Case Report

Alagille Syndrome and Its Clinical and Laboratory Features: A Case Report

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Abstract: Alagille syndrome (ALGS) is a genetic-driven condition of chronic cholestasis, involving the intrahepatic bile ducts, heart, vessels, kidneys, skeletal tissues, eyes, and nervous system. Pathological mechanisms are still not defined. JAG1 and NOTCH2 gene mutations are responsible for most cases (96–97%). Diagnosis is based on clinical and laboratory findings—especially the presence of chronic cholestasis—and on genetic assessment. Bone abnormalities, deficiency of liposoluble vitamins, heart issues, and pruritus are the most prominent features of ALGS. Diagnostic imaging, such as ultrasonography, magnetic resonance imaging, and bone mass density assessment, is useful to study hepatic disease progression, estimate the risk of bone fracture, and rule out malignities. Therapy is based on ursodeoxycholic acid, rifampicin, cholestyramine, and supplementation of liposoluble vitamins. New therapeutic approaches are under investigation. Here, we describe a case of an individual with ALGS presenting with congenital chronic cholestasis and a long clinical history, in which pruritus is the main symptom.

Keywords: liver disease; genetic; follow-up; clinical records

1. Introduction

Alagille syndrome (ALGS, OMIM #118450) is a multisystemic condition with autosomal dominant genetic etiology, characterized by variable expressiveness, involving the intrahepatic bile ducts, heart, vessels, kidneys, skeletal tissues, eyes, and nervous system [1]. Pathological mechanisms of ALGS leading to a paucity bile ducts and cholestasis are still not well defined. It is also not fully understood how hepatobiliary disease correlates with congenital abnormalities of other organs and systems [2]. JAG1 (chromosome 20p12, OMIM *601920) and NOTCH2 (chromosome 1p13, OMIM *600275) pathogenic variants have been reported in 96–97% of individuals with ALGS. The genetic etiology of the remaining cases remains unknown [1]. Clinical diagnosis of ALGS follows the criteria first established in 1969 by Daniel Alagille and requires the presence of bile duct paucity shown after hepatic biopsy in association with at least three of the following: chronic cholestasis, heart abnormalities, ocular abnormalities, skeletal abnormalities, and/or characteristic facies. Chronic cholestasis develops during early childhood and becomes evident with jaundice, hepatomegaly, splenomegaly, hypocholic feces, itching, and xanthomas. Hyperbilirubinemia is present (50% conjugated); alkaline phosphatase (AP) and gamma-glutamyl-transpeptidase (GGT) may show very high values and correlate with cholestasis levels. A direct consequence of cholestasis is the malabsorption of liposoluble vitamins (vitamins A, D, E, and K), which leads to an increased risk of osteopenia/osteoporosis (vitamin D), peripheral axonal neuropathy, and hemolytic anemia (vitamin E) [1]. Rarely, hepatitis and cirrhosis may develop. Cardiac diseases include cardiac murmur and pulmonary artery stenosis, which are present in 97% and 90% of patients, respectively [3]. Ocular abnormalities include posterior embryotoxon, abnormal retinal pigmentations,
and striae of the iris. Skeletal abnormalities commonly reported in ALGS are “butterfly vertebrae”, clinodactyly, increased risk of fractures, reduced bone age, growth retardation, insensitivity to growth hormone (GH), and increased levels of GH-binding protein. Characteristic facies usually presents during childhood and becomes more evident with aging, leading to the characteristic “inverted triangular” facies, with a broad forehead, sunken eyes, hypertelorism, small and pointed lower jaw, flat malar eminence, and prominent ears [3]. Even if not included among diagnostic criteria, a high prevalence of renal and vascular abnormalities has been reported [1]. The condition was originally defined as arteriopathic dysplasia, after its typical skeletal and vascular issues. Early detection and diagnosis of ALGS can lead to improved outcomes [4]. A strict clinical and laboratory monitoring of the patient with ALGS is recommended, based on ultrasonographic follow-up of the heart with particular focus on the pulmonary trunk, cholestasis and liver necrosis and functionality indices monitoring, skeletal involvement assessment to prevent osteoporosis and fractures, and periodic evaluation of renal function [1–4]. The main causes of mortality are related to cardiac and vascular involvement [1]. As part of management, an adequate caloric intake is deemed, with prevention and correction of the insufficient intake of liposoluble vitamins. Pruritus is a major clinical issue in ALGS and affects patients’ quality of life. Treatment of pruritus is based on cholestyramine and rifaximin. Severe pruritus and hypercholesterolemia may benefit from external bile diversion, but not when cirrhosis is present. Intractable itching and progressive, degenerating disease represent indications for liver transplantation. Furthermore, in some ALGS cases, the development of hepatocellular carcinoma has been reported, though there is still little knowledge about its epidemiology or etiology factors [5]. New therapeutic approaches are currently under investigation and look promising: ileal bile acid transporter (IBAT) inhibitors and other targeted interventions increase the NOTCH signaling pathway in ALGS tissues [2]. For example, maralixibat, a new orally administered, small-molecule IBAT inhibitor, has been approved for the treatment of rare cholestatic liver diseases including Alagille syndrome (ALGS). Firstly introduced for the treatment of cholestatic pruritus in ALGS patients, its pharmacodynamics include a decreased reabsorption of bile acids from the terminal ileum and augmented excretion of bile acids through the intestine. Clinical trials have reported significant reductions in bile acids and pruritus in ALGS patients. This resulted in an improvement in patients’ quality of life [6]. Here, we report a long history of ALGS, illustrating its clinical and therapeutical follow-up from birth to the present day, in order to compare it with other cases of this rare syndrome with its typical features in the literature.

2. Case Report

We report the case of a Caucasian 27-year-old female, born at term to unrelated parents.

- Forty-eight hours after birth: overt jaundice developed. The newborn was treated with fluorescent blue-light phototherapy, which led to the amelioration of jaundice.
- After hospital discharge: the newborn showed reduced appetite, irritability, low weight gain, and peri-oral cyanosis during breastfeeding.
- Ten days after birth: she was re-hospitalized to assess the scarce weight gain along with suspected congenital heart disease.
- Twentieth day of life: cholestatic jaundice developed (total bilirubin 8 mg/dL, >60% conjugated), with hypochole stools. After excluding hepatomegaly, a therapy with phenobarbital was initiated but no significant clinical response was noted.
- Two months after birth, the infant underwent heart ultrasonography which demonstrated the presence of a moderate ventricular septal defect (VSD), with left–right shunt and peripheric pulmonary trunk stenosis. An ophthalmologic evaluation showed no abnormalities. Given the neonatal episode of jaundice and the cardiovascular issues, in light of a possible congenital bile duct abnormality, a liver biopsy was performed, showing bile duct hypoplasia, compatible with the diagnosis of ALGS. The patient was then discharged with a therapy based on ursodeoxycholic acid (UDCA).
- At six months of age, the patient underwent another ophthalmologic assessment which detected a posterior embryotoxon in the right eye, while it was almost absent in the left one. The patient continued the therapy with UDCA.
- At the age of 3, she was hospitalized again due to growth retardation and the presence of severe itching, not responding to treatment with phenobarbital, cholestyramine, UDCA, and rifampicin. In this circumstance, percutaneous biliary drainage was attempted without success and UDCA dosage was then increased.
- In subsequent years, the levels of bile acids fluctuated between 50 and 200 mmol/l, while alpha-fetoprotein remained in the range of normality.
- At ten years of age, the child was evaluated with magnetic resonance imaging (MRI): intra- and extrahepatic bile ducts showed no pathological enlargements. An inhomogeneous hypointense area (6 cm of diameter) between IV and V liver segments was found. The gallbladder, spleen, kidneys, and pancreas were normal.
- At the age of 12, an ultrasonographic exam performed showed important hypertrophy of the caudate lobe, and the presence of the same inhomogeneous area (now 5 cm wide) reported two years before between IV and V liver segments, not pushing nor compressing any adjacent vascular structures, was addressed as angioma or focal steatosis. The gallbladder was still normal, while the spleen volume was increased (11.5 cm) with a homogenous ultrasonographic structure. The portal vein had normal caliber and flow.
- The last evaluation at the pediatric center (February 2008) included heart ultrasonography whose results showed hypoplasia of the left branch of the pulmonary trunk, with normal pressure gradient. Short stature and elevated thyroid-stimulating hormone (TSH) levels were observed, along with the presence of anti-thyroglobulin (anti-TBG) and anti-thyroxoperoxidase (anti-TPO) antibodies, pointing out a diagnosis of autoimmune thyroiditis, in the absence of thyroid nodules. Hepatomegaly and splenomegaly were evident at clinical palpation. Radiography of the trunk demonstrated the presence of left-convex scoliosis, with augmented lumbar lordosis, without the presence of “butterfly vertebrae”.
- At the age of 13 years, the patient reported general clinical well-being, no jaundice, normal coagulation parameters, inflammatory markers, and serum protein levels, and normal kidney and pancreas functionality. She maintained her therapy with UDCA (600 mg/day), rifampicin, liposoluble vitamin supplementation, and ranitidine (150 mg/day). A genetic assessment was then performed, ruling out JAG1 pathogenic variants and parental screening was negative for other ALGS-related mutations. ALGS with characteristic facies, pulmonary trunk hypoplasia, and chronic cholestatic liver disease was pointed out. The main complaint of the patient remained itching. From 11 to 13 years old (October 2008), AP levels slightly fluctuated between 420 and 550 U/L, while GGT fluctuated between 250 and 400 U/L; total cholesterol levels remained steadily and slightly above 200 mg/dL, while total bilirubin levels did not exceed the value of 2.3 mg/dL, with a mean value of 1.4 mg/dL.
- The patient missed the follow-up evaluations from 2013 to 2016, reporting general well-being except for occasional itching flares that were treated with cholestyramine 4–8 g/day with a fair control of the symptom.
- In 2016, the patient came to the attention of our gastroenterology unit for the first time. The laboratory examination reported: total bilirubin 1.19 mg/dL, conjugated bilirubin 0.37 mg/dL, alanine transaminase (ALT) 36 U/L, AP 140 U/L, GGT 123 U/L, total amylase 111 U/L, pancreatic amylase 65 U/L. Inflammation markers, C-reactive protein (CRP), and alpha-fetoprotein were all normal. Vitamin D levels were in the range of normality (29.7 ng/mL). TSH was slightly elevated (5.280 uU/mL) while FT3 and FT4 levels were in the normal range. In December 2016, a re-assessment conducted by abdomen ultrasonography detected a right lobe hepatic variation (Riedel’s accessory lobe), with a normal ultrasonographic structure, normal gallbladder, without signs of gallstones, and a slightly enlarged spleen (longitudinal diameter of 125 mm).
Intra- and extrahepatic bile ducts and portal vein were normal in caliber, without enlargements. Assessment of bone-mass density with dual energy X-ray absorptiometry (DEXA) reported an increased risk of fractures within the femoral neck, while a normal index was detected at the lumbar level. An ophthalmological reassessment stated the presence of posterior embryotoxon and normal range of visus, without other pathological findings. The patient was discharged with a therapeutic protocol of UDCA 1650 mg/day, liposoluble vitamin supplementation, and rifampicin.

- From 2016 to 2018, the patient reported general well-being except for flares of itching at the verge of tolerability that were treated with cholestyramine 4–8 g/day, which led to amelioration of the symptom.

- At 23 years of age (2018), she was re-admitted to our unit after finding altered laboratory values from another center. Our evaluation reported normal direct bilirubin, ALT 51 U/L, aspartate transaminase (AST) 42 U/L, AP 177 U/L, GGT 162 U/L, total amylase 125 U/L, pancreatic amylase 67 U/L, anti-TPO 3704 U/mL, anti-TGB 343 U/mL, normal TSH, FT3, and FT4 levels. Heart ultrasonography was conducted, showing normal left ventricular function values (ejection fraction 60%), flow acceleration in the left pulmonary artery branch, not hemodynamically significant, a small pulmonary regurgitation, and a small tricuspidal insufficiency jet. The patient was discharged with UDCA 1800 mg/day, cholestyramine 4 g ×2/day, rifampicin 300 mg on demand, and vitamin supplementation.

- At a new clinical evaluation in July 2020, the patient reported general well-being, except for occasional itching flares, treated with cholestyramine.

- In July 2022, at 26 years and 11 months of age, the patient reported only rare flares of pruritus, which responded positively to the treatment with cholestyramine. She took her therapy with compliance and maintained her clinical follow-up regularly with laboratory and imaging checks. The last ultrasonography (January 2022) showed a homogenous hepatic structure, Riedel’s accessory lobe, normal gallbladder without gallstones, and normal spleen with a longitudinal diameter of 12 cm. The patient is working and socially active and overall satisfied with her life quality. Laboratory results collected during this recent period are shown in Figure 1. As expected and reported in the literature, the cholestasis levels of our patient progressively decreased over time, until they reached the actual steady state, without UDCA dosage increase during the last 4 years.

![Figure 1. Trend over time of gamma–GT, alkaline phosphatase, and direct bilirubin blood values.](image)

### 3. Discussion

The case reported describes a typical clinical presentation of ALGS, with chronic cholestasis, intrahepatic bile ductopenia, characteristic facies, osteopenia with increased risk of fracture, and pulmonary trunk stenosis, which appears to be not hemodynamically significant. The main concern emerging from the clinical history has been pruritus, which has been treated successfully with pharmacological therapy based on rifampicin and cholestyramine on demand during flare-ups. The cholestasis trend showed an improvement with aging—which is consistent with what has been reported in the literature—with a reduction in serum levels of bilirubin, AP, and GGT over the years. An observational
study conducted in 2020 on 243 molecularly defined patients with ALGS reported how total bilirubin was higher for younger patients ($P = 0.03$), with a median of 6.9 mg/dL for those less than 1 year old versus a median of 1.3 mg/dL for individuals of 13 years or older. The median GGT also decreased with aging in the same age groups [7]. No JAG1 pathogenic variants were found, while her NOTCH2 genotype is still unknown. Up to now, no inflammatory liver disease has developed. The same study reported the development of definite portal hypertension by 20 years of age in 40% of individuals [7]. Fortunately, no signs of portal hypertension have been found up to now in our patient, except for a slightly augmented spleen volume. Additionally, the study reported that 25% of patients reach young adult age without liver transplantation [7]. In our case, the patient has not required liver transplantation. Imaging techniques are not the gold standard for ALGS diagnosis, which is mainly clinical, but they are useful in the follow-up of the patient to spot and rule out other suspected lesions of malignancy. Focal liver hyperplasia in advanced cirrhosis in ALGS has been described. In a case, the lesion was in the caudate lobe, mimicking a tumor at ultrasonography. At laparotomy, the caudate lobe had a pseudotumoral appearance, but at a biopsy, the liver parenchyma was preserved, while the sample from the right and left lobes showed an absence of intrahepatic biliary ducts [8]. In our case, imaging exams reported hypertrophy of the caudate lobe and Riedel’s accessory lobe. MRI imaging did not show any focal lesions suggestive of malignancy. The scientific literature includes various reports of randomly discovered intrahepatic lesions in ALGS. MRI is the most useful imaging technique to address the origin of the lesion, especially when liver transplantation is indicated [9].

Psychiatric manifestations of ALGS are not well discussed in the literature. A case report showed how a 12-year-old female addressed her depressive symptoms to her self-image, associated with anhedonia, feelings of guilt and worthlessness, poor energy, and suicidal ideation [10]. Pruritus was the main complaint of our patient and affected her quality of life, especially during severe flare-ups, and psychological consequences of this symptom are not to be underestimated. Early onset of chronic liver disease is not common in ALGS, nor reported in our patient, but a case report has shown, in a 10-year-old boy with ALGS, uncommon café-au-lait spots and upper limb bone fractures with an early onset of hepatic disease revealed with liver biopsy; in detail, a portal area with mild inflammation, a conspicuous absence of interlobular bile ducts adjacent to the hepatocytes, some degree of fibrosis, occasional nodules, and few feathery hepatocytes without inflammation [11].

4. Conclusions

In our case, we show a typical presentation of ALGS, a chronic congenital cholestatic disorder with multisystemic involvement. Heart, bone, and nervous system issues are often present. Main clinical features such as pruritus and increased risk of bone fractures accentuate the burden of the disease, and may severely impact the quality of life, but in our case, they are well controlled by pharmacological and supplementation therapy. The need for liver transplantation is high, even before reaching adult age, and a periodic assessment of liver function and cholestatic values, such in our case, is needed to promptly manage disease progression. New therapeutic approaches are under investigation, which shed light on the future of ALGS management. More randomized controlled trials are needed to assess the best treatment options for individuals with ALGS.

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