

ALAGILLE SYNDROME- CASE SERIES AND REVIEW OF LITERATURE OF RARE AND FATAL SYNDROME IN TELANGANA STATE, INDIA

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INTRODUCTION

Alagille syndrome is a complex multi system disorder involving primarily the liver (cholestasis), heart (peripheral pulmonary stenosis), eye (posterior embryotoxon), face and skeleton. Renal and CNS anomalies can also occur. The clinical features are highly variable even within the families because of its autosomal dominant nature.

Alagille syndrome is a rare autosomal dominant disease first described by Alagille Watson and Miller. They established the possible dominant inheritance and variable expressivity pattern of this disease.¹ The incidence is 1:30000 to 1:45000 with no difference in gender. The clinical diagnostic criteria include intralobular bile duct paucity on liver biopsy and at least three out of five major clinical features while confirmatory diagnosis being genetic analysis.

1. Cholestasis (pruritus, xanthomas, hepatocellular carcinoma).
2. Cardiac disease with peripheral pulmonary stenosis (TOF/DORV/ASD/VSD).
3. Skeletal abnormalities- classical butterfly shaped thoracic vertebra, other abnormalities may include pointed anterior process of C1, spina bifida occulta, fusion of adjacent vertebra, hemi vertebra and absence of 12th rib.
4. Eye- posterior embryotoxon (90%), optic drusen, diffuse hypopigmentation of fundus.
5. Typical facial features- triangular face with deep set eyes, pointed chin, moderate hypertelorism and

prominent forehead. With age, protrusion of mandible and chin becomes more prominent.²

Renal anomalies include tubule interstitial nephropathy & mesangiolipidosis, structural changes with cysts. Vascular abnormalities include intracranial vascular anomalies detected on MRA in 15% of patients which leads to intracranial bleeding accounting for up to 34% of mortality. ALGS is caused by loss of function mutation in either JAG1 (>94% of patients) or NOTCH2 (1-2%). Autosomal dominant pattern with 'sporadic' or 'denovo' mutation is possible to cause Alagille syndrome.¹

Case Report 1

A 45 days old male child was brought by mother with complaints of yellowish discoloration of eyes since 3rd day of life associated with high coloured urine and intermittent passage of white coloured stools. No h/o abdominal distension/bleeding manifestation. No h/o cry during micturition/reduced urine output. Neonatal history is significant for neonatal jaundice for which phototherapy was given and jaundice decreased.

On general examination, icterus was present up to palms and soles. Central cyanosis was present involving tongue, lips. No pallor/clubbing/pedal oedema/lymphadenopathy /petechiae/ecchymoses. Visible pulsations were present over the precordium. Vitals: temperature 98.4°F pulse rate: 130/ min, respiratory rate: 48/ min, BP=70/50 in right arm, 80/40 in remaining all 3 limbs. SpO₂ = 65-70% in room air with all 4 limbs. Per abdomen examination reveals liver 3 cm palpable below right costal margin, soft in consistency, smooth margin and non-tender with liver span of 6.5 cm and spleen is not palpable. On CVS examination, apical impulse in left 4th intercostal space 1 cm lateral to midclavicular line, hyperdynamic in character. Systolic thrill was present over the precordium. On auscultation, S1 is normal, S2 appears

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to be single. Pansystolic murmur of grade 4 best heard with diaphragm of stethoscope heard over left sternal border. The murmur got radiated to left side of chest with decreased intensity in axillary, infra-axillary areas and back of chest. There is no variation with phases of respiration. Murmur not conducted to carotid. Rest of physical examination was unremarkable.

Investigations

Revealed Hb of 11.8 g/dl, WBC- 12700/cumm and platelet of 2.5 lakh/cumm. Blood picture revealed normochromic normocytic RBCs. LFT with serum enzymes: total serum bilirubin 17 mg/dl, direct 16.3 mg/dl, indirect 0.7 mg/dl. SGOT & SGPT are normal, ALP = 796.2 U/l, GGT= 178 U/l, Sr. Cholesterol and serum bile acids were increased. Total serum protein, albumin and globulin are normal. PT/APTT/INR/RFT/Sr. electrolytes are within normal limits. Complete urine examination, urine for culture & sensitivity, urine for metabolic profile are found to be within normal limits. Ophthalmological examination is normal. TORCH profile was negative and thyroid profile was found to be normal. Chest x-ray:

Chest x-ray showing cardiomegaly (CTR- 0.65) with butterfly shaped thoracic vertebrae. ECG showed right ventricular hypertrophy with right axis deviation.³ 2D ECHO: Double outlet right ventricle, moderate to large VSD, long segment pulmonary atresia, critical pulmonary stenosis.⁴ USG abdomen suggests normal study and HIDA scan suggests high possibility of biliary atresia. Liver biopsy showing absence of bile duct in portal triad.⁵

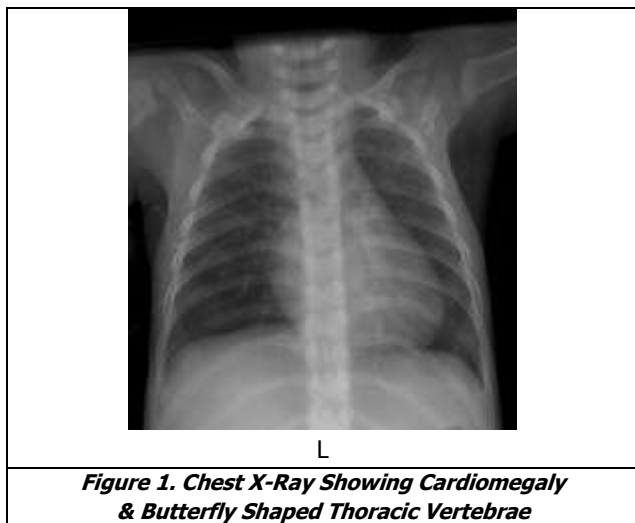


Figure 1. Chest X-Ray Showing Cardiomegaly & Butterfly Shaped Thoracic Vertebrae

Liver biopsy showed intracanalicular and intra hepatic cholestasis and focal giant cell transformation. Portal areas shows reduced size along with decreased number of bile ducts portal inflammation & periportal fibrosis s/o Alagille Syndrome.^{6,2} Genetic testing couldn't be done due to financial constraints.

Presence of intra hepatic bile duct paucity, peripheral pulmonary stenosis, neonatal cholestasis and butterfly shaped thoracic vertebrae (3 out of 5 features and liver biopsy suggest Alagille Syndrome).

Case Report 2

A 2 year old female child, born out of 2nd degree consanguineous marriage came with c/o yellowish discoloration of eyes from birth associated with clay coloured stools, high coloured urine and intense pruritus, abdominal distension for 6 months duration, insidious in onset, gradually progressive in nature, more in upper abdomen, not associated with pain abdomen/pedal oedema/facial puffiness/shortness of breath. H/o blood in stools for 10 days, frank blood mixed with stools, 1-2 episodes/day, not associated with any other bleeding manifestations. Neonatal history is significant for neonatal jaundice for which child was admitted for 20 days (records not available).



Figure 2. Liver Biopsy Showing Absence of Bile Duct in Portal Triad

On general examination Child is thin built and malnourished, icterus present, pallor present, no Cyanosis/clubbing/koilonychia/lymphadenopathy. No oedema /petechiae /ecchymoses.

Head to toe examination revealed triangular facies, alopecia, Bitot's spots, pointed chin, depressed nasal bridge, short and stubby fingers, pruritus marks present. Anthropometry: weight 8 kgs (<1st centile), height 73 cms (<1st centile), head circumference 41 cms (<3rd centile), mid upper arm circumference 11 cms. Vitals are stable. Per abdomen examination revealed liver extends 8 cm below right costal margin, firm in consistency, non-tender, smooth surface with liver span of 11.5 cms. Spleen extends 4 cms below left costal margin, smooth margin, firm in consistency, non-tender. Fluid thrill present. Rest of physical examination was unremarkable.

Investigations

Revealed Hb of 8.8 g/dl, WBC -11700, platelet 5.6 lakh, serum total bilirubin was 2.47 mg/dl, direct bilirubin =1.24 mg/dl, indirect =1.23 mg/dl. Serum cholesterol and bile acids are increased.⁷ Total serum protein, PT/APTT/INR, renal function test and serum electrolytes are within normal limits. Gastric aspirate for acid fast bacillus was negative. Chest x-ray and vertebral x-ray revealed normal study. 2D ECHO and ophthalmologic examination was normal. Wilson's profile was normal. Ascitic fluid analysis: proteins 884 mg/dl, sugar -103 mg/dl, culture- no bacterial growth, ADA- 1.3 u/l,

SAAG- 1.45. Autoimmune profile (DCT, Anti LKM, ANA, anti SMA) are negative. USG abdomen and portal vein doppler revealed liver coarse architecture with span of 12.6 cms, spleen increased in size with normal echo texture (size=10 cm). Moderate ascites. Portal vein diameter = 6.6 cm, Normal colour uptake, velocity 21 cm/sec.



Figure 3. Icterus and Distended Abdomen



Figure 4. Multiple Xanthomas Over Bilateral Feet Lichenification due to Prolonged Scratching

Upper GI endoscopy revealed portal hypertensive gastropathy. Liver biopsy revealed mild cirrhosis change with ballooning degeneration of hepatocytes, intracanalicular and intra hepatic cholestasis. Portal areas showed reduced size along with decreased number of bile ducts, portal inflammation and periportal fibrosis. Histological features are in favour of Alagille syndrome and suggested clinical correlation. Liver biopsy showing absence of bile duct in portal triad.⁵

Absence of KF ring on slit lamp examination, normal serum ceruloplasmin, normal serum copper, normal 24-hour urinary copper rules out Wilson's disease. Absence of autoimmune markers and presence of intra hepatic bile duct paucity on liver biopsy suggest ALAGILLE SYNDROME (liver biopsy features + 2/5 criteria present) rather than autoimmune hepatitis, PFIC and BRIC. As Alagille syndrome is inherited in autosomal dominant pattern, clinical features are highly variable in expression.⁸



Figure 5. Chest X-Ray and Vertebral Column Normal



Figure 6. Liver Biopsy: Fibrosis Between Hepatocytes

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