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CASE REPORT

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Alagille syndrome and liver: an adult case report

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Abstract

Background Alagille syndrome is a rare autosomal-dominant disorder, representing 10 to 15% of the causes of neonatal cholestasis with no gender predominance. The diagnosis is based on the association of liver, heart, eye, skeleton abnormalities, and characteristic facial appearance.

Case presentation An 18-year-old male patient, with a family history of benign recurrent intrahepatic cholestasis in a brother, was diagnosed at birth with bile duct paucity. He consulted in adulthood for cholestatic jaundice and pruritus. Physical exam found cutaneous jaundice, particular face, skeletal abnormality of fingers, posterior embryotoxon, and splenomegaly. An echocardiogram found cardiovascular abnormalities. The diagnosis of Alagille syndrome was made in front of five major criteria. A liver biopsy revealed a cirrhosis liver. Upper gastrointestinal endoscopy revealed grade II esophageal varices of portal hypertension. Laboratory tests revealed bicytopenia related to hypersplenism, hypoferritinemia, cytolysis with cholestasis, high bilirubin levels, low prothrombin time, hypoalbuminemia, decreased factor V activity, and hypocholesterolemia. The patient had vitamin K supplementation and was put on ursodeoxycholic acid, propranolol for the liver disease, a high protein hypercaloric diet for malnutrition, vitamin D supplementation and bisphosphonate for the osteoporosis, therapeutic abstention with monitoring for the asymptomatic cardiac disease. After a year of treatment, the patient had an overall health status improvement. Abdominal ultrasound found liver nodules. A biliary MRI showed a multinodular liver. The complement by CT hepatic angiography did not show any nodules while the MRI angiography revealed multiple dysplastic nodules. A liver biopsy was performed and found regenerative nodules.

Conclusion The treatment of Alagille syndrome is based on managing the cholestasis and its complications, especially pruritus because it can have a significant impact on quality of life. Due to the complexity of presentation and multi-organ involvement, management of cases with Alagille syndrome should be done by a multidisciplinary team. Liver disease is responsible for morbidity while cardiac disease is a mortality risk factor in this population.

Keywords Liver, Neonatal cholestasis, Bile duct paucity, Characteristic abnormalities, JAG1 and NOTCH2 mutation, Alagille syndrome, Case report

Background

Alagille syndrome is an autosomal-dominant disorder. It is characterized by variable combinations of hepatic anomalies, characteristic facial features, and ocular, skeletal, cardiovascular, and renal abnormalities [1]. This syndrome represents 10 to 15% of the causes of neonatal cholestasis (1 case out of 100,000 births) with no gender predominance [2]. Molecular diagnosis has increased the number of cases detected and the true incidence is probably close to 1 in 30,000 [3]. We report a case of a bile

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duct paucity diagnosed at birth who consulted in adulthood in the setting of Alagille syndrome.

Case presentation

An 18-year-old male patient, 3rd of a sibling group of five, he had a family history of a brother with Benign Recurrent Intrahepatic Cholestasis (ABCB 11 mutation), no parental consanguinity, and no alcohol or drug consumption. The disease history goes back to day 8 of his birth with the appearance of a cholestatic jaundice associated with a hemorrhagic syndrome. The liver biopsy found a bile duct paucity. The patient received a vitamin supplementation and was put on ursodeoxycholic acid by his pediatrician for a few years but he stopped consulting because of a lack of financial means. He consulted in adulthood for cholestatic jaundice and pruritus, with ascites. He was no longer part of a pediatric ward; his referring physician put him on a low-sodium diet and spironolactone for ascites and referred the patient to us. The physical exam found a sad and shy, patient, hemodynamically and respiratory stable, apyretic, BMI = 15.7 kg/m^2 (weight = 33 kg, height = 1.45 m), a delay in weight and height, 4 school years delay. The patient had cutaneous jaundice, a triangular face with a prominent forehead, a small pointed chin, deep-set eyes, and straight nose with a bulbous tip (Fig. 1), a square shape of the fingertips, profuse xanthomas, skin scraping lesions, thoraco-abdominal collateral venous circulation and splenomegaly. Eye examination revealed a posterior embryotoxon (Fig. 2). Echocardiogram found a right heart dilatation, dilated atrial mass, atrial septum defect measuring 3 mm, left to right shunts, pulmonary hypertension with pulmonary artery systolic pressure at 57 mmHg, normal systolic function. Spine X-ray did not show any butterfly vertebrae. Research for JAG1 and NOTCH2 mutation is not available at the hospital.

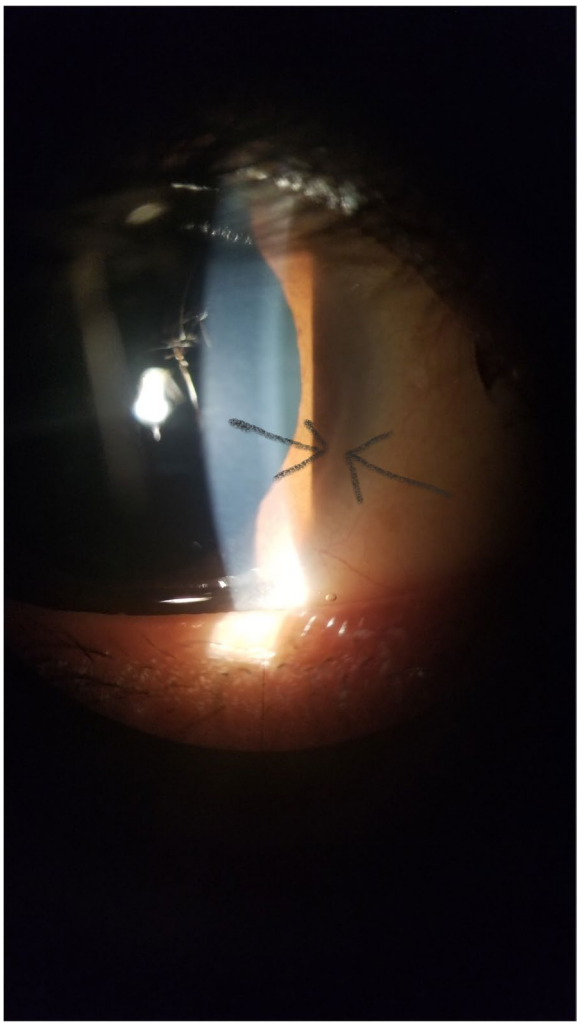

Fig. 2 Eye examination with slit lamp image revealing a posterior embryotoxic

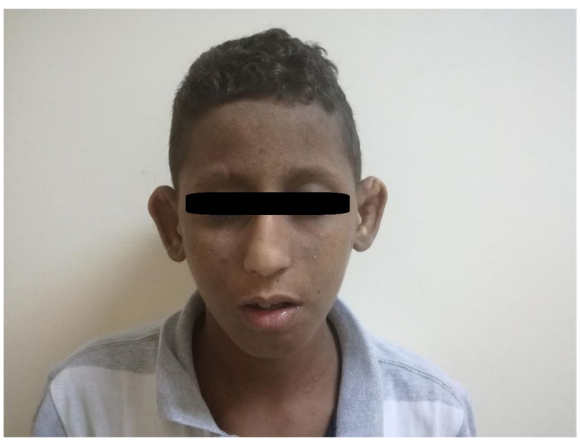

Fig. 1 Characteristic facies image of Alagille syndrome showing a triangular face with a prominent forehead, a small pointed chin, deep-set eyes, and a straight nose with a bulbous tip

Therefore, the diagnosis of Alagille syndrome was made in front of five major criteria: bile duct paucity with chronic cholestasis, dysmorphic facies, skeletal abnormality of fingers, cardiovascular malformation, and posterior embryotoxon.

We performed a workup to look for minor criteria:

On the endocrine level, the physical exam found growth retardation (− 3 standard derivations) and good development of secondary sexual characters. Thyroid hormone levels and thyroid ultrasound were normal. Blood sugar and glycated hemoglobin were normal. The pancreas was normal on ultrasound.

Renal ultrasound combined with Doppler showed normal kidneys and no renal artery stenosis. Kidney function tests were normal.

Bone densitometry revealed osteoporosis of the lumbar spine with *Z*-score of − 4.

Laboratory tests revealed bicytopenia related to hypersplenism, hypoferritinemia, cytolysis with cholestasis, high Bilirubin Levels, low prothrombin time, hypoalbuminemia, decreased factor V activity, hypocholesterolemia (Table 1). In front of the chronic cytolysis; abdominal ultrasound ruled out a biliary lithiasis or bile duct dilatation. HCV tests found positive HCV antibody and negative viral RNA. HBV serology found negative Hbs Ag, negative anti-Hbc, and positive anti-Hbs (Immune due to hepatitis B vaccination). HIV serology was negative. EBV serology showed negative Ig M and positive Ig G (Immune due to previous contact with EBV). CMV serology showed negative Ig M and positive Ig G (Immune due to previous contact with CMV). Autoimmune hepatitis test revealed negative antinuclear antibody, negative anti-smooth muscle antibody, negative anti-SLA, negative anti-LKM1, and negative ant-LC1. Primary biliary cirrhosis test revealed negative anti-mitochondrial antibody.

On the hepatic level, we performed an abdominal ultrasound that showed a normal size liver, with irregular contours and no focal images, portal vein permeable and dilated to 17 mm, splenomegaly at 18 cm, and no ascites (patient on salt restriction and diuretic therapy). Liver biopsy showed collagen deposition with architectural distortion, vascularized fibrotic septa, mononuclear inflammatory infiltrate, and marked cholestasis. Upper gastrointestinal endoscopy revealed grade II esophageal varices (Fig. 3).

In conclusion, the patient has cirrhosis associated with portal hypertension. We respected his hemoglobin level that was at 8 g/dL according to the Baveno consensus. He had vitamin K supplementation 10 mg/day for 3 days for vitamin K deficiency and put on ursodeoxycholic acid 10 mg/kg/day for the cholestasis, hydroxyzine 2 mg/kg/day for the pruritus, propranolol 20 mg/day for primary prophylaxis against variceal hemorrhage, vitamin D 100,000 IU/2 weeks with bisphosphonate 70 mg/day for osteoporosis, high protein hypercaloric diet for malnutrition, avoidance of combat and contact sports because of osteoporosis and vitamin K deficiency. Given that the patient was asymptomatic for cardiac disease, the cardiologist advocated therapeutic abstention with monitoring.

After a year of treatment, the patient had an overall health status improvement; disappearance of jaundice and pruritus, he regained joy and social integration, with weight and height gain, and improvement of the laboratory tests (Table 2). As part of the semiannual screening protocol for hepatocellular carcinoma, abdominal ultrasound found liver nodules (Fig. 4). Biliary MRI showed a multinodular liver that may be compatible with regenerative nodules (Fig. 5), but an injection of contrast medium was necessary for characterization. The

Table 1 Blood test results of our patient

Hemoglobin (g/dL)	7.9
MCV (fl)	82
MCHC (%)	30
Leukocytes (/mm^3)	2510
Neutrophil (/mm^3)	1000
Lymphocyte (/mm^3)	1120
Platelets (/mm^3)	188,000
Ferritin (ng/mL)	10
C-reactive protein (mg/L)	4
Aspartate aminotransferase (UI/L)	116
Alanine aminotransferase (UI/L)	57
Alkaline phosphatase (UI/L)	271
Gamma-glutamyl transferase (UI/L)	20
Total bilirubin (mg/L)	85
Conjugated bilirubin (mg/L)	63
Albumin (g/L)	22
Prothrombin time (%)	43
Factor V (%)	41
Total cholesterol (g/L)	0.67
HDL (g/L)	0.05
LDL (g/L)	0.47
Triglyceride (g/L)	0.76
TSH (µUI/mL)	3.15
T4 (ng/dL)	1.03
T3 (pg/mL)	2.8
Total protein (g/L)	64
Phosphorus (mg/L)	28
Corrected Calcium (mg/L)	96
Vitamin D (ng/mL)	5
Vitamin B9 (ng/mL)	7.4
Vitamin B12 (g/mL)	1073
Vitamin A	NA
Vitamin E	NA
Urea (g/L)	0.19
Creatinine (mg/L)	4
24-h urine protein (g/24h)	0.06
Fasting blood Sugar (g/L)	0.75
Glycated Hemoglobin (%)	5
Na+ (mEq/L)	136
K+ (mEq/L)	4.2
Cl- (mEq/L)	107
HCO3 (mEq/L)	22
International normalized ratio	1.57

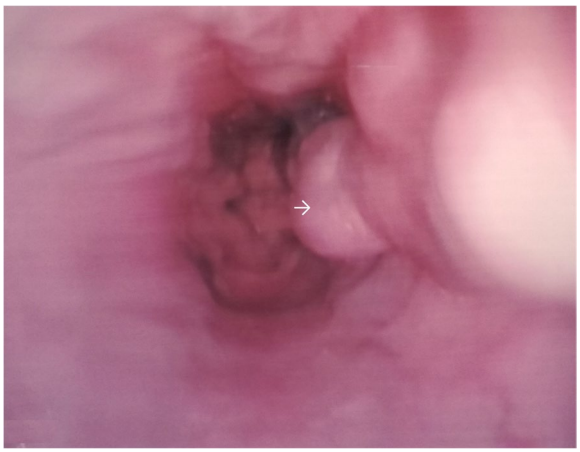

Fig. 3 Upper gastrointestinal endoscopy image revealing grade II esophageal varices

complement by CT hepatic angiography did not show any nodules (Fig. 6) while the MRI angiography (Fig. 7) revealed multiple dysplastic nodules. Because of the diagnostic doubt, we performed a liver biopsy of a nodule that revealed it was a regenerative nodule.

We continued with the same therapeutic and monitoring protocol, and the patient is on the waiting list for a liver transplant for his Child class A5 and MELD 8 cirrhosis.

Discussion

The association of cholestasis with pulmonary artery hypoplasia or stenosis, minor skeletal features, and unusual facial appearance was initially described by Alagille et al. in 1969 and by Watson and Miller in 1973 [4]. Alagille syndrome is an autosomal dominant multisystem disorder with variable phenotypic penetrance, caused by heterozygous mutations in JAG1 (20p12) or rarely NOTCH2 (1p13), encoding for the components of the Notch signaling pathway, a highly conserved pathway that is fundamental to the transcription of genes for cell fate and differentiation of multiple organ systems [3]. In patients with a suspected diagnosis of Alagille syndrome, initial evaluation should include [5]:

- Liver function tests, including g-glutamyl transferase, serum cholesterol and triglycerides, bile acids, complete blood cell count, coagulation studies, and liver ultrasound. A liver biopsy may be done depending on the clinical scenario.
- Cardiology evaluation, including echocardiogram
- Renal ultrasound and renal function tests
- Anteroposterior spine radiograph
- Ophthalmic evaluation

Table 2 Evolution of the blood test results of our patient under treatment

	Start	4 months	12 months
Hemoglobin (g/dL)	7.9	8	13.8
MCV (fl)	82	68	83
MCHC (%)	30	30	34
Leukocytes (/mm^3)	2510	3060	2290
Neutrophil (/mm^3)	1000	1950	970
Lymphocyte (/mm^3)	1120	540	1060
Platelets (/mm^3)	188,000	80,000	134,000
Ferritin (ng/mL)	10	90	37
C-reactive protein (mg/L)	4	11	2
Aspartate aminotransferase (UI/L)	116	51	24
Alanine aminotransferase (UI/L)	57	49	14
Alkaline phosphatase (UI/L)	271	377	287
Gamma-glutamyl transferase (UI/L)	20	16	20
Total bilirubin (mg/L)	85	13	3
Conjugated bilirubin (mg/L)	63	7	2
Albumin (g/L)	22	34	44
Prothrombin time (%)	43	95	76
Factor V (%)	41	–	56
Total cholesterol (g/L)	0.67	0.66	0.93
HDL (g/L)	0.05	0.24	0.32
LDL (g/L)	0.47	0.31	0.52
Triglyceride (g/L)	0.76	0.53	0.47
TSH (µUI/mL)	3.15	–	1.61
T4 (ng/dL)	1.03	–	0.9
T3 (pg/mL)	2.8	–	3.15
Total protein (g/L)	64	60	76
Phosphorus (mg/L)	28	48	47
Corrected calcium (mg/L)	96	101	95
Vitamin D (ng/mL)	5	–	33
Vitamin B9 (ng/mL)	7.4	8.6	4.9
Vitamin B12 (g/mL)	1073	676	–
Vitamin A	NA	NA	NA
Vitamin E	NA	NA	NA
Urea (g/L)	0.19	0. 13	0.22
Creatinine (mg/L)	4	3.7	5.5
24-h urine protein (g/24h)	0.06	–	0.05
Fasting blood sugar (g/L)	0.75	0.78	0.9
Glycated hemoglobin (%)	5	–	4.7
Na+ (mEq/L)	136	138	138
K+ (mEq/L)	4.2	3.6	4.9
Cl- (mEq/L)	107	107	103
HCO3 (mEq/L)	22	25	24
Alpha-fetoprotein (ng/mL)	0.89	0.56	0.50
International normalized ratio	1.57	1.03	1.11

- Nutritional assessment, including fat-soluble vitamins
- Genetic testing (JAG1 and NOTCH2 mutations)

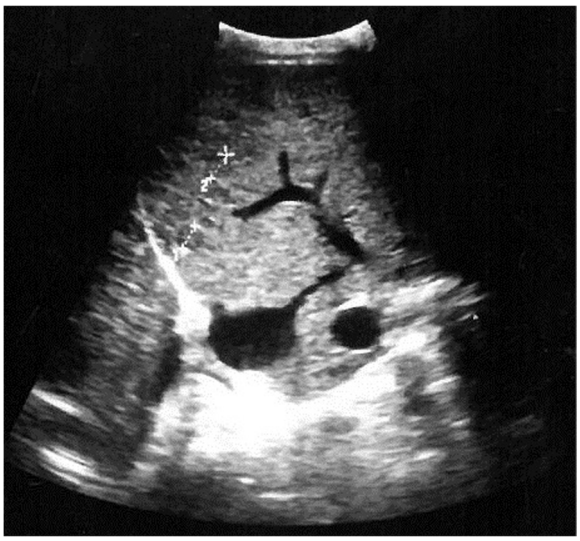

Fig. 4 Abdominal ultrasound image revealing hypoechoic liver nodules

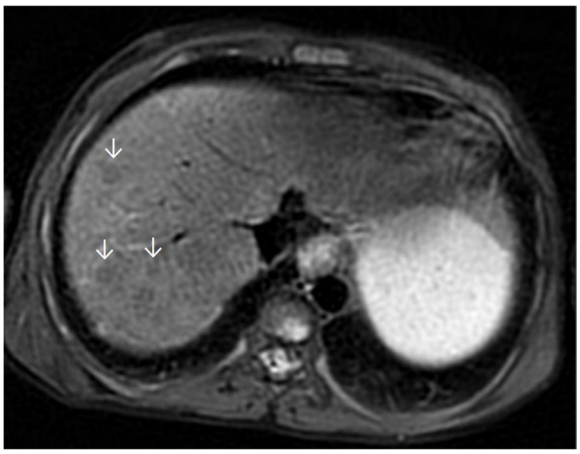

Fig. 5 Biliary MRI image showing multinodular liver that may be compatible with regenerative nodules

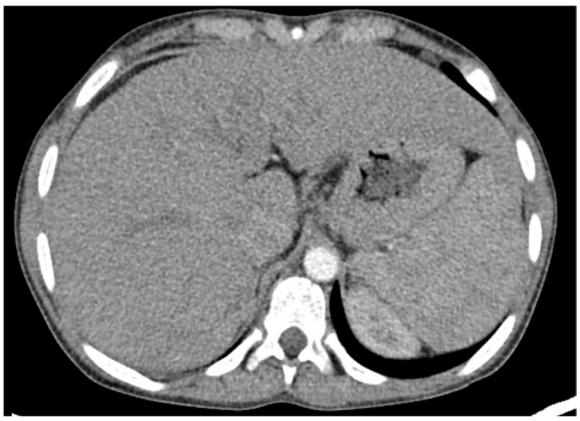

Fig. 6 CT hepatic angiography image not showing any nodules

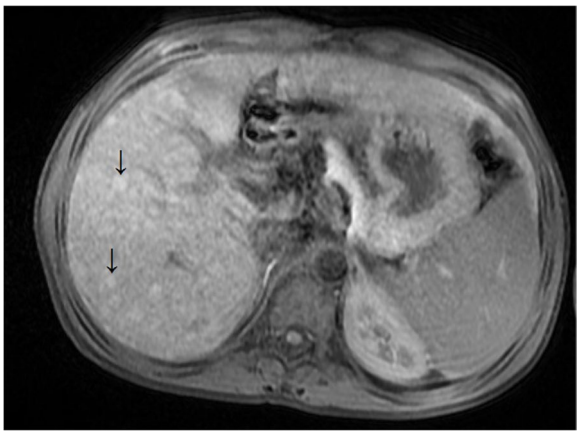

Fig. 7 MRI angiography image showing heterogeneous liver with several fibrous trabeculae associated with nodules, some of which are high signal intensity on T1, not enhanced after injection of contrast medium corresponding to dysplastic nodules

Alagille syndrome is characterized by the association of five major criteria:

Chronic cholestasis

Alagille syndrome is defined histologically as a significant decrease in the ratio of portal areas [2]. Jaundice is present in the majority of symptomatic patients in the neonatal period [4]. Cholestasis is manifest by xanthomas that can appear by the age of 10 months and can form on the extensor surfaces of the fingers, palmar creases, nape, popliteal fossae and inguinal areas, elbows, knees, helixes, and gluteal areas, causing disabling pruritus. Xanthomas tend to disappear together with a decrease in serum cholesterol levels after the age of 10 or shortly after liver transplantation [2]. Laboratory findings most commonly include raised serum bile acids, conjugated bilirubin, alkaline phosphatase, cholesterol, and gamma-glutamyl transpeptidase, indicative of a defect in biliary excretion. Less frequently, raised serum aminotransferases and triglycerides may be present. Hypercholesterolemia and hypertriglyceridemia may be profound in severe cholestasis [4]. Bile duct paucity is the most consistent histopathology feature of Alagille syndrome (60% of liver biopsies done prior to 6 months of age and 95% of those done after 6 months of age). The normal bile duct to portal space ratio ranges from 0.9 to 1.8. Alagille based his original definition of bile duct paucity on a bile duct to portal tract ratio of less than 0.5. Ductular proliferation and giant cell hepatitis can also be seen in infancy and have led to misdiagnosis of biliary atresia [5].

Characteristic facies

Patients with Alagille syndrome have a triangular face, that includes a prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin, and saddle or straight nose with bulbous tip [4].

Cardiovascular abnormalities

Stenosis/hypoplasia of the branch pulmonary arteries was the most common and found in 76% of patients, followed by tetralogy of Fallot. Other anomalies were documented including coarctation of the aorta, sinus of Valsalva aneurysm, ventricular septal defect, pulmonary vein stenosis, and right aortic arch [5]. Cardiac lesion determines prognosis in Alagille syndrome. Patients with cardiac abnormalities have an approximate 40% rate of survival to the age of twenty compared to 80% in those without cardiac abnormalities [6].

Ophthalmologic abnormalities

The most common ocular abnormalities in patients with AS were posterior embryotoxon (78% of patients) followed by Axenfeld anomaly. Other anomalies were reported including retinitis pigmentosa, severe keratoconus, hypoplasia of the optic discs, Reiger anomaly, and optic disc drusen [6].

Skeletal abnormalities

Butterfly vertebrae are present in 33 to 66% of patients. Other abnormalities include a square shape to the proximal finger with tapering of the distal phalanges and extradigital flexion creases, and aseptic necrosis of the femoral or humeral head [5].

Other so-called "minor" signs are reported during Alagille syndrome;

Renal abnormalities

Renal disease can be observed in 40% of patients, they can be divided into [6]

- Structural anomalies such as small hyperechoic kidney, ureteropelvic obstruction, renal cysts, duplex collecting system
- Functional anomalies including renal tubular acidosis, recurrent urinary tract infection, infantile-onset renal insufficiency, adult-onset renal insufficiency

Minor skeletal anomalies

They involve the spine and hands, such as shortened interpedicular distance, shortened distal phalanges or shortening of the distal ulna and radius, craniosynostosis, non-familial macrocephaly, spina bifida occulta [6], and temporal bone abnormalities that increase the risk of chronic otitis media. Those patients also have an increased fracture risk and lower bone density due to deficiencies in vitamin D [5].

Growth retardation

Growth retardation is defined as length and weight below the 5th percentile in the first 3 years of life, it is present in 87% of patients [6].

Psychomotor development retardation

In an American study published in 1999, delays in gross motor skills were found in 16% of cases, and mental retardation in 2% [6].

Intracranial bleeding

It is present in about 14% of cases and can be responsible for death (31%). It can be spontaneous, or secondary to a head trauma or a coagulopathy [6], or congenital vascular brain abnormalities such as Moyamoya disease, whose presence is a poor prognostic factor [5].

Others

Endocrine abnormalities such as hypothyroidism, insulin-dependent diabetes, agenesis of the fallopian tube [6], and delayed puberty [2].

Digestive abnormalities include ileal atresia, malrotation, and exocrine pancreatic insufficiency [6].

Patients with all five major characteristics are defined as having the complete type; those with four characteristics have the incomplete type, and patients with only two of these characteristics represent the minor type [2]. Table 3 represents the frequency of anomalies observed in Alagille syndrome.

Table 3 Frequency of abnormalities observed in Alagille syndrome [6]

	Emerick 1999	Alagille 1987	Deprettere 1987
Bile duct paucity	85%	100%	81%
Chronic cholestasis	96%	91%	93%
Cardiac murmur	97%	85%	96%
Vertebral anomalies	51%	87%	33%
Facies	96%	95%	70%
Eye findings	78%	88%	56%
Renal disease	40%	73%	–
Minor features			
Growth retardation	87%	50%	73%
Mental retardation	2%	16%	0%
Developmental delay	16%	–	52%
Pancreatic insufficiency	41%	–	–

Differential diagnosis of Alagille syndrome can be difficult. Emergent causes of neonatal cholestasis (such as sepsis and galactosemia) should first be considered. Cholestasis resulting from extrahepatic causes such as biliary atresia can be differentiated by a DISIDA scan. Extrahepatic structural duct abnormalities such as choledochal cysts can be eliminated from consideration by hepatic ultrasound. Intrahepatic causes of cholestasis include genetic disorders such as autosomal recessive Byler syndrome, autosomal recessive Norwegian cholestasis (Aegenaes syndrome), North American Indian cholestasis (NAIC), autosomal recessive benign recurrent intrahepatic cholestasis (BRIC), Zellweger syndrome, and a-l-antitrypsin deficiency. Posterior embryotoxon is seen in Rieger syndrome, Bannayan-Riley-Ruvalcaba syndrome, as well as in a small proportion of the normal population. Stenosis in the pulmonary tree can be seen in Watson syndrome. LEOPARD syndrome, Down syndrome, and Williams syndrome are easy to differentiate from Alagille syndrome based on other findings. Intrauterine exposure to rubella can lead to cholestasis and pulmonary stenosis as well [4].

The treatment is based on managing the cholestasis and its complications, especially pruritus because it can have a significant impact on quality of life. Skin emollients, cutting nails short, and avoiding bathing in hot water can all help minimize itching and excoriations. Ursodeoxycholic acid is a choleretic and stimulates bile flow, making it the first-line treatment of cholestasis [5], 10–15 mg/kg/day, in two divided doses, has been used to treat pruritus too [2]. Cholestyramine [5], hydroxyzine (2 mg/kg/day), and rifampicin (10 mg/kg/day) can be used for disabling pruritus [2]. Fat-soluble vitamins should be checked routinely and replaced as needed. Each of the vitamins should be dosed individually because a multivitamin contains a fixed ratio and may result in excessive intake of some vitamins to treat insufficient of others. As discussed previously, patients are at risk of malnutrition and growth failure. Therefore, oral nutrition should be optimized with high-calorie supplements as needed. Some patients may require nasogastric feeds or the placement of a gastrostomy tube to reach caloric intake goals [5]. Patients who fail medical therapy can be referred for a biliary diversion or ileal resection prior to transplantation [5]. Liver transplantation must be discussed in patients with severe, prolonged, chronic cholestasis and malnutrition, growth retardation, deforming xanthomas, and progressive portal fibrosis. Each patient must be judged on the severity of the hepatic compromise and associated malformations [2]. Liver transplantation in Alagille syndrome cases showed an improvement of the liver parameters and some catch-up growth in almost 90% of cases [7]. A life expectancy of 20 years was documented in 75% of patients in one study, with 60% of these requiring a liver transplantation [2]. The fate of liver transplantation usually depends on associated cardiac and renal impairment; therefore both of these systems should be properly evaluated and regularly accessed during pre and post liver transplant period [7]. Despite hepatocellular carcinoma (HCC) is a rare complication of Alagille syndrome, it can appear at any age from childhood to the fifth decade of life, mostly at 30–40 years of age. Patients can develop HCC without cirrhosis, Alagille syndrome itself may be a risk factor for the development of HCC. There are no recommendations for the surveillance of HCC in Alagille syndrome. However, annual screening for HCC in Alagille syndrome patients by serum alpha-fetoprotein and ultrasonography is encouraged due to the fact that the development of HCC is unpredictable, and the treatment of HCC at an early stage has a relatively good prognosis [1]. The French study published in 2001 reported a single case of hepatocellular carcinoma in a 44-year-old adult and one case of hepatocellular carcinoma in a patient with Alagille syndrome and no cirrhosis [8].

The cases with Alagille syndrome should be evaluated in a systematic manner. Detailed assessment should be done by the treating pediatrician, physician, or gastroenterologist, or by all of them, and evaluated by doing regular liver function tests, serum lipid profile, coagulation profile, ultrasound abdomen and pelvis, scintiscan, and liver biopsy in selected cases; detailed cardiac assessment should be done from time to time; regular ophthalmic assessment; renal color Doppler ultrasound, renal function tests, and vertebral X-ray. In infants and children, regular growth monitoring, psychosexual development, dietary pattern, nutritional status, renal tubular function, and pancreatic function should be accessed regularly [7].

Our patient was diagnosed at birth with bile duct paucity, but the absence of follow-up due to lack of financial means aggravated his disease. Chronic cholestasis was the cause of the patient's cutaneous jaundice, xanthomas and pruritus, growth retardation, and osteoporosis. All these factors, in addition to facial and skeletal deformity, had repercussions on the patient's social life and integration into society, resulting in shy behavior and educational backwardness.

The evolution of patients with Alagille syndrome is linked to the degree of hepatic and cardiac involvement. Fortunately, the cardiac abnormality of our patient was asymptomatic and did not occur at a very young age. However, the lack of management of liver disease since childhood led to the development of liver cirrhosis associated with portal hypertension. Treatment with ursodeoxycholic acid for cholestasis, hydroxyzine for pruritus, and vitamin supplementation significantly improved clinical symptoms. The patient is on the waiting list for a

liver transplant and screening protocol for hepatocellular carcinoma to improve survival.

Conclusion

Alagille syndrome is a cholestatic liver disorder affecting multiple systems such as the heart, eyes, face, and skeletal system. Due to the complexity of presentation and multi-organ involvement, management of cases with Alagille syndrome should be done by the combined effort of a multidisciplinary team. Liver disease is a major cause of morbidity in this population, whereas cardiac involvement accounts for most of the mortality.

Key learning

- Alagille syndrome is a rare autosomal-dominant disorder responsible of neonatal cholestasis.
- The diagnosis is based on the association of five major criteria.
- The management of cases with Alagille syndrome requires multidisciplinary care. Liver disease is responsible for morbidity, whereas cardiac and vascular involvement is responsible for mortality.

Abbreviations

BMI	Body mass index
HCV	Hepatitis C virus
RNA	Ribonucleic acid
HBV	Hepatitis B virus
EBV	Epstein–Barr virus
CMV	Cytomegalovirus
Anti-SLA	Antibodies against soluble liver antigen
Anti-LKM1	Liver/kidney microsomal antibody type 1
Anti-LC1	Anti-liver cytosolic antigen type 1
CT	Computerized tomography
MRI	Magnetic resonance imaging
DISIDA	Diisopropyl iminodiacetic acid
HCC	Hepatocellular carcinoma

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Authors' contributions
OK: concepts, design, definition of intellectual content, literature search, manuscript preparation, manuscript editing, garantor. MB: definition of intellectual content, manuscript preparation, manuscript review. FZA: definition of intellectual content, manuscript preparation, manuscript editing, manuscript review. All authors have read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the patient.

Consent for publication
Written informed consent was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

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