Alagille Syndrome – A Rare Type of Birth Defect- A Case Overview

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Abstract: Alagille syndrome (AGS) is a complex multisystem disorder that involves mainly the liver, heart, eyes, face, and skeleton. The main associated clinical features are chronic cholestasis due to a paucity of intrahepatic bile ducts, congenital heart disease primarily affecting pulmonary arteries, vertebral abnormalities, ocular embryotoxon, and peculiar facies. AGS is caused by defects in the Notch signalling pathway due to mutations in JAG1. It is inherited in an autosomal dominant pattern with a high degree of penetrance, but variable expressivity results in a wide range of clinical features. Here we report on a one and half year-old female child who presented with elevated serum alkaline phosphatase with transaminitis and coagulopathy, and was diagnosed with AGS associated with the JAG1 mutation after a comprehensive workup.

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

INTRODUCTION:

A birth defect also known as a congenital disorder, is a condition present at birth. It may result in disabilities that may be physical, intellectual or developmental. It may result from genetic or chromosomal disorders exposure to certain medications, chemicals or certain infections during pregnancy.

Alagille syndrome is a rare genetic disorder that can affect multiple organ systems of the body including the liver, heart, skeleton, eyes and kidneys. Primarily this genetic disorder with autosomal dominant trait affects the liver and the heart. Problems associated with the disorder generally become evident in infancy or early childhood. It is named after the French paediatrician Daniel Alagille, who first described the condition in 1969.

DEFINITION:

Alagille Syndrome is an inherited condition in which bile builds up in the liver because there are too few bile ducts to drain the bile. It is a Genetic disorder (JAG 1 gene). Children usually have a liver disease characterized by a progressive loss of the bile ducts within the liver over the first year of life and narrowing of the bile ducts outside the liver. This leads to a build-up of bile in the liver, causing damage to liver cells. Scarring may occur and lead to cirrhosis in about 30 to 50 percent of affected children.

SYNONYMS :

- Alagille- Watson Syndrome/ Watson –Alagille Syndrome
- Hepatic Ductular hypoplasia
- Arterio hepatic Dysplasia (AHD)
- Cardio vertebral syndrome
- Cholestasis with peripheral pulmonary stenosis
- Hepato facio neuro cardio vertebral syndrome
- Paucity of interlobular bile ducts
- Watson-Miller syndrome

INCIDENCE:

Incidence rate is one out of 70,000 babies and occurs in both sexes. However, about half the time, the mutation is new and not from a parent. The disorder is inherited in an autosomal dominant pattern, and the estimated prevalence is about 75% of people diagnosed with the syndrome in childhood live to at least age 20. Alagille syndrome usually appear shortly after birth or in early infancy. For this reason, Alagille syndrome is often diagnosed in children younger than age 1.

CAUSES:

- JAG1 gene mutation. If you have one parent with Alagille syndrome, you have a 50% chance of developing the condition.

SIGNS AND SYMPTOMS:

Symptoms of Alagille syndrome usually appear in the first two years of life which often develop during the first three months of life. 90 percent of individuals with Alagille syndrome have a reduced number of bile ducts (bile duct paucity) within the liver.

HEPATIC SYSTEM :

- Cholestasis (blockage of the flow of bile from the liver)
- Jaundice (yellowing of the skin and mucous membranes-Most common symptom)
- Acholia(Pale stools)
- Pruritis (severe itching).
- Icterus
- Hepatomegaly,splenomegaly

- Blood clotting problems (vitamin K deficiency).

CARDIOVASCULAR SYSTEM

- Heart murmur
- Pulmonary artery stenosis
- Congetital Heart Defects- TOF,ASD,VSD,PDA, Coarctation of the aorta.
- Cyanosis
- Abnormal enlargement of the right ventricle
- Wolff-Parkinson-White syndrome, a condition characterized by electrical disturbances in the heart.

MUSCULOSKELETAL SYSTEM :

- Butterfly vertebrae
- Malabsorption of vital nutrients can also lead to rickets, a condition marked by softened, weakened bones (vitamin D deficiency)
- Poor coordination and developmental delays

FACIAL ABNORMALITIES :

- Vision problems (vitamin A deficiency)
- Hypertelorism of eyes
- Pointed chin
- Broad forehead, and low-set eyes
- Malformed eyes.
- Prognathia

OTHERS:

- Growth deficiencies and failure to thrive
- Pale-colored stools
- Dark urine
- Poor weight gains and growth
- Xanthomas
- Posterior embryotoxon (thickening of the ring that normally lines the cornea in the eye).
  A physician may suspect Alagille syndrome if an individual has three of the following, five clinical findings in addition to bile duct paucity: symptoms of liver disease or cholestasis, heart defect, skeletal abnormality, eye (ophthalmologic) abnormality, and/or distinctive facial features.

DIAGNOSTIC FINDINGS:

- History collection and Physical Examination
- Liver biopsy
- LFT
- Eye examination
- Spine X-ray
- Abdominal USG
- ECG
- Kidney function tests
- Genetic testing
- Urine analysis

MANAGEMENT:

Doctors may refer people with Alagille syndrome to hepatologists and also refer patients to specialists who focus on other parts of the body such as heart, blood vessels or kidneys. Doctors also recommend changes in diet and nutrition.

- Ursodiol – to improve the flow of bile from the liver to small intestine
- Cholestyramine ,rifampsin, naltrexone ,antihistamines
- Partial external biliary diversion (PEBD).
- Liver transplant.
- Doctors may also recommend using skin moisturizers, keeping baths and showers short, and trimming fingernails to prevent skin damage from scratching.

COMPLICATIONS:

Half of the children, the flow of bile out of the liver improves by age 5. In the other half, the buildup of bile in the liver gets worse and leads to complications.

- Cirrhosis of Liver
- Portal Hypertension
- Liver Failure
- Increases the risk for liver cancer.
- Osteoporosis

- Delayed Puberty

PROGNOSIS

Alagille syndrome with mild symptoms and can lead normal lives with normal life expectancy. Eventhough severe or life-threatening complications such as liver failure, serious heart defects, and bleeding or stroke may arise.

CASE REPORT -

The present report examines the journey of the parents of a child with Alagille Syndrome, through identification and management by discussion of health history, investigations and current management of the clinical problems. The report is intended to raise awareness among health care providers regarding the condition to be competent to deliver comprehensive nursing care and support for the child and parents.

CASE PRESENTATION.

The mother of one and half year-old female child with Alagille Syndrome was interviewed to obtain detailed history during clinical posting. The child was admitted to the tertiary care hospital with complaints of fever and abscess of right thigh for 5 days following immunization. The child had similar episode of abscess formation at left thigh following the immunization at six weeks. The index child was diagnosed with Alagille Syndrome at the age of 4 months and is on regular treatment and follow up.

PAST HISTORY

The index child under study had history of neonatal jaundice on Post Natal Day 3 and received phototherapy for hyperbilirubinemia. The child had yellowish discolouration of eyes and pale coloured stools. It was not subsiding with phototherapy and the symptoms persisted and was found to have direct hyperbilirubinemia with transaminitis and coagulopathy. The case was referred to tertiary care centres for detailed diagnostic measures.

BIRTH HISTORY.

The child under the study is the first child of a non-consanguineous marriage and had no siblings. Mother had normal pregnancy and attended all antenatal clinics regularly. The child was born by LSCS due to non-reactive NST after 38 weeks of gestation. Birth weight was 2.4kg. Normal APGAR score and no history of NICU admission

FAMILY HISTORY

There is no history of any congenital, chromosomal anomalies, jaundice or liver diseases in the family. Genetic testing was conducted for both parents and it was found to be negative.

GROWTH AND DEVELOPMENT

The child's growth and development were reported to be delayed. As per the reports, there was mild delay in achieving all milestones compared to normal.

INVESTIGATIONS.

Lab investigations of the child revealed elevated bilirubin levels and elevated GGT, coagulopathy and anaemia. Bilirubin-18.5mg/dl, PT-12.6sec, INR-0.92,SGPT-22O/SGOT-156,Alkaline phosphatase-561u/L.Hemoglobin-8.3gm/dl. Genetic study was done for the child at 4 months and was suggestive of Alagille Syndrome-JAG1 gene affected. Liver biopsy result showed paucity of intra hepatic bile duct which was consistent with Alagille Syndrome. Spine X- ray showed butterfly vertebrae, Echo test was done for cardiac evaluation and revealed Pulmonary Stenosis. Ophthalmic examination was also carried and revealed negative result for Posterior embryotoxon.

CURRENT HEALTH STATUS

Child is immunized for age, feeding well, no fever spikes and has hematoma and cellulitis at right thighs following immunization. Child has yellowish discolouration of eyes, pruritis, dysmorphic facies and butterfly vertebrae.

MANAGEMENT

Child is managed with symptomatic and supportive therapy. Child is on regular medications with calcium supplements, iron supplements, hepatoprotective drugs - Ursodiol sachet, Vitamin A,E , K & D supplements and Rifampicin.

DISCUSSION

As discussed above AGS has been rarely reported in the Indian Journals so far. The index child is a striking case of Hepatofacioneurocardiovertebral syndrome because the child shows classic features of liver dysfunction, dysmorphic facies, butterfly vertebrae and pulmonary stenosis along with mild delay in growth and development.

The child was diagnosed AGS at 4 months of age following detailed evaluation in view of persistent jaundice since 3rd of life. The Diagnosis is made on the basis of thorough history, clinical examination and laboratory investigations. Biopsy of liver shows characteristic features of Alagille syndrome which revealed bile duct paucity. Other laboratory investigations were also done for the child and it showed hyperbilirubenemia with transaminitis and coagulopathies. Cardiac evaluation was also done for the child and revealed mild valvular pulmonary stenosis. Diagnosis was confirmed with molecular genetic testing which exposed the gene JAG1 for the child. But genetic screening for both parents were carried out and found to be negative for JAG 1 gene.

Management of Alagille syndrome is mainly focused on the main symptoms which are mostly due to liver involvement like supplementation of fat soluble vitamins, ursodeoxcholic acid for cholestasis and antihistamines for pruritus. Liver transplantation may be required depending the severity of symptoms. Now the child is getting only the supportive treatments like Vitamin supplements and Rifampicin. The parents have been discussed regarding liver transplantation even though the prognosis is poor.

CONCLUSION:

Alagille syndrome is a rare autosomal dominant disorder affecting multiple organs involving liver, heart, eyes, skeleton, kidney etc. In the case described the child has presented with typical features of Alagille syndrome and fulfils the standard criteria of diagnosis with all the necessary investigations pointing in the direction of Alagille syndrome.

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