Alagille Syndrome: About Two Cases and Literature Review

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Authors' contributions

Article Information

Case Study

ABSTRACT

Alagille syndrome is a multi-systemc genetic disorder with variable phenotypic penetrance that was first described in 1969 by Daniel Alagille.It is characterized by anomalies of the intrahepatic bile ducts, heart, eye and skeleton, which are associated with facial features . The prognosis depends on the severity of the liver and heart diseases. The authors reported two cases characterized by the variability of clinical expression and evolution. The study concerned two girls aged of 2 and 4 months with no family history, who developed cholestatic jaundice evolving from the first month of life. The aim of this work is to remind the different clinical expressivity and the differentmodalities to manage the patients in order to ensure a best quality of life.

1. INTRODUCTION

Alagille syndrome (ALGS) is a multisystemc disorder with variable phenotypic penetrance.

Incidence of Alagille Syndrome (ALGS) is 1/100,000 live births. Transmission follows an autosomal dominant pattern, with a high degree of penetrance but variable expressivity [1]. A

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more rare autosomal recessive pattern has also been described . The gene defect in 60 to 75% of cases is an intragenic (94%) mutation in the *JAG 1* gene located on chromosome 20p12 or deletion *JAG1* mutations are found in one third of patients presenting with only one or two clinical features of Alagille syndrome. Mutations in the gene encoding *NOTCH 2* have been described as well [2]. Initial diagnosis was based on the presence of intrahepatic bile duct paucity and at least 3 other clinical features: Chronic cholestasis, cardiac disease, ocular abnormalities, skeleton abnormalities, and characteristic facial features.

2. MATERIALS AND METHODS

We report the case of two girls aged of 2 and 4 months with no family history, who developed cholestatic jaundice evolving from the first month of life. We have consulted several references, to enrich the discussion and address the subject in its different approaches. This manuscript allowed us to review the clinical and biological manifestations of this syndrome. It has allowed us to has also made it possible to judge the quality of the initial care of these sick.

A literature review has enriched this work with the aim of understanding the diversity of this pathology and the advances in genetic research, in particularin Alagille syndrome.

3. CASE REPORT

3.1 Case Number

Infant 2 months old, third of 3 siblings, with no family history, who developed since the 4th day of life cutaneous-mucosal jaundice of progressive aggravation with colored urine and pale yellow stools without other associated signs. The general review found apyretic infant, Icteric on a pale background, dysmorphic fasciae: bulging forehead, implanted low ears, hypertelorism, sunken eyes and pointed chin. The rest of the clinical examination was unremarkable. Laboratory examination results were as follow: Hepatic cytolysis : aspartate aminotransferase : 193 (N: 15-55 U/L); alanine aminotransferase: 152 (N: 5-45 U/L),. Hepatic cholestasis: alkaline phosphatase : 719(N: 145-420 U/L); gamma-glutamyltranspeptidase: 1711, total bilirubin 103mg/dL, conjugated bilirubin: 79mg/dL . TSH: 2.44 (normal). Cervico dorso lumbar rachis X-ray revealed Butterfly wing vertebrae pathognomonic for alagille syndrome.

Abdominal ultrasound was normal. Ophthalmological examination revealed posterior embryotoxon in both eyes. Cardiac evaluation demonstrated thymic hypertrophy and systolic acceleration of the flow at the passage of the pulmonary bifurcation suggestive of branch stenosis probably in the process of formation to be documented by angio-scanner: compatible with an alagille syndrome, with in addition a continuous flow suggestive of a permeable arterial canal. The patient received appropriate correction of vitamin deficiences : Vitamin K, Vitamin D. Vitamin A and vitamin E.

3.2 Case Number

- A 4-month-old girl, hospitalised 40 days later for prolonged jaundice related to Escherichia coli urinary tract infection (Hepatobiliary ultrasound was normal), a persistence of cutaneous mucous jaundice, with intermittent discoloured stools and dark urine. No pruritus or hemorrhagic syndrome. The general review found an infant in good general condition, apyretic, icteric on a pink background, tonic, reactive. Facies doesn't find obvious dysmorphia outside of a bandbag forehead. Psychomotor development was normal. Abdomen's soft, there was not hepato splenomegaly. Cardiopulmonary auscultation was normal. Neurological exam was normal. The rest of the somatic examination was unremarkable. Laboratory examination results were as follow : Hepatic cholestasis: Total Bilirubin: 99 mg/l, Direct Bilirubin: 74mg/l.: gamma-glutamyltranspeptidase 1500 IU/l(N: 5-32 U/L). Hepatic cytolysis: aspartate aminotransferase: 411 IU/l(N: 15-55 U/L) , alanine aminotransferase: 375 IU/l. (N: 5-45 U/L).Reduced prothrombin: 58%.Serologies of syphilitic, toxoplasmosis, rubella, HIVand Hepatitis B,C were negative. He has no hydroelectrolytic disturbance, kidney function was normal. Serum total protein and albumin were normal. Alpha Foetoprotein: 550 ng/ml, Ferritin: 400. TSH: 2.97µUI/ml, CBEU: sterile**.** Amino acid chromatography in the blood: normal. Amino acid chromatography in urine: normal. Amoniemia: 194 g/dlµ (N :31-123). Abdominal ultrasound was normal, the main bile duct was not dilated. Direct radiography of the vertebral column

revealed non pathologic signs. Bili MRI appearance that may be compatible with type IV extrahepatic biliary atresia. Anapathic account of the liver biopsy concludes to a morphological aspect of a Cholestase liver secondary to intra-hepatic ductular paucity (ductopenia). Ophthalmologic examination revealed an incomplete embryontoxon. Cardiac evaluation demonstrated hypoplasia of the pulmonary bronchi. On the symptomatic therapeutic level , the patient has been put on : Vitamin K. Vitamin D , Vitamin A and vitamin E.

4. DISCUSSION

Alagille syndrome is a multisystemic disorder involving predominately the liver, heart, skeleton, eyes, and face. The diagnosis of Alagille syndrome is traditionally based on bile duct paucity in association with at least 3 of 5 major clinical features: chronic cholestasis; cardiac defect; skeletal abnormalities; ocular abnormalities and characteristic facial features.

Several mechanisms which may cause paucity of intrahepatic bile ducts. One mechanism may be the poor development of intrahepatic arterial branches. Expansion of the portal vein mesenchyma(PVM) also appears to be dependent on *JAG1* signaling: Jagged1 in the portal vein mesenchyma (PVM) regulates intrahepatic bile duct development and controls the formation of the second layer of the ductal plate, allowing the biliary epithelial cells (BECs) to eventually remodel into a lumenized duct [1].

Alagille based his original definition of bile duct paucity as a bile duct to portal tract ratio less than 0.5, one of our patients, the second one, has bile duct paucity. More recent reports found cholestasis in only 89% of patients and bile duct paucity in 75%. both of our patients have cholestasis.

If a patient has liver disease, it typically develops in the neonatal period and presents with direct hyperbilirubinemia. Liver disease does not develop outside of early childhood, and mild disease often improves during this time period [3].

Stenosis/hypoplasia of the branch pulmonary arteries was the most common of cardiovascular involvement ,and found in 76% of subjects, followed by tetralogy of Fallot. Cardiac involvement significantly increases mortality.

Survival to 6 years is decreased to 40% compared with 95% in patients without intracardiac disease. The exact mechanism of disease remains unknown and there is no correlation between the genetic mutation in JAG1 and the presence or type of cardiovascular disease [4]. One of our patients have systolic acceleration of the flow at the passage of the pulmonary bifurcation suggestive of branch stenosis, the other one have hypoplasia of the pulmonary bronchi.

Fig. 1. Cervico dorso lumbar rachis X-ray revealed Butterfly wing vertebrae pathognomonic for alagille syndrome

Systemic vascular anomalies of the aorta (both aneurysmand coarctation), renal, celiac, superior mesenteric, and subclavian arteries have all been reported [5]. There is no genotype-phenotype correlation, so the exact mechanism of the development of these vascular abnormalities remains unknown. The expression of JAG1 in all major arteries, however, has been established in studies of human embryos [6]. It has been proposed that vasculopathy is the primary abnormality in ALGS and causes bile duct paucity as the development of intrahepatic bile ducts is dependent on intrahepatic arterial branch formation.

Vertebral anomalies have been misreported in 54% of cases so imaging should always be reviewed with a radiologist familiar with these cases [7]. The presence of butterfly vertebrae does not confirm the diagnosis because it can be found in normal children or associated with other diseases, such as VATER association (vertebral anomalies, imperforate anus, tracheo-

esophageal fistula and renal anomalies) and 22q deletion syndrome. Additional skeletal abnormalities include square shape to the proximal finger with tapering of the distal phalanges and extradigital flexion creases, ulna shortening, aseptic necrosis of the femoral or humeral head, and temporal bone abnormalities that increase the risk of chronic otitis media [8]. One of our patients has Butterfly wing vertebrae.

Patient with ALGS have typical facial features that are often described as triangular and can include a prominent forehead , deeply set eyes, moderate hypertelorism, pointed chin and bulbous tip of the nose , one of our patients have bulging forehead , implanted low ears, hypertelorism , sunken eyes and pointed chin.

There is a wide range of Ocular Abnormalities, but posterior embryotoxon is most common. posterior embryotoxon is found in 56% to 95% of patients with ALGS, it was also detected in 22% of children evaluated in general ophthalmology clinic [9]. One of our patients have posterior embryotoxo in both eyes, other have incomplete embryontoxon.

Growth deficiencies are more significant in children with ALGS, however, compared with other chronic liver diseases, indicating a possible role for JAG1. [10].Poor nutritional status and severe cholestasis are contributing factors of neurologic deficits and can also be targets to improve outcomes. The neurologic deficits are greater, however, than those seen in other chronic liver disease patients [11]. None of our patients had any neurodevelopmental delays.

A more recent report found renal involvement in 39% of cases with the most common manifestation being renal dysplasia (58.9%) followed by renal tubular acidosis (9.5%), vesicular ureteric reflux (8.2%), and urinary obstruction (8.2%) [12]. Based on these findings, it has been proposed that renal anomalies be considered a disease-defining criterion in ALGS.

A molecular diagnosis is confirmed in up to 96% of individuals with clinically diagnosed ALGS. A majority of JAG1 and NOTCH2 mutations can be identified by sequencing all exons, and the immediately adjacent intronic regions to identify splice site mutations, of each gene. Because mutations in JAG1 are predominant, sequencing of this gene occurs first followed by deletion or duplication analysis via multiplex ligation-dependent probe amplification, chromosomal microarray, or fluorescence in situ hybridization. Sequencing of JAG1 identifies approximately 85% of ALGS mutations, and deletion/duplication analysis yields an additional approximately 9% of molecular diagnoses. In the absence of an identified mutation in JAG1, sequencing of NOTCH2 identifies another 2% to 3% of mutations in ALGS. There have been no reported large deletion or duplication mutations in NOTCH2. A causative mutation for the remaining 2% to 4% of clinically diagnosed ALGS patients has not yet been identified, and the application of various next-generation sequencing techniques could help identify a molecular origin in this population [13].

Conditions that cause cholestasis must be included in the differential diagnosis. Interlobular bile duct paucity also can be found in patients with alpha-1 antitrypsin deficiency, cystic fibrosis, childhood primary sclerosing cholangitis, mitochondrial disorders, congenital hepatic fibrosis, infection (congenital syphilis, congenital cytomegalovirus, congenital rubella and hepatitis B), childhood autoimmune hepatitis, hypopituitarism, graft versus host disease, Zellweger syndrome, Ivemark syndrome and Smith-Lemli-Opitz syndrome. Cholestasis can be found in neonates with biliary atresia, sepsis, galactosemia, tyrosinemia, choledochal cyst or other extrahepatic structural abnormalities. It is also found in individuals with progressive familial intrahepatic cholestasis types 1 and 2, arthrogryposis-renal dysfunction-cholestasis syndrome, benign recurrent intrahepatic cholestasis, and Norwegian cholestasis (Aagenaes syndrome). Pulmonic vascular abnormalities also are seen with Noonan syndrome, Watson syndrome, William syndrome, Down syndrome, and LEOPARD syndrome. Ventricular septal defects and Tetralogy of Fallot are common in patients with deletion 22q11.2 as well as butterfly vertebrae and failure to thrive. Posterior embryotoxon also can be seen in 8% to 15% of the general population as well as other syndromes like Bannayan-Riley-Ruvalcaba syndrome and Axenfeld-Rieger syndrome [14].

Prognosis depends on the severity of liver disease (it is more severe in neonatal onset forms) and on the severity of cardiac disease:

- Total bilirubin >6.5 mg/dL, conjugated bilirubin >4.5 mg/dL, and cholesterol >520 mg/dL in children younger than 5 years of age are likely to be associated with severe liver disease in later life. [15];

- Cardiac disease predominantly accounts for the early mortality in infancy;
- Hepatic complications mostly account for later mortality. Consequences of severe cholestasis in early childhood, may indicate liver transplantation (20 to 30% of AGS patients will undergo a liver transplantation). Progression towards cirrhosis and liver failure is relatively slow, implying careful follow up throughout life;
- Early development of Hepatocellular Carcinoma (HCC) has been reported in AGS patients as young as 1.5 years of age regardless of the presence or not of cirrhosis. It could be a reflection of a deregulated cell fate pathway resulting from the disrupted Notch signaling. HCC should be regularly screened for with alpha-foetoprotein.

For liver disease therapy, appropriate correction of vitamin deficiencies is paramount. Cholestyramine (12—15 g/day) is indicated for pruritus and/or hyperlipidemia. Recalcitrant pruritus may also respond to rifampin (starting with 10 mg/Kg/day) and antihistamine agents. Ursodeoxycholic acid (10—15 up to 45 mg/Kg/day) is usually effective in improving cholestasis. Diet should contain medium-chain triglycerides. Appropriate prophilactic measures should be undertaken when liver transplantation is planned [1].

Indications for liver transplantation and biliary : Severe chronic cholestasis resulting in poor quality of life, including refractory pruritus, disfiguring xanthomas, bone fractures, growth retardation are more frequent transplantation indications than end stage liver disease. Transplant assessment requires an accurate evaluation of the cardiac and renal involvement. Cardiac performance should be tested with preoperatively dynamic stress tests, comparable to the hemodynamic changes happening during liver transplantation [16]. Many aspects of the syndrome improve after liver transplantation, but short stature is usually not significantly affected. Surgical ileal exclusion has been proposed for symptomatic ALGS refractory to medical management as an alternative to external biliary diversion or liver transplantation.

At present, available therapies for ALGS patients are supportive and focused on clinical manifestations involving each organ system. In the future, new therapeutic approaches may involve modulation of Notch pathway signaling, cell-based therapies, or correction of specific mutations in vitro or in vivo. Although structural cardiac defects occur in early development and are present at birth, involvement of other organs may be more amenable to postnatal interventions. For example, bile duct paucity evolves after birth and there may be a window of time during which a therapeutic intervention could augment bile duct development and branching [13].

There are several different approaches that could be taken to modulate Notch signaling *in vivo* [17]. In a recent study, the mouse extrahepatic biliary tree was successfully reconstructed using human cholangiocyte organoids [18]. Given the oncogenic potential of Notch pathway overexpression, any therapy designed to increase Notch signaling would need to be used with caution and preferably for a short window of time.

5. CONCLUSION

Alagille syndrome (ALGS), or syndromic bile duct paucity, is a dominantly inherited multisystemic disorder characterized by chronic cholestasis associated with anomalies of heart, skeleton, eyes and characteristic facial features. ALGS is caused by several mutations in JAGGED1 (JAG1), which encodes the ligand Jagged1 in the Notch signaling pathway. Most of patients have a detectable mutation in JAG1 (more than 90%), but there is also a smaller percentage with mutations inNOTCH2. Liver disease is a major cause of morbidity in this population, whereas cardiac and vascular involvement account for most of the mortality. Current therapies for ALGS patients are supportive and focused on clinical manifestations. Liver transplantation now makes it possible to improve the evolutionary course of severely affected patients. In the future, new therapeutic approaches may involve modulation of Notch pathway signaling, cell-based therapies, or correction of specific mutations in vitro or in vivo.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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