Article 2
Physicians Academy
April 2018

Alagille Syndrome in a Neonate

Ghulam Nabi, MD, Omar Al-Siyud, MD and Omar Nabi Siraj, MBBS

Introduction:

Alagille syndrome (arteriohepatic dysplasia) is the most common syndrome with intrahepatic bile duct paucity. Bile duct "paucity" (often erroneously called *intrahepatic biliary atresia*) designates an absence or marked reduction in the number of interlobular bile ducts in the portal triads, with normal-size branches of portal vein and hepatic arteriole. Biopsy in early life often reveals an inflammatory process involving the bile ducts; subsequent biopsy specimens then show subsidence of the inflammation, with residual reduction in the number and diameter of bile ducts, analogous to the "disappearing bile duct syndrome" noted in adults with immune-mediated disorders. Serial assessment of hepatic histology often suggests progressive destruction of bile ducts[(1)]. X ray lumbosacral spine showed complete absence of sacrum and coccyx with medially deviated both iliac bones. Lumbar vertebrae are normal. Caudal dysplasia, also known as sacrococcygeal agenesis or the caudal regression syndrome. It is a congenital malformation characterized by varying degrees of developmental failure involving the lower lumbar, sacral, and coccygeal vertebrae, and the corresponding segments of the spinal cord[(2)].

Keywords: Alagille syndrome with caudal dysplasia.

Case report:

Female baby, late preterm, 36 weeks gestation, born to multigravida mother after lower segment cesarean section (Breech presentation). Routine resuscitation done and the baby shifted to nursery. Apgar score 7 and 9 at 1 and 5 minutes. Weight 1.8 Kilogram, length 43 centimeters, head circumference 30 cm. All growth parameters were below the 10th percentile. Intrauterine growth retardation. Respiratory rate 65 per minute with mild respiratory distress, heart rate 150/min, temperature 36.9C. Blood pressure 64/47, mean arterial pressure (MAP) 32 mm Hg. Low set ears. Broad base nose, broad forehead, deep-set eyes and pointed chin. On auscultation pan systolic murmur conducted all over precordial region. Chest basal crepitation (conducted sounds). Abdomen liver 4 cm below costal margin. Back: no gluteal folds, prominent right iliac crest. Small buttocks. Passing clay colored stool. Biliary obstruction? Moving all the four limbs (Figure 1). Obstetric history 40 years old mother, para two, other sibling is normal. Gestational diabetes mellitus on injection insulin. Preeclampsia toxemia. Antenatal one dose dexamethasone given. X-ray lumbosacral spine: complete absence of sacrum and coccyx with medially deviated both iliac bones. Lumbar vertebrae are normal, Caudal Regression (Figure2). Ultrasonography both kidneys echogenic. Baby needed respiratory support for three days. Nasal CPAP (continuous positive airway pressure). Orogastric feeding started at day two. By three week of age, baby had full oral demand feeding. At age of three weeks baby developed acute renal failure (urea 19.6 mg/dl, Creatinine 2.7mg/dl). Responded to conservative treatment and kidney function was normal in two weeks. TORCH (Toxoplasmosis, other agents (syphilis, varicella, parvovirus B), Rubella, Cytomegalovirus, Herpes simplex virus) screening test negative. Serum Alfa protein negative. Echocardiography done showed bicuspid aortic valve, left auricle and ventricle hypoplastic. Patent ductus arteriosis, congestive cardiac failure. Baby was put on diuretic medication and showed improvement. Viral hepatitis profile negative. Skeletal survey: sacral and coccygeal agenesis. Ultrasonography brain normal. Serum bilirubin high 14

mg/dl direct bilirubin more than 27%, passing clay colored stool. At the age of two weeks patient got Sepsis and urinary tract infection blood and urine culture yielded Klebsiella pneumonia and was treated with appropriate antibiotics. At two weeks age patient showed marked rise of Ferritin 614.5 ng/ml (normal 25-200), serum iron high 191ug/dl (normal 95—170) and returned to normal in one month period. At one-month age patient developed anemia and was corrected with blood transfusion. Metabolic screening done result showed elevated Cystathianine consistent with hepatic immaturity and vitamin B6 deficiency (cystothianase deficiency). At the age of one month hepatobiliary contrast study (Tc 90M bridatec (0.5 mCi ease injected) was done Imaging, hepatic blood flow was reduced. There was uniform hepatic activity with poor clearance of the blood circulation. Impression of Biliary atresia was made. Patient was seen by pediatric surgeon and suggested that case is having complex heart disease if possible Kasai operation latter and suggested liver biopsy. In spite of demand feeding(on medium chain triglyceride milk and multivitamins) failed to gain weight. Patient was on diuretic medication .Discharged at the age of five weeks, undernourished, distended abdomen due to liver enlargement yellow colored due to jaundice but general condition was stable. Weight of the baby 1.6 kg. (Figure 3) and was advised to attend outpatient clinic. Parents informed that patient died at home at the age of ten weeks.

Figure 1. Alagille Syndrome: Low set ear, broad base nose, broad forehead, deep-set eyes and pointed chin.

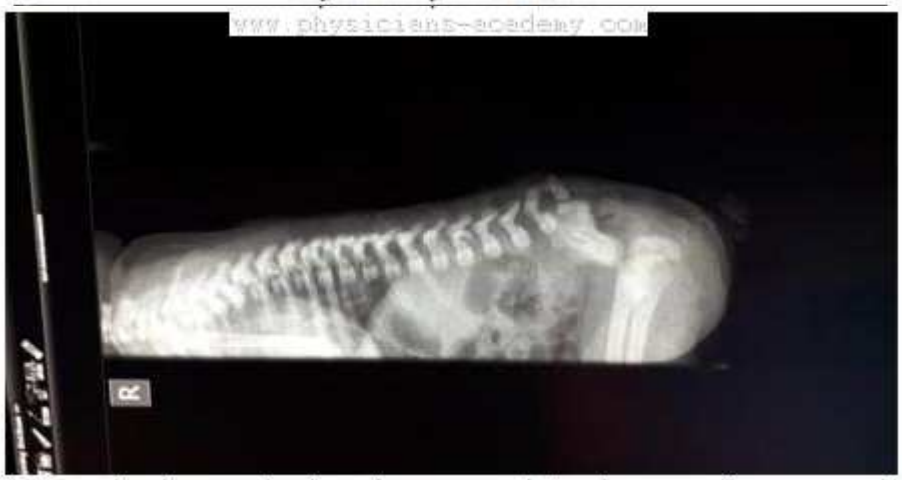

Figure 2. X-ray lumbosacral spine shows complete absence of sacrum and coccyx

Figure 3. Alagille Syndrome. Undernourished, yellow colored due to jaundice, distended abdomen due to hepatomegaly.

Discussion:

Alagille syndrome was initially described by Alagille and colleagues in 1969. This disorder was more completely described in 1973 by Watson and Miller who reported five families with 21 affected individuals. In 1975, Alagille et al described several patients with hypoplasia of the hepatic ducts with associated features. Since then more than 200 cases have been described[3]. Alagille syndrome is an autosomal dominant disorder with variable expression. Mutations in either jagged-1 (*JAG1*) or notch-2 (*NOTCH2*) have been reported. The syndrome has been mapped to the 20p12-jagged-1 locus, *JAG1*, which encodes a ligand critical to the notch gene–signaling cascade that is important in fetal development. Notch signaling has been found to regulate formation of 3-dimensional intrahepatic biliary architecture in murine models[4]. A minority (6-7%) of patients have complete deletion of *JAG1*, and approximately 15-50% of mutations are spontaneous. Most children are evaluated when younger than 6 months of age for either neonatal jaundice (70%), or cardiac murmurs and symptoms (17%). Patients who are less affected, such as family members, are often diagnosed after an index case. Presentation of Alagille syndrome varies. Some patients are diagnosed after prolonged neonatal jaundice or when liver biopsy findings reveal paucity of intrahepatic bile ducts. Others may be diagnosed during evaluation for heart disease. Some individuals are diagnosed by careful examination after an index case is identified in the family[5]. The incidence rate is approximately 1 in 100,000 live births. Major contributors to morbidity arise from bile duct paucity or cholestatic liver disease, and underlying cardiac disease. Males and females are affected equally. General growth retardation (50%). Typical facies (95%) consisting of deep set eyes, broad forehead, long straight nose with flattened tip, prominent chin, small low set or malformed ears[6]. Retinal degeneration, strabismus, ectopic pupil. choroidal folds, refractive errors posterior embryotoxon[7]. Cardiac: ASD, VSD, PDA, Coarctation of Aorta, right sided defects or pulmonary circulation defects and 67% have peripheral pulmonary artery stenosis with or without associated complex cardiovascular abnormalities[8]. Recent data have reported an association between Wolff-Parkinson-White syndromes. Our patient has complex heart disease with hypo plastic left heart syndrome. Hepatic abnormality is a key feature of this disease. Most infants present with cholestasis jaundice. Hepatosplenomegaly is common. Hepatic paucity of intrahepatic interlobular bile ducts (85%) chronic cholestasis (96%) hypercholesterolemia. Extrahepatic biliary duct involvement and Primary hepatocellular cancer[9]. In our patient metabolic screening showed elevated Cystathianine consistent with hepatic immaturity and vitamin B6 deficiency (cystothianase deficiency). Hepatobiliray contrast study was done Imaging, hepatic blood flow is reduced. There is

uniform hepatic activity with poor clearance of the blood circulation, impression biliary atresia[10]. Vertebral defects, butterfly vertebrae, fused vertebrae, spina bifida occulta, rib anomalies have been reported. Caudal regression syndrome also known as sacrococcygeal agenesis, caudal dysplasia, is a congenital malformation characterized by varying degrees of developmental failure involving the lower lumbar, sacral, and coccygeal vertebrae, and the corresponding segments of the spinal cord Affected Patients have neurological abnormalities that range in severity from mild impairment of bladder control to total motor and sensory paralysis below the level of the defect[11]. Our patient had caudal regression dysplasia, sacral, and coccygeal vertebrae absent and no neurological defect. They can have nephropathy tubulointerstitial type[12]. Pancreatic insufficiency can contribute to nutritional deficiency and malnutrition as in our case (Figure 3). The prognosis for prolonged survival is good, but patients are likely to have pruritus, xanthomas with markedly elevated serum cholesterol levels, and neurologic complications of vitamin E deficiency if untreated. Mild mental retardation (16%)[13]. Elevations in serum bile acids often result in severe pruritus and xanthomas (hypercholesterolemia). Fat-soluble vitamin deficiencies, including coagulopathies and rickets, are frequent in these patients. Prenatal testing can determine if the fetus has inherited a Jagged 1 mutation or deletion, it can't predict the severity of the disorder, which might range from serious cardiac and liver disease to more benign manifestations. Other prenatal tests such as a fetal echocardiogram designed to look for severe heart defects may offer some further information, but they are also limited[14]. Growth failure, delayed puberty and malnutrition are common in children with Alagille syndrome. They have worse growth failure than children with other chronic liver diseases, such as biliary atresia.

Conclusion:

Alagille syndrome (Alagille-Watson syndrome) is an autosomal dominant genetic disorder that affects the liver, heart, kidney and other systems of the body. Major contributors to morbidity arise from bile duct paucity or cholestatic liver disease, underlying cardiac disease. Males and females are affected equally. Problems associated with the disorder generally become evident in infancy or childhood in our case at birth. Prevalence of this syndrome is 1; 100,000 live births. Growth failure, delayed puberty and malnutrition are common in children with Alagille syndrome. Children with Alagille syndrome have worse growth failure than children with other chronic liver diseases, such as biliary atresia.

References:

1. Hassan HAK. Balistreri WF. Alagille syndrome (arteriohepatic dysplasia). Nelson textbook of Pediatrics. International Edition 20.vol.2.2016. 1932-33. Elsevier Philadelphia USA.
2. Rani, V. U. Rao, N. S. Kumar C. J & Saritha S. Caudal regression Syndrome (sirenomelia) and its pathogenesis correlation: a case report. International Journal. 2015. 3(11): 3406
3. Jones kl. Jones MC. Campo MD. Alagille Syndrome. Smith's Recognizable Patterns of Human malformation.7th Edition.2013. 758-59.Elsevier Saunders. Philadelphia USA.
4. McDaniel Warthen DM. Sanchez-Lara PA, et al. NOTCH2 mutations cause Alagille Syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet*. 2006 Jul. 79(1):169-73
5. Emerick KM, Rand EB, Goldmuntz E, et al. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology*. 1999 Mar. 29(3):822-9.
6. Mouzaki M, Bass LM, Sokol RJ, Piccoli DA, Quammie C, Loomes KM, et al. Early life predictive markers of liver disease outcome in an International, Multicenter Cohort of children with Alagille syndrome. *Liver Int*. 2015 Jul 22.

7. Hingorani M, Nischal KK, Davies A, et al. Ocular abnormalities in Alagille syndrome. *Ophthalmology*. 1999 Feb. 106(2):330-7.
8. Kamath BM, Spinner NB, Emmerich KM, et al. Vascular anomalies in Alagille Syndrome significant cause of morbidity and mortality. *Circulation*. 2004. 110:1354-8.
9. Mouzaki M, Bass LM, Sokol RJ, Piccoli DA, Quammie C, Loomes KM, et al. Early life predictive markers of liver disease outcome in an International, Multicenter Cohort of children with Alagille syndrome. *Liver Int*. 2015 Jul 22.
10. Hoffenberg EJ, Narkewicz MR, Sondheimer JM, et al. Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. *J Pediatr*. 1995 Aug. 127(2):220-4.
11. Correa, T. K., Martins, J. G., & Verma, U. 2069007 Caudal Regression Syndrome: A Case Report and Review of Literature. Ultrasound in Medicine and Biology, 2015. 41(4): S111.
12. Kamath BM, Podkameni G, Hutchinson AL, et al. Renal anomalies in Alagille Syndrome: A disease-defining feature. *Am J Med Genet A*. 2011 Nov 21.
13. Kamath BM, Chen Z, Romero R, et al. Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. *J Pediatr*. 2015 Aug. (2):390-6.e3.
14. Quiros-Tejeira RE, Ament ME, Heyman MB, et al. Variable morbidity in Alagille Syndrome a review of 43 cases. *J Pediatr Gastroenterol Nutr*. 1999 Oct. 29(4):431-37.

Author Information: Dr. Ghulam Nabi, MD is Pediatric Consultant and Neonatologist at the Bugshan Hospital, Jeddah, Kingdom of Saudi Arabia. Dr. Omar Al-Siyud, MD is Pediatric Consultant and Neonatologist at the Bugshan Hospital, Jeddah, Kingdom of Saudi Arabia. Dr. Omar Nabi Siraj, MBBS is Head of the Patient Affairs Department, Thumbay Hospital, Ajman, United Arab Emirates.
Corresponding Author: Dr. Ghulam Nabi, MD. PO Box: 5860 Jeddah 21432. Saudi Arabia. Mobile. 00966 502310661. Email: drgnabi2@gmail.com

How to cite this article:
Nabi G, Al-Siyud O and Siraj ON. Alagille Syndrome in a Neonate. Physicians Academy. 2018. 12(4): 52-56