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Case Report

Alagille syndrome with unusual common bile duct hypoplasia and gallbladder dysmorphism: Lesson based on a case report ☆,☆☆

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ABSTRACT

Alagille syndrome is an autosomal dominant and multisystemic disease that generally manifests itself with intrahepatic bile ducts paucity, chronic cholestasis, xanthomas and with other less frequent clinical manifestations such as congenital heart disease, skeletal abnomalies, ophthalmic, vascular, renal and growth failure. Symptoms can be subclinical or very severe. Is caused by various genetic mutations and the majority of patients have a detectable mutation in JAG1 (90%), the remainder have mutations in NOTCH2. The diagnosis is molecular and the incidence is approximately 1 in 30,000 – 50.000. Patient management can be very complex and treatment depends on the district affected and on the symptoms. In more serious cases, with terminal liver disease, liver transplantation is used. We describe a case with main bile duct hypoplasia, intrahepatic bile ducts paucity, cholestasis and gallbladder dimorphism associated with renal malrotation and butterfly vertebrae.

Introduction

Alagille syndrome (AS) [1] is an autosomal dominant disorder first described in 1969 by Daniel Alagille [2]. It is a multisystemic syndrome that typically presents with intrahepatic bile duct paucity, chronic cholestasis, and other clinical disorders such as xanthomas, congenital heart defects, skeletal, ophthalmic, vascular, renal anomalies, and growth retardation. Symptoms can be subclinical, clinical, or severe. The diagnosis is molecular, and the incidence is approximately 1 in 30,000 to 50,000 [3]. AS is caused by various genetic mutations, with the majority of patients having a detectable mutation in JAG1 (90%), while the remainder have mutations in NOTCH2 [4–6].

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Biliary tract involvement is almost always present, while other clinical manifestations have a lower and highly variable incidence. Bile duct paucity has been documented in only 65% of patients in the first 3 months of life, and in 95% of all individuals with the disease. Clinical manifestations can be summarized as:

- Renal: Renal abnormalities in AS are characterized by glomerular mesangiolipidosis, renal tubular acidosis, anatomical defects, and renal failure (prevalence of 40%).
- Cardiac: Cardiac abnormalities significantly contribute to mortality and commonly include congenital heart defects (90% of patients) such as Tetralogy of Fallot, peripheral pulmonary stenosis, ventricular and atrial septal defects, stenosis, and aortic coarctation.
- Skeletal: Skeletal abnormalities are characterized by vertebral dimorphisms known as "butterfly vertebrae," resulting from the incomplete fusion of the anterior arches of vertebral bodies, typically asymptomatic (prevalence of 51%–66%). Patients with AS also have an increased risk of fractures and reduced bone density due to vitamin D deficiency [7]. Skeletal anomalies may also involve facial features such as a prominent forehead, sunken eyes, prominent ears, bulbous nasal tip, and a triangular face with a pointed chin.
- Ophthalmological: Ophthalmological features mainly include posterior embryotoxon [8] and, less commonly, microcornea, retinal pigment granularity, mesodermal dysgenesis, and lens opacity [9].
- Vascular: Vascular manifestations include epidural, subdural, subarachnoid, and intraparenchymal bleeding (affecting 25% of patients) [10], as well as aneurysms of aorta, kidneys artery, superior mesenteric artery, and subclavian artery.
- Growth disorders: Patients with AS often experience growth retardation and are smaller in height and weight compared to their peers [11]. Malnutrition can occur as a consequence of severe cholestasis and encephalopathy.
- Xanthomas: Children with AS frequently suffer from itching and develop drug-resistant xanthomas due to cholestasis.

Treatment varies depending on the affected areas and severity of symptoms, ranging from medical management in less severe cases to liver transplantation in cases of end-stage liver disease. We describe a case with main bile duct hypoplasia, intrahepatic bile ducts paucity, cholestasis and gallbladder dimorphism associated with renal malrotation and butterfly vertebrae.

Case presentation

A 6-month-old child was referred to our Imaging Department from the Pediatric Department of our Hospital due to cholestasis. Upon physical examination, the child exhibited intact sensorium, fair general condition, and a body temperature of 36.8°C. Specifically, direct bilirubin was 0.25 mg/dL (normal range: 0.00 – 0.20 mg/dL), S-AST (GOT) was 138 U/L (normal range: 0 – 35 U/L), S-ALT (GPT) was 106 U/L (normal range: 0 – 35 U/L), alkaline phosphatase was 482 U/L (normal range: 30 – 120 U/L), gamma GT was 50 U/L (normal range: 0 – 38 U/L), and LDH was 388 U/L (normal range: 0 – 248 U/L). Bile acids were also elevated at 84 μmol/L (normal range: 0 – 6 μmol/L). Diagnostic tests including Ultrasound (US) and magnetic resonance imaging (MRI) were conducted. The US examination utilized a May Lab Nine device (Esaote biomedica, Genoa) with a 1.5-8 MHz convex probe. US revealed a significant reduction in the diameter of the main bile duct (1.6 mm) measured at the hepatic hilum (Fig. 1), along with "corkscrew'' appearance of the gallbladder (Fig. 2). The US study was conducted by an operator with twenty years of experience.

MRI was performed under sedation using a closed-configuration superconducting 1.5-T system (Signa HDxT; GE Healthcare, Milwaukee, WI, USA). The MRI revealed widespread paucity of the intrahepatic bile ducts, reduced diameter of the main bile duct (1.6 mm) (Fig. 3). Furthermore, MRI showed morphological alterations in a thoracic vertebra, which exhibited a "butterfly" appearance (Fig. 4) due to the failure of fusion of the anterior arch, and an anomalous position of the left kidney, which had its hilum facing laterally. The "corkscrew'' appearance of the gallbladder highlighted by US and the paucity of the intrahepatic bile ducts highlighted by MRI, associated with laboratory data, led us to suspect AS and led us to deepen the study with molecular investigations. Molecular investigations identified genetic mutations in JAG1, typical of AS. The patient was treated with choleretic agents (ursodeoxycholic acid) for fifteen days until a significant decrease in cholestasis indices and liver enzymes: direct bilirubin (0.15 mg/dL), S-AST (68 U/L), S-ALT (46 U/L), alkaline phosphatase (262 U/L), gamma GT (40 U/L), and LDH (258 U/L), bile acids (34 μmol/L). The patient was then discharged with instructions for laboratory tests and US follow-up every 3 months.

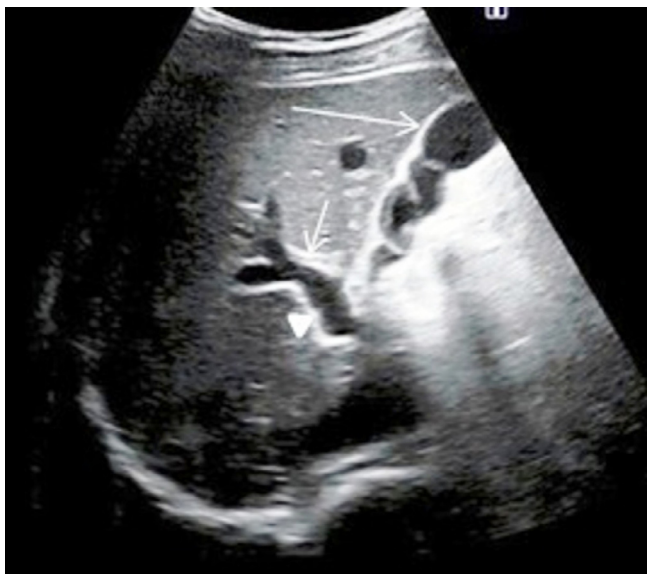

Fig. 1 – Abdominal ultrasound. The gallbladder and cystic duct exhibit an atypical morphology with a "corkscrew" appearance (long arrow), and the common bile duct (short arrow) has a small caliber. Portal vein (arrow head).

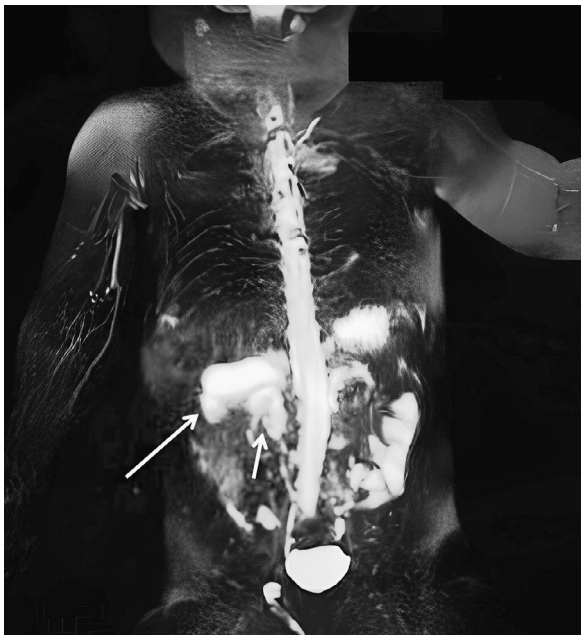

Fig. 2 – Magnetic resonance cholangiopancreatography (MRCP) in Alagille syndrome. The 3D sequence in coronal view reveals the paucity of the intrahepatic bile ducts and failure to visualize of the common hepatic duct and common bile duct due to their small caliber. The gallbladder appears hyperdistended (long arrow). Duodenum (short arrow).

Discussion

ALGS is an autosomal dominant disease caused by alterations linked to the JAG1 and NOTCH2 genes, which has a mortality rate of approximately 10%, mainly due to the hepatic, cardiac and vascular anomalies caused by the disease. Biliary alterations are the most typical and frequent and are essentially represented by cholestasis caused by the scarcity of the intrahepatic bile ducts and the reduced caliber of the common bile duct.

AS should be suspected in newborns with direct bilirubin elevation greater than 1 mg/dL (> 17.1 micromol/L), especially if the gamma-glutamyl transferase-cholestasis (GGT) is high. Due to the multisystemic nature of the disease it is necessary to rule out involvement of other body district through laboratory and diagnostic tests. Specifically, the following tests should be conducted:

- Liver function tests: These should include a complete blood count, measurement of gamma-glutamyl transferase, cholesterol, triglycerides, bile acids, and coagulation profile.
- Ultrasound (US) of the liver: This should assess gallbladder and biliary ducts morphology. In our case, we observed a significant reduction in the diameter of the main bile duct; in adults, the diameter of the main bile duct ranges from 5 to 7 mm, and by the age of 4, it should have a diameter between 3 and 5 mm.

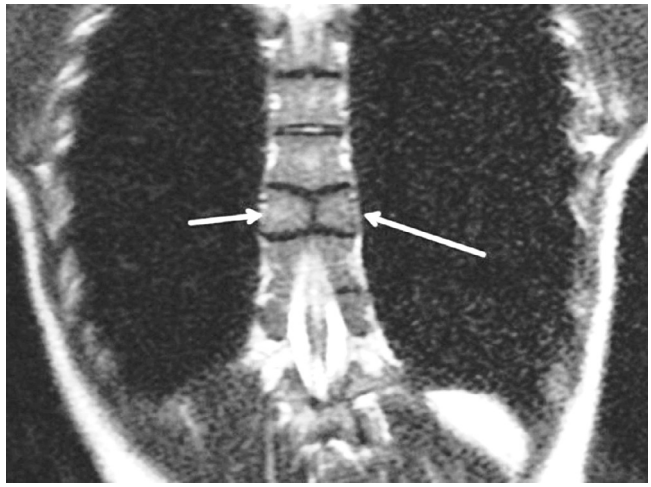

Fig. 3 – MRI, T2 SSFSE (Single shot fast spin echo) sequences. In this coronal view, there is a failure of fusion of the anterior vertebral arch of the eighth thoracic vertebra, which appears divided into right (short arrow) and left (long arrow) hemisomes.

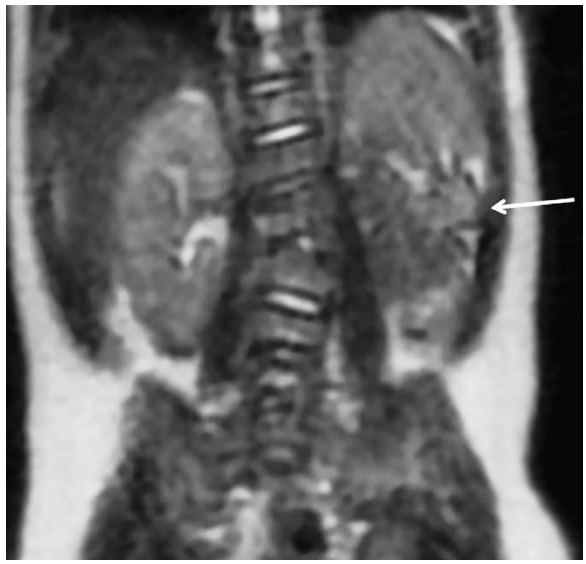

Fig. 4 – MRI, T2 SSFSE (Single shot fast spin echo) sequences. In this coronal view, an anatomic defect of the left kidney is evident, appearing rotated with the hilum (arrow) facing laterally.

"The "corkscrew" appearance of the gallbladder is probably due to the reduction in the caliber of the main bile duct which therefore hinders the emptying of the gallbladder, this appearance should not be confused with the multiseptate gallbladder where there are complete or incomplete septa but it is probably due to hypertrophy phenomena associated with alteration of the normal peristalsis of the gallbladder. This aspect has not yet been reported in the literature and could be a pathognomonic pattern of AS. This appearance of the gallbladder was persistent in US examination performed before the patient was discharged while fasting.

During the MRI examination, the corkscrew appearance of the gallbladder was not evident, probably because the gallbladder was much more distended compared to the ultrasound examination.

-Liver biopsy: While liver biopsy was previously necessary to document intrahepatic bile duct paucity, it should be noted that infants younger than 6 months may not exhibit marked bile duct paucity or may even show ductal proliferation [12]. Currently, especially in newborns, the disease must be suspected if a family member is affected by the syndrome and in this case prenatal genetic testing can be performed. The positivity of genetic tests allows the diagnosis of certainty but does not allow a prediction of the severity of the symptoms due to the highly variable expressivity related to JAG1 and NOTCH2. In the absence of information on family history, in our opinion, the US finding of a gallbladder with a "corkscrew'' appearance, of an extrahepatic bile duct with reduced caliber, associated with high indices of cholestasis, should suggest further investigations with MRI and genetic tests. For the symptoms caused by cholestasis, treatment is mainly supportive, trying to alleviate severe itching when present, and to reduce the xanthomas that occur when cholesterol levels are above 500 mg/dL. Xanthomas are generally asymptomatic and are located at the joint level (ankles, knees, elbows, wrists) [13], and regress as cholestasis decreases for which drugs that reduce it such as ursodeoxycholic acid, rifampin, etc. are used. Ophthalmological and vertebral alterations generally do not require treatment. Malnutrition can be treated with nutritional supplements. Cardiac, renal, and vascular involvement are treated based on clinical manifestations. In more severe cases of end-stage liver disease, the most effective alternative is liver transplantation which has demonstrated a five-year survival rate of 80% [14]. To be effective, however, you need to ensure that kidney function is intact as immunosuppressant drugs can impair it.

Conclusions

The diagnosis of AGS is very difficult due to the non-specificity of the symptoms and the lack of knowledge due to the disease rarity, the prevalence is in fact estimated at 1:30,000-50,000 live births. The disease must first be suspected if there is clinical familiarity and positive laboratory data, proceeding with genetic tests. In the absence of familiarity, the "corkscrew'' appearance of the gallbladder associated with the intrahepatic bile ducts paucity, other signs such as "butterfly" vertebrae and increased cholestasis indices should lead to genetic testing. Failure to diagnose can expose patients to serious health risks.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent

The consent was obtained from the patient for the publication of this case report and accompanying images.

Author contributions

RF Study design/planning collected data, preparation of manuscript, data analysis/statistics, data interpretation and involved in project development, literature analysis/search **AG, PVF, CI, CM, SG, MC, AI, LG** and **DG** collected data, wrote the manuscript, literature analysis/search. **RF, MD** and **AB** wrote the manuscript.

REFERENCES

[1] Mitchell E, Gilbert M, Loomes KM. Alagille syndrome. Clin Liver Dis 2018;22(4):625–41. doi:10.1016/j.cld.2018.06.001.

[2] Alagille D, Odièvre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. J Pediatr 1975;86(1):63–71. doi:10.1016/s0022-3476(75)80706-2.

[3] Leonard LD, Chao G, Baker A, Loomes K, Spinner NB. Clinical utility gene card for: Alagille Syndrome (ALGS). Eur J Hum Genet 2014;22. doi:10.1038/ejhg.2013.140.

[4] Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. Nat Genet 1997;16(3):243–51. doi:10.1038/ng0797-243.

[5] Gilbert MA, Bauer RC, Rajagopalan R, Grochowski CM, Chao G, McEldrew D, et al. Alagille syndrome mutation update: comprehensive overview of JAG1 and NOTCH2 mutation frequencies and insight into missense variant classification. Hum Mutat 2019;40(12):2197–220. doi:10.1002/humu.23879.

[6] Hofmann JJ, Zovein AC, Koh H, Radtke F, Weinmaster G, Iruela-Arispe ML. Jagged1 in the portal vein mesenchyme regulates intrahepatic bile duct development: insights into Alagille syndrome. Development 2010;137(23):4061–72. doi:10.1242/dev.052118.

[7] Olsen IE, Ittenbach RF, Rovner AJ, Leonard MB, Mulberg AE, Stallings VA, et al. Deficits in size-adjusted bone mass in children with Alagille syndrome. J Pediatr Gastroenterol Nutr 2005;40(1):76–82. doi:10.1097/00005176-200501000-00014.

[8] Nischal KK, Hingorani M, Bentley CR, Vivian AJ, Bird AC, Baker AJ, et al. Ocular ultrasound in Alagille syndrome: a new sign. Ophthalmology 1997;104(1):79–85. doi:10.1016/s0161-6420(97)30358-3.

[9] Hingorani M, Nischal KK, Davies A, Bentley C, Vivian A, Baker AJ, et al. Ocular abnormalities in Alagille syndrome. Ophthalmology 1999;106(2):330–7. doi:10.1016/S0161-6420(99)90072-6.

[10] Lykavieris P, Crosnier C, Trichet C. Bleeding tendency in children with Alagille syndrome. Pediatrics 2003;111(1):167–70. doi:10.1542/peds.111.1.167.

[11] Rovner AJ, Schall JI, Jawad AF, Piccoli DA, Stallings VA, Mulberg AE, et al. Rethinking growth failure in Alagille syndrome: the role of dietary intake and steatorrhea. J Pediatr Gastroenterol Nutr 2002;35(4):495–502. doi:10.1097/00005176-200210000-00007.

[12] Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. Gut 2001;49(3):431–5. doi:10.1136/gut.49.3.431.
[13] Kohut TJ, Gilbert MA, Loomes KM. Alagille Syndrome: a focused review on clinical features, genetics, and treatment. Semin Liver Dis 2021;41(4):525–37. doi:10.1055/s-0041-1730951.
[14] Kamath BM, Munoz PS, Bab N, Baker A, Chen Z, Spinner NB, et al. A longitudinal study to identify laboratory predictors of liver disease outcome in Alagille syndrome. J Pediatr Gastroenterol Nutr 2010;50(5):526–30. doi:10.1097/MPG.0b013e3181cea48d.