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Case Report

Alagille Syndrome in an Infant: A Rare Case Report

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Abstract

Alagille syndrome is a rare autosomal dominant disorder that affects multiple organs and systems including liver, heart, bones, vascular system, and kidneys and also causes facial abnormalities. Majority of the cases involve mutation in one copy of the JAG1 gene while rarely some patients may have mutations in NOTCH2 gene. There is substantial variation in the extent of symptomatology with which patients may present. However, mostly patients present in infancy with symptoms concerning liver like jaundice, pruritus due to cholestasis, vitamin A, D, E and K deficiencies. Additional symptoms include specific triangular facies, back pain due vertebras involvement and kidney failure. Diagnosis is generally made up on the basis of clinical manifestations, genetic studies and liver biopsy. Additional laboratory tests concerning the affecting organs like liver function tests etc. may further aid up in the diagnosis. There is no specific treatment and may require symptomatic treatment with multiple disciplinary approach. A 7 months old boy is presented as a case of Alagille syndrome with its typical features.

Introduction

Alagille syndrome (AGS), first described by David Alagille in 1975, is a rare autosomal dominant genetic disease that affects various organs and systems, including the liver, heart, eyes, skeleton, and face. Paucity of interlobular bile ducts, characteristic facies (Table 1), posterior embryotoxon (an accumulation of pigmentary material on the inner aspects of the cornea near its junction with the iris, observed by slit-lamp examination), butterfly-like vertebral-arch defects, and peripheral pulmonary stenosis are some of the characteristic features of this disorder (Table 2). Skin symptoms, early-onset chronic liver disease, growth retardation renal impairment, mental retardation and a high-pitched, soft voice are also seen in rare cases of Alagille syndrome, the specific symptoms and severity of Alagille syndrome can vary greatly from one person to another, even within the same family. Some individuals may present with milder symptoms while others may have more serious symptoms [1]. ALGS is a very rare condition and is predicted to affect 1 in 30,000–50,000 people in the general population, regardless of gender [2].

Forehead	Broad, Prominent
Mandible	Prominent, triangular facial look due to pointed and small chin
Eyes	Hypertelorism (deeply set and widely positioned), upward slanting of the palpebral fissure, and anterior chamber abnormalities with posterior embryotoxin
Nose	Straight nose with broad nasal tip, depressed nasal bridge
Ears	Large and prominent

Table 1: Characteristic facial features in Patients with Alagille Syndrome.

Liver	Biliary duct hypoplasia
Vascular	Pulmonary stenosis
Facial	Distinctive triangular facies
Ocular	Posterior embryotoxon
Vertebra	Anterior fusion defects (butterfly vertebra)

Table 2: Characteristic features of Alagille syndrome.

Alagille syndrome is caused by mutations in either the JAG1 (20p12) or NOTCH2 genes. JAG1 has up to 98 percent heterozygous pathogenic variant mutations, while NOTCH2 has just 2% [3]. In about 7% of people with Alagille syndrome, JAG1 gene deletion is the cause of the disease. According to a study, heterozygous loss of function mutations in JAG1 was responsible for as much as 94 percent of Alagille syndrome patients, with a minor percentage of Alagille syndrome patients having heterozygous loss of function mutations in NOTCH2, which encodes a JAG1 receptor. JAG1 is a ligand that is vital for embryonic development and is encoded by the notch gene–signaling cascade. In murine models, Notch signaling has been shown to regulate the development of three dimensional intrahepatic biliary architecture [4].

Over the years the diagnosis of Alagille syndrome has changed and nowadays it is diagnosed clinically and by genetic studies. Clinical criteria is satisfied by having three out of five clinical characteristics: Hepatocellular cholestasis, ocular diseases (posterior embryotoxon), typical facial features, cardiovascular involvement (pulmonary artery stenosis), and skeletal malformation (butterfly vertebrae). Almost 96 percent of patients are diagnosed clinically; a molecular diagnosis is confirmed by revealing the existence of a JAG1 or NOTCH2 gene mutation. Although bile duct paucity seen on liver biopsy is considered a key characteristic of Alagille syndrome, this finding may not always be present in infants with this disorder [5].

Case Presentation

As a follow-up case, a 7-month-old boy was admitted to the pediatric unit at Hayatabad Medical Complex in Peshawar with chronic persistent jaundice, abdominal distension, and failure to thrive since one month of life. He was born to non-consanguineous parents with a normal birth history. At the age of four months, he began smiling and holding his neck but unable to roll over or set with support (developmental delay). The child has received all vaccines to date. There is no history of this problem in his family. active, alert, pale-looking, mildly icterus, stunted child with a height of 60 cm (normal range 65.1-73.25cm) and a low weight for age of 4.8 kg on general examination (normal range 6.7-10.2 kg).Facial examination showed a broad forehead, prominent ears, a depressed nasal bridge with a bulbous tip nose, a triangular face with a pointed chin, a deep set and up slanting palpebral fissure with hypertelorism (Figure *1*)

Figure 1: Alagille syndrome facial features.

On abdominal examination, there was no palpable hepatosplenomegaly. At 6 cm and 4 cm below the subcostal margin, respectively, the liver and spleen were palpable. There were no bruises, rashes, lymphadenopathy, or xanthomas. The rest of the systemic examinations were normal. All labs, radiological investigations, and liver biopsy reports are given in Table 3 below;

	Investigation	Report	Normal range
Labs	WBC	8.42×10^3/ µL	4-11 × 10^3/ µL
	RBC	**3.25×10^6/ µL**	4-6 × 10^6/ µL
	HB	**7.72 g/dl**	11.5-17.5 g/dl
	PLT	232×10^3/ µL	150-450 × 10^3/ µL
	Na^+	**130 mmol/L**	135-150 mmol/L
	K^+	3.55 mmol/L	3.5-5.1 mmol/L
	Cl^-	**88 mmol/L**	96-112 mmol/L
	Blood urea	28 mg/dl	18-45 mg/dl
	Creatinine	0.7 mg/dl	0.6-1.2 mg/dl
	Bilirubin indirect	**1.8 mg/dl**	0.1-0.7 mg/dl
	Bilirubin direct	**6.4 mg/dl**	0.1-0.3 mg/dl
	Bilirubin total	**8.2 mg/dl**	0.1-1.0 mg/dl
	ALT	**251 U/L**	10-50 U/L
	AST	**125 U/L**	8-33 U/L
	ALP	**315 U/L**	40-129 U/L
	Peripheral smear	Microcytic hypochromic anemia with target cells and anisopoikilocytosis	
	MP	No malarial parasite seen	
	Urine R/E	Normal urine routine examination	
Radiological	Ultrasound abdomen	Hepatomegaly (16cm) with normal shape and parenchymal echogenicity; Splenomegaly (9cm).	
	X-ray abdomen	Butterfly shape vertebrae [Figure 2]	
Liver biopsy and histopathology	Showed paucity of bile ducts, hepatocytes were showing focal rossetting and giant cell changes; Extensive intracytoplasmic cholestasis, lymphocytes infiltration and fibrosis [Figure 3,4]		
Note: bold values shows deranged labs; WBC: White Blood Cell, RBC: Red Blood Cell, HB: hemoglobin, PLT: Platelets, Na^+: Sodium, K^+: Potassium, Cl^-: chloride, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, MP: Malarial Parasite, Urine R/E: Urine routine examination			

Table 3: All investigations of the patient along with normal values.

Characteristic X-ray findings are given in the figure below [Figure 2]

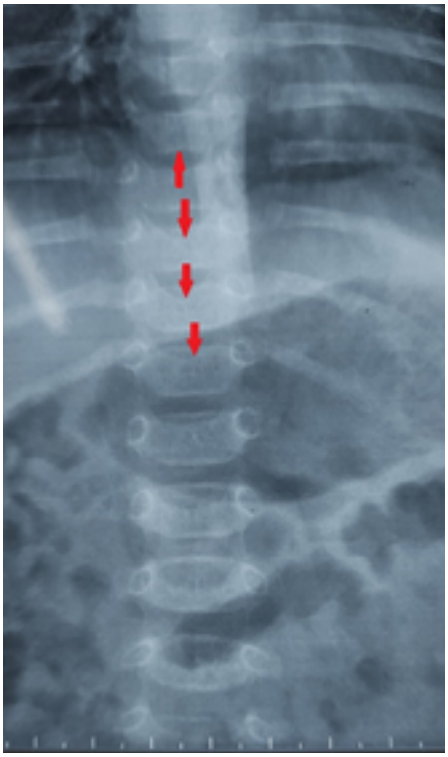

Figure 2: X ray showed butterfly shaped vertebrae (red arrows).

Liver biopsy; Approximately 25 portal areas were identified out which 04 portal areas shows well-formed bile ducts while rest shows absent/paucity bile ducts, hepatocytes focal giant cell changes and intracytplasmic cholestasis, lymphocytes infiltration and fibrosis (Figures 3 and 4).

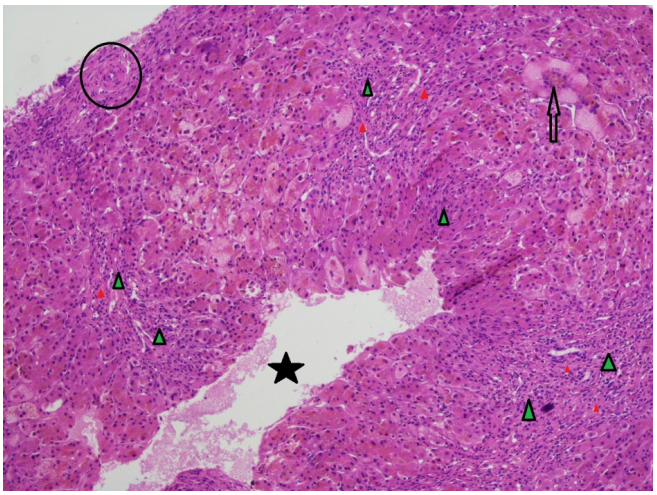

Figure 3: Histopathology section of liver biopsy. Portal triad region shows portal venule (black star), hepatic arteriole (black circle), single bile duct (black arrow), lymphocytic infiltration (green arrow heads), and fibrosis (red arrow head).

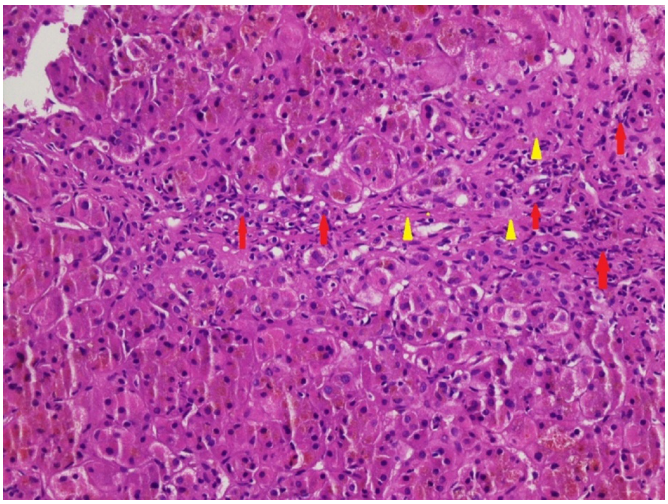

Figure 4: Histopathology section of liver biopsy shows lymphocytes infiltration (red arrows), and fibrosis (yellow arrow-head).

All these findings along with liver biopsy report confirm Alagille syndrome. This patient was started on home treatment of Vitamin A(dose 10000-15000 IU/day), Vitamin E(dose 50-400 IU /day),Vitamin D(dose 5000-8000 IU/day), Vitamin K (dose 2.5-5mg on alternate day), Ursodeoxycholic acid(dose 10-15mg/kg/day). Patient was counseled about the condition and dietary plan for this child.

Discussion

Alagille syndrome is an infrequent autosomal dominant syndrome involving a variety of organs encompassing liver, heart, eyes, nose, ears, kidneys and skeleton [6]. It was first of all described by David Alagille in 1975. It is caused by mutations in either the JAG1 or NOTCH2 genes. Majority of cases are due to JAG1 gene mutations with NOTCH2 only affecting up to 7% of the cases. JAG 1 is ligand that plays an important role in the early stages of embryonic development and is encoded by NOTCH gene. NOTCH gene is crucial for the development of intrahepatic biliary system [7].

Clinical manifestations of Alagille syndrome may vary not only according to a wide range of symptomatology but also according to age. Most commonly affected organ is liver in up to 90% of patients. Manifestations of liver involvement are due to decreased number of bile ducts and bile ducts malformation that lead to jaundice, cholestasis, pruritus, pale stools, dark color urine, poor growth and fat soluble vitamins deficiencies. These clinical features appear in the first three to four months of life. Later complications like cirrhosis and portal hypertension may develop. Many patients have also cardiac abnormalities and may cause murmurs which are mostly due to pulmonary stenosis

and structural heart defects atrial septal defects, ventricular septal defects, patent ductus arteriosus etc. Characteristic facial features include triangular facies with broad forehead and pointed chin, hypertelorsim, upward slanted palpebral fissures, anterior chamber disease with posterior embryotoxin, depressed nasal bridge, large and prominent ears. Skeleton abnormalities mainly include butterfly shaped vertebra due to anterior fusion defects. Renal abnormalities are mostly found in patients associated with NOTCH2 mutations and include small kidneys and impaired renal function. Vascular abnormalities are also present and may affect vessels brain, liver, heart, lungs and kidneys [8].

Alagille syndrome is diagnosed on the basis of thorough history, clinical examination and laboratory investigations. Biopsy of liver shows characteristic features of Alagille syndrome which reveals bile duct paucity. Other laboratory investigations are also done for the affected organs which help in the diagnosis and mainly include liver function tests for liver involvement, fat soluble vitamin deficiencies, ophthalmological examination, ultrasound of heart and hepatobiliary system and some radiological investigations like x-ray of spine for vertebral defects. Diagnosis can be confirmed with molecular genetic testing which exposes the involved genes JAG1 and NOTCH 3 but in some people genetic testing may not reveal these mutations [9].

Nowadays diagnosis of Alagille syndrome is made on the basis of standard protocol in which three out of the five typical clinical characteristics must be present. Features included are hepatic cholestasis, ocular diseases (specifically posterior embryotoxin), typical facial features, cardiovascular abnormalities (specifically pulmonary stenosis) and skeletal malformation (specifically butterfly shaped vertebra [10].

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[6] may be required depending the severity of symptoms. For other systems involvement like eyes, heart, and kidneys multidisciplinary approach with ophthalmologist, cardiologist and nephrologist should be done [11].

In this case we have discussed the patient who fulfills the standard criteria for the diagnosis of Alagille syndrome. Patient has presented with characteristic features of Alagille syndrome with liver involvement which mainly includes jaundice, abdominal distention and failure to thrive. Patient has characteristic triangular facies along flat nasal bridge and hypertelorism. Laboratory investigations also support the diagnosis showing features of liver involvement with raised bilirubin and abnormal liver function tests like raised alkaline phosphatase showing cholestasis. X-ray of spine shows butterfly defect. Finally the liver biopsy which reveals the cornerstone features of Alagille syndrome of bile duct paucity.

Conclusions

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

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All co-authors listed above have contributed equally and should be considered as first co-authors.

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