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CASE REPORT

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Suspected Alagille syndrome in a preterm newborn at Muhimbili National Hospital: A case report

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Abstract: Alagille syndrome is a rare genetic disorder characterized by abnormalities in the liver function caused by narrowing and malformation of the biliary tree which leads to cholestasis and hepatic failure. It also encompasses cardiac and skeletal anomalies with characteristic facial appearance. The diagnosis of Alagille syndrome is mainly through clinical presentation and genetic testing. This case report highlights the clinical features characterizing the syndrome and the diagnostic challenges in resource-limited settings.

Keywords: Alagille syndrome, JAG1, NOTCH2, Cholestasis, Bile duct paucity.

Résumé: Le syndrome d'Alagille est une maladie génétique rare. Il est caractérisé par des anomalies de la fonction hépatique causées par le rétrécissement et la malformation de l'arbre biliaire ; ce qui entraîne une cholestase et une insuffisance hépatique. Il implique également des anomalies cardiaques et squelettiques avec une apparence faciale caractéristique. Le diagnostic du syndrome d'Alagille repose principalement sur la présentation clinique et les tests génétiques. Ce cas clinique met en évidence les caractéristiques cliniques de ce syndrome et les difficultés du diagnostic dans les régions à ressources limitées.

Mots clés: Syndrome d'Alagille, JAG1, NOTCH2, cholestase, insuffisance des voies biliaires.

Introduction

Alagille syndrome (ALGS) is a complex autosomal dominant disorder due to defects in the Notch signaling pathway which was first reported by Alagille in 1969.[1] It is a multisystemic disorder that affects the heart, liver, skeleton, eyes, kidneys, and central nervous system. The majority of cases are due to mutations in *JAG1* (20p12), and a few are due to deletions incorporating *JAG1 or* mutations in *NOTCH2* (1p13).[2] ALGS may be referred to as type 1 (*JAG1*-associated) or type 2 (*NOTCH2*-associated).[3] There is a great variability in the symptoms and penetrance even within members of the same family.

The main clinical features and malformations are chronic cholestasis due to paucity of intrahepatic bile ducts, congenital heart disease primarily affecting the pulmonary outflow tract and vasculature, butterfly vertebrae, characteristic facies with a broad nose and forehead, posterior embryotoxon and/or anterior segment abnormalities of the eyes, and pigmentary retinopathy. Additional features are intracranial bleeding and dysplastic kidneys[4]

Diagnosis of ALGS is based on both genetic testing and phenotypic understanding, and this is often challenging with the lack of genetic tests available and the great variability of its phenotypic features.[5]
The management approach is multifaceted, often requiring actively screening for the associated features and managing the complications.

Case Report

We report a case of a male preterm baby aged 40 days, born to a 23-year-old mother and a 28-year-old father with no history of parental consanguinity. Pregnancy was uneventful and Mother's blood group was B positive. He was delivered at 32 weeks of gestation due to spontaneous onset of labor with pre-labor rupture of membranes. The baby, weighing 1.7 kg at birth, was referred to us at day 21 of life with complaints of difficulty in breathing which started shortly after birth for which he received oxygen therapy. His oxygen saturation dropped to 60% whenever he was kept in room air and improved to 80% on oxygen therapy, due to this he was kept on oxygen therapy throughout his hospital stay. He subsequently developed persistent yellowish discoloration of the body, first noticed at one week of age. The jaundice, which progressed from the face

downwards to the palms and soles, did not improve despite intensive phototherapy. His stool color varied from pale yellow to green. At one week of life, he started presenting with a few episodes of non-projectile vomiting about half an hour after feeding with no abdominal distension reported. He had severe anemia that warranted blood transfusions on two separate occasions before transfer to our facility and obtained two more while in our NICU.

Upon review baby was lethargic, severely wasted with significant weight loss of about 20% (birth weight 1.7kg, admission weight 1.35kg), and severely reduced skin turgor with subsequent poor growth, deeply jaundiced (fig 2) and pale. He had a broad forehead, prominent nasal bridge with a bulbous nose, and an elongated face with a pointed chin and high-arched palate (fig 1). His abdomen was slightly distended; however, it was soft with no organomegaly. Bowel sounds were normal. He had a micropenis with an empty scrotal sac. His anal orifice was patent.
He had features of respiratory distress with loud pan systolic murmur on the left lower sternal border.
His CBC showed leukocytosis, normocytic normochromic anemia (Hemoglobin 9 g/dl) and thrombocytopenia (Platelets 70x1000/µL) with peripheral smear showing inflammatory process suggestive of an infection. Total bilirubin level was critically raised (427mmol/L) with significant Direct hyperbilirubinemia (256mmol/L). Liver enzymes and coagulation profile were however within the normal range. (AST 30µmol/L, ALT 10.27µmol/L, GGT 154µmol/L). TORCHES screening was also normal. Baby's blood group was O positive. C –reactive protein levels remained persistently high despite using broad-spectrum antibiotics for two weeks (from 42µmol/L to 33µmol/L) and blood culture isolated a gram-negative bacillus (Klebsiella pneumoniae) which was sensitive to Meropenem only.

On Abdominal ultrasound a full gall bladder was visualized however we were not able to conclude on bile duct paucity. Liver, spleen, and kidneys were all normal in size and echogenicity. His echocardiography revealed a complex congenital cardiac anomaly – Double outlet right ventricle with mild pulmonary stenosis, subaortic ventricular septal defect (fig 3), small atrial septal defect (3mm) and small patent ductus arteriosus (2mm).
His chest radiography (fig 4) showed bilateral consolidation however the vertebral bodies appeared to be normal.
From these findings, a clinical diagnosis of Alagille syndrome which was complicated with late-onset neonatal sepsis and severe pneumonia was made. This patient was treated with Antibiotics (Meropenem) at a dose of 40mg/kg 8 hourly for 14 days, Supplemental fat-soluble vitamins (A, B, D, E and. K), Ursodeoxycholic acid at a dose of 15mg/kg/day for 21days, Antifailures (oral Furosemide and Spironolactone) at a dose of 1mg/kg/day each along with optimal feeding (fortified breastmilk with caloric intake targeted at 135kcal/kg per day).
Apart from a slight reduction in respiratory distress, the patient showed no desirable outcomes. Weight loss worsened, and sepsis did not respond to antibiotics. Unfortunately, on day 40 of life, the baby went into cardiac arrest. Despite attempts at cardiopulmonary resuscitation, the efforts were unsuccessful, and the baby was pronounced dead.

Fig 1: showing triangular face with bulbous nose and pointed chin

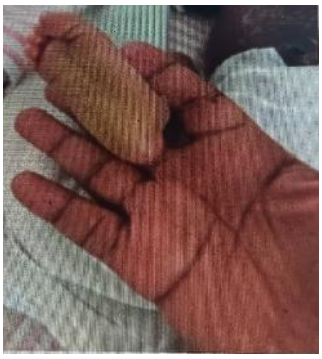

Fig 2: showing severe Jaundice

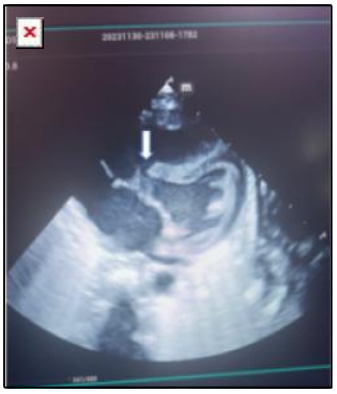

Fig 3: Echocardiography showing ventriculoseptal defect

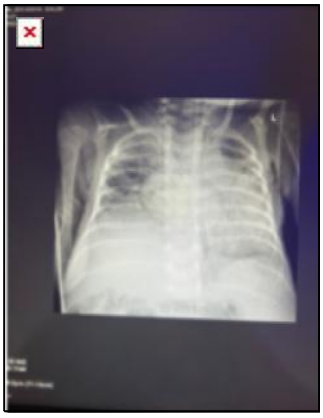

Fig 4: Chest radiography with bilateral infiltrates

Discussion

Alagille syndrome is a genetic disease with an autosomal dominant inheritance that primarily affects the liver and cause cholestatic liver disease.[6] Characteristic clinical features include persistent jaundice, typically caused by bile duct paucity, indicated by a bile duct-to-portal ratio of less than 0.5 (normal range 0.9-1.8) on liver biopsy and immunohistochemistry panels. These features are often accompanied by congenital cardiac anomalies such as pulmonary stenosis, septal defects, patent ductus arteriosus, and tetralogy of Fallot, as well as skeletal abnormalities like butterfly vertebrae.[7] Other important features include abnormal facies, ophthalmological abnormalities, growth failure and renal disease.[8]

Of these signs our patient presented with persistent cholestatic jaundice, however, liver transaminases appeared to be within normal range with no symptoms suggestive of coagulopathy, unfortunately due to progressive clinical deterioration liver biopsy to confirm the paucity of bile duct could not be performed. Nevertheless, bile duct paucity on liver histology is no longer considered mandatory for the diagnosis of Alagille syndrome, the presence of cholestasis can be used instead.[9]

Furthermore, failure to thrive was evident from visible severe wasting as well as significant weight loss of more than 20% within six weeks. He exhibited abnormal facial features and signs of respiratory distress, accompanied by a loud systolic murmur. Echocardiography confirmed a complex congenital cardiac anomaly, including double outlet right ventricle with mild pulmonary stenosis, septal defects, and patent ductus arteriosus, all of which could explain the persistence of respiratory distress. However, as expected with Alagille syndrome, spine radiography done on our patient did not reveal any abnormalities in the vertebral bodies.

Diagnosis of Alagille syndrome can be confirmed by molecular genetic testing to reveal the presence of JAG1 or NOTCH2 gene mutation although some studies have reported no evidence of such mutation in people with features of Alagille syndrome.[10] Due to limitation of resources in our facility it was difficult to obtain genetic tests from our patient.

To our knowledge, this is the first reported case of Alagille syndrome in a preterm neonate in our setting. The information obtained from this case may aid in the early detection of symptoms, prompt diagnosis, and effective management of complications associated with Alagille syndrome, ultimately contributing to the reduction of neonatal mortality caused by rare congenital anomalies.

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