascular complications of Alagille syndrome remain absent. Ophthalmological and vertebral anomalies do not necessitate management [7,8].

Secondary complications may be prohibited by circumventing contact sports, especially within subjects with splenomegaly, chronic liver disease and vascular conditions. Meticulous monitoring remains mandatory and superior mode of disease evaluation [7,8].

Bibliography

1. Diaz-Frias J and Kondamudi NP. "Alagille Syndrome". Stat Pearls International. Treasure Island, Florida (2025).
2. Bufler P., *et al*. "The burden of Alagille syndrome: uncovering the potential of emerging therapeutics - a comprehensive systematic literature review". *Journal of Comparative Effectiveness Research* 14.2 (2025): e240188.
3. Spinner NB., *et al*. "Alagille Syndrome". In: Adam MP, Feldman J, Mirzaa GM et al. editors (2024).
4. Ranchin B., *et al*. "Kidney and vascular involvement in Alagille syndrome". *Pediatric Nephrology* 40.4 (2025): 891-899.
5. Yan J., *et al*. "Clinical, pathological and genetic characteristics of 17 unrelated children with Alagille Syndrome". *BMC Pediatrics* 24.1 (2024): 532.
6. Ayoub MD., *et al*. "Management of adults with Alagille syndrome". *Hepatology International* 17 (2023): 1098-112.

7. Baumann U., *et al*. "Effects of odevixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study". *Clinics and Research in Hepatology and Gastroenterology* 45 (2021): 101751.

8. Himes R., *et al*. "Real-world experience of maralixibat in Alagille syndrome: Novel findings outside of clinical trials". *Journal of Pediatric Gastroenterology and Nutrition* 78.3 (2024): 506-513.

9. Image 1 Courtesy: Science direct.

10. Image 2 Courtesy: Child liver disease research network.