



Alagille syndrome with characteristic phenotype in a 7-month-old infant: Case presentation

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Abstract

The syndromic ductopenia or also known Alagille syndrome constitutes one of the causes of cholestasis in pediatrics. A genetic disorder characterized mainly by chronic cholestasis secondary to hypoplasia of the intrahepatic biliary ducts. Histological lesion is characterized by a decrease in the number of biliary ducts in the portal spaces. It is a disease with a mortality close to 20% and patients may need hepatic transplantation. A 7-month patient with previous family history of brother deceased at 2 years old with Alagille syndrome is presented, who was admitted in the José Luis Miranda Pediatric University Hospital, Villa Clara, Cuba, for study due to chronic cholestasis. Clinical studies performed allowed to diagnose the syndrome in this patient, who presented a characteristic phenotype, accompanied by cardiovascular alterations, ocular embryotoxon and vertebrae in butterfly wings. It is concluded that the presence of cholestasis in infants makes it necessary to look for the presence of others signs of this syndrome that allow to do the early diagnosis of this rare disease.

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Introduction

Alagille Syndrome (AS) is a disease that affects the liver, heart, spinal column, the eyes, face, kidneys, and blood vessels. It constitutes a genetic disease given by the presence of decreased intra-hepatic bile ducts and the presence of 3 of the following 5 classic criteria [1-4]:

1. Chronic cholestasis (Mandatory criteria)
2. Congenital heart disease
3. Vertebral abnormalities
4. Posterior ocular embryotoxon
5. Quirky Facie.

It is an autosomal dominant disorder and two types of AS are described, AS type I due to mutations in the JAG 1 gene (20p12) and deletions that constitute 94% of cases and AS type II due to mutations in the gene. NOTCH 2 (1p13) in 1-2% of cases. The prevalence of the disease varies according to the geographical area, from 1 to 100,000-400,000 births [5].

Watson and Miller were the first to report the first cases of neonatal liver disease, with pulmonary valve stenosis, in 1973; however, Daniel Alagille is the first to describe, a few years later in 1975, hypoplasia of the intra-hepatic bile ducts associated with chronic cholestasis and abnormalities of the heart, eyes,



skeleton, kidneys and a typical facies [6-7].

The presence of decreased bile canaliculi is responsible for a state of chronic cholestasis that may be responsible for biliary cirrhosis and the patient may need a liver transplant [7-8].

Case presentation

Male infant, 7 months old, product of a risky pregnancy due to vaginal infection in the three trimesters, urinary tract infection, type II intra-uterine growth retardation, oligohydramnios and short intergenetic period. Dystocic delivery by caesarean section at 36.2 weeks with a birth weight of 1800g, remaining hospitalized in the neonatal department until reaching ideal weight.

During this period of hospitalization, the patient presented an icterus, and the first urinary tract infection was found with a positive urine culture for E.coli. It was assessed with cardiology and the persistence of the ductus arteriosus with slight hemodynamic repercussion was confirmed, and treatment with spironolactone was required. A humoral and clinical pattern of cholestasis is demonstrated and begins to be evaluated by gastroenterology by plating a first diagnosis of neonatal hepatitis, treatment with Ursochol begins, and the study of cholestatic syndrome begins.

From the first evaluation, a peculiar phenotype is verified and an evaluation by genetics is decided. Subsequently, he was admitted at 3 months of age for a second urinary tract infection with a positive urine culture for Enterobacter, taking Amikacin treatment. Protein energy malnutrition appears, being followed up by a nutrition specialist. At 5 months, he was admitted again for out-of-hospital bronchopneumonia taking treatment with oral Amoxicillin and Oseltamivir. During this admission, severe thymic hypoplasia was observed. Family pathological history of older sister (alive) with persistent ductus arteriosus, brother (deceased) with diagnosis of interatrial communication plus Alagille syndrome

Upon physical examination of the patient at admission, it is found:

- Icterus marked greenish hue.
- Hepatomegaly of more than 1 cm that exceeds the rib margin and visible venous circulation.
- Phimosis.
- Coluria and acolia.
- Asymmetry of the folds in the lower limbs.
- Supernumerary right palmar crease.
- III / VI systolic murmur in the left infra-clavicular region with mitral rumble.
- Phenotype with some dysmorphias.



Figure 1: Photo of the patient's face showing some dysmorphies such as: Prominent forehead, sunken eyes, ascending oblique eyelid fissures, large ears, small and pointed chin, wide and depressed nasal bridge. (owner's face). Weight: 5.5 kg Size: 63cm

Blood test

- Complete blood count (Hb: 10 g / L, Leukogram: Leukocyte: 11.4×10^9 / L, neutrophils 0.44, Lymphocytes 0.55, Monocytes 0.00 Eosinophils 0.01, Platelets: 270×10^9 / L
- Coagulogram: Normal.

Hemochemistry

- Glucose, Fasting: 3.6 mmol / L
- Creatinine: 38 umol / L
- Cholesterol: 10.5 mmol / L
- Triglycerides: 2.1 mmol / L
- Total protein: 74g / L
- Albumin: 40g / L
- Globulins: 34g / L
- Total Bilirubin: 71umol / L
- ALT: 620 ud / L
- AST: 380 ud / L
- FAL: 683 u / L
- Urine culture: negative
- Urine pH: 6.5 and Urinary density: 1010
- Chest x-ray: negative.
- Bone pelvis x-ray: Hip dysplasia



Figure 2: Total spinal x-ray reports: conserved bone density. It draws the attention in 3, 4, 7 and 9 dorsal vertebrae, being very evident in the 7th and 9th vertebrae in butterfly wings. No rib alterations defined.

Renal and abdominal ultrasound: Normal size gallbladder and no images of lithiasis inside, intrahepatic and extrahepatic bile ducts with normal characteristics. Liver of uniform echogenicity, without nodules, that does not exceed the rib margin. Pancreatic area and spleen of normal size and homogeneous echogenicity. Both kidneys have a normal shape, size and normal situation with a good medullary cortical relationship, there is no cavity dilation or lithiasis with an increase in echogenicity grade (I). Aorta of normal caliber and normal bladder.

Transfontanelar ultrasound: Normal.

Ophthalmological examination: A posterior ocular embryotoxon of the left eye observed.

Final comment: AS, also known as Alagille-Watson syndrome and arteriohepatic dysplasia (7), can be a cause of cholestasis that occurs in the first year of life due to hypoplasia of the intra-hepatic bile ducts associated with other malformations. The alterations in the laboratory analyzes usually demonstrate the presence of elevation of the conjugated bilirubin, hypertransaminasemia of variable degree with predominance of the cholestasis enzymes as well as alterations in the coagulogram due to the affectation in the absorption of vitamin K, elevation of cholesterol, triglycerides, serum bile acids and a decrease in the concentration of fat-soluble vitamins [5].

The cardiovascular alteration most frequently found in these cases is atresia or stenosis of the peripheral pulmonary artery (75%), however in this patient it did not appear. Other associated cardiovascular abnormalities can be tetralogy of Fallot, defects of the atrial or ventricular septum, stenosis or aortic coarctation.

The presence of severe congenital heart disease can lead to early death [5-8]. Two forms of AS are considered: the complete one, if it presents the 5 major criteria, and the incomplete one with at least 3 major criteria (one of them being cholestasis) [8].

In the case presented, all the major criteria of the disease were present. The most frequent ocular manifestation is the posterior ocular embryotoxon, which occurs in 90% of patients with AS, as occurred in this patient. Other ophthalmological abnormalities described are microcornea, keratoconus, congenital macular dystrophy and cataracts [5].

The presence of the vertebrae in butterfly wings are the result of failure in the fusion of the anterior vertebral arches and may be associated with other congenital skeletal abnormalities such as spina bifida, fusion of vertebrae, hemi-vertebrae, absence of the 12 rib and craniosynostosis. Skeletal changes acquired by osteoporosis can be found, which can become severe and cause pathological fractures [9-10].

Other causes of cholestasis that may present in the infant stage, such as extrahepatic bile duct atresia, progressive familial intrahepatic cholestasis, and cholestatic neonatal hepatitis, should be considered in the differential diagnosis of AS.

The presence of supernumerary interdigital palm folds is also reported in the literature. The presence of this clinical finding has been associated with the JAG1 gene mutation [9].

Once this disease is diagnosed, an adequate diet should be indicated, which can be enriched with formulas with Medium Chain Triglycerides (MCT), fat-soluble vitamins, Zinc, adequate supply of calcium, pancreatic enzymes and ursodeoxycholic acid. Liver transplantation may become indicated in 20-30% of patients. Adequate genetic counseling should also be provided to parents [9].

References

1. Bravo Angelo, Astudillo Carlos. Severe aortic stenosis in a patient with Alagille syndrome. *Rev Chil Cardiol.* 2015 ; 34: 214-219.
2. Diniz Bruna L, Floriani Maiara A, Ferreira Maria Angélica T, Gonzales João Francisco O., Lisboa Nathan H., Jakimiu André Ricardo et al. Aumento de los niveles de quitotriosidasa en un paciente con síndrome de Alagille: ¿asociación o coincidencia? *J. Bras. Patol. Medicina. Laboratorio.* [Internet]. Febrero de 2018 [consultado el 29 de marzo de. 2020; 54: 37-39.
3. Spinner NB, Gilbert MA, Loomes KM, et al. Alagille Syndrome. 2000. Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
4. Di Pinto Diana, Adragna Marta. Anomalías renales en niños con síndrome de Alagille. *Arch. argent. pediatr.* 2018; 116: 149-153.
5. Ortiz-C Lidia María, Samudio-D Gloria Celeste. Síndrome de Alagille. *Presentación de un caso. Pediatr. (Asunción).* 2014 ; 41: 51-56.
6. Sara I. Marín Urueña, M. Mar Montejo Vicente, José Antonio Garrote Adrados. JAG1Alagille syndrome with atypical phenotype diagnosed by molecular tests: unreported JAG1 mutation. *Medicina Clínica.* 2017; 149; 462.
7. Ortega Pérez SN, González Santana D, Ramos Varela JC, Cañizo Fernández D, Peña Quintana L. Síndrome de Alagille; una patología que tener en cuenta. *Rev Pediatr Aten Primaria* [Internet]. 2017; 19: 267-270.

8. Sara González Pastor, Montserrat Montraveta Querol, Ricard del Alcazar Muñoz, María Isabel Ojanguren Sabán, Guillem Pintos Morell, Jesus Quintero Bernabeu, Javier Juamperez Goñi, Margarita Sala Llinas. Alagille syndrome associated with intestinal atresia. *Gastroenterología y Hepatología*. 2016; 39: 667-668.
9. Han S, Jeon TY, Hwang SM, Yoo SY, Choe YH, et al. Imaging findings of Alagille syndrome in young infants: differentiation from biliary atresia. *The British journal of radiology*. 2017; 90: 20170406.
10. Kamath BM, Baker A, Houwen R, Todorova L, Kerkar, N. Systematic Review: The Epidemiology, Natural History, and Burden of Alagille Syndrome. *Journal of pediatric gastroenterology and nutrition*. 2018; 67: 148–156.