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CASE REPORT

Gastrointestinal bleeding as the first manifestation of Alagille syndrome - Case report

Thayse Packo Campos[1], Patrícia Stambovsky Guimarães Baldanza[1], Maria Angela Bellomo Brandão[1]

Keywords:
Alagille Syndrome, Hemorrhage, Cholestasis, Intrahepatic.

Abstract

Introduction: The aim of this report is to describe a case of gastrointestinal bleeding that started at 1 month of age in a patient with Alagille Syndrome. **Case report:** Patient started recurrent gastrointestinal bleeding, leading to hypovolemic shock in the second month of life. During the investigation, cholestasis and incoagulable INR were evidenced. The facial stigmata, associated with the posterior embryotoxon in the ophthalmologic examination and transthoracic echocardiogram with stenosis of the pulmonary branches and patent foramen ovale, suggested the hypothesis of Alagille Syndrome, later confirmed by compatible liver biopsy and genetic testing with a mutation in the JAGGED1 gene. After administration of vitamin K, the patient evolved with normalization of the coagulogram, without new episodes of gastrointestinal bleeding. At follow-up, replacement of fat-soluble vitamins and treatment with ursodeoxycholic acid were initiated. **Discussion:** Reports in the literature describe bleeding episodes in patients with Alagille Syndrome, however, the main site of bleeding is the central nervous system. There is no description of bleeding in the gastrointestinal tract as the initial and neonatal manifestation of the syndrome. The case reported is an uncommon form of presentation and shows the importance of diagnostic suspicion in cases of neonatal cholestasis with gastrointestinal bleeding, allowing for adequate treatment and improved prognosis.

[1] Universidade Estadual de Campinas, Departamento de Gastroenterologia e Hepatologia Pediátricas - Campinas - São Paulo - Brazil.

Correspondence to:
Thayse Packo Campos.
Universidade Estadual de Campinas. Rua Vital Brasil, 80. Cidade Universitária Zeferino Vaz. CEP 13083-888. Campinas/SP, Brasil E-mail: thaysepacko@gmail.com

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INTRODUCTION

Digestive bleeding (DB) is a rare event in the first months of life, with an increase in the percentage of cases as age progresses[1] . The most common causes in infants include cow's milk allergy, esophagitis, and Mallory Weiss tears. Some diseases with a more insidious/silent evolution can become risk conditions for bleeding and will often only be identified after an episode of DB, as it happens in coagulation disorders - hemorrhagic disease of the newborn and hemophilia, as well as in liver disorders that lead to portal hypertension, or even congenital changes in the gastrointestinal tract, such as intestinal duplication or Meckel's diverticulum[2]. Hepatobiliary diseases that lead to cholestasis in the neonatal period can manifest, very rarely, with digestive hemorrhage secondary to vitamin K deficiency. Among these diseases, we can mention Alagille Syndrome[3] . The objective of this report is to describe a case of digestive bleeding that began at 1 month of life in a patient with Alagille Syndrome.

CASE REPORT

Male patient, born at 35 weeks of gestational age by cesarean section and weighing 2,195 grams, was undergoing medical follow-up due to unsatisfactory weight gain (less than 10 grams/day) and jaundice, with an instruction to sunbathe. Upon completing 1 month of life, he started vomiting and had dark stools, progressing to small amounts of bloody content. After 1 week, he had 3 episodes of moderate hematemesis, when he was taken to the Emergency Room. He was admitted in regular general condition, pale 3+/4+, jaundiced 2+/4+, dehydrated +/4+, irritated, with slow capillary refill time, weight of 2,390 grams, presenting hematemesis during the evaluation, in addition to holosystolic murmur radiating to the back. Initial tests showed hemoglobin of 4.7 g/dL, incoagulable coagulogram and cholestasis (total bilirubin (BT) 7.01 mg/dL and direct bilirubin (BD) 3.79 mg/dL). He received intravenous hydration, packed red blood cells, fresh frozen plasma and vitamin K – which controlled the bleeding and stabilized the patient. The investigation of neonatal cholestatic syndrome was carried out, with tests described in tables 1 and 2. Due to facial stigmata, an ophthalmological examination was carried out, with fundus analysis and slit lamp analysis. The patient had posterior embryotoxon and optic disc changes with papilledema. The chest x-ray was unremarkable. The transthoracic echocardiogram showed stenosis of pulmonary branches and patent foramen ovale. A liver biopsy was performed, which showed moderate to intense canalicular and intrahepatic cholestasis, foci of extramedullary erythropoiesis and focal gigantocellular transformation of hepatocytes; focal ductopenia; Kupfferian grade 2 siderosis. The set of findings above was compatible with the diagnosis of Alagille Syndrome. After 13 days of hospitalization, he was discharged using vitamin A, D and E, multivitamins and mixed breastfeeding with 1% medium chain triglycerides (MCT). During outpatient follow-up, he maintained clinical signs of cholestasis, and after one month, ursodeoxycholic acid was started. The patient improved and after 6 months, tests showed BT 1.63 mg/dL and BD 0.87 mg/dL. A cholestasis genetic panel was carried out, which identified a heterozygous variant in the JAGGED1 gene (jagged canonical Notch ligand 1, OMIM* 601920), confirming the diagnosis of Alagille Syndrome.

DISCUSSION

Alagille syndrome is a predominantly hereditary disease, resulting from mutations in the Jagged1 gene, which involves several systems, including the liver, heart, eyes, face and skeleton. Its main clinical manifestations involve cholestasis secondary to the scarcity of intrahepatic bile ducts, congenital heart defects mainly in the pulmonary arteries, butterfly vertebrae, defects in the anterior chamber of the eye, typically posterior embryotoxon and facial dysmorphism[4] . To diagnose the syndrome, it is necessary to identify at least three of these changes. The patient described in the report presented such characteristic findings, except for the change in the vertebrae. There are reports, less frequent, of other clinical findings such as renal malformations, pancreatic insufficiency and vascular malformations. These vascular anomalies have been observed since the first descriptions of the syndrome, previously known as arteriohepatic dysplasia, and may be a risk factor for bleeding[5] . Other causes of bleeding are due to the intense cholestasis presented by these patients, which leads to vitamin K deficiency, or even secondary to cirrhosis, which can lead to portal hypertension. In the case presented, the patient presented bleeding from the gastrointestinal tract and very altered coagulation rates, probably due to vitamin K deficiency, resulting from cholestasis and also low weight gain. Given this manifestation in newborns, the hypothesis of hemorrhagic disease of the newborn and hemophilia must be excluded. In the present case, such hypotheses would not justify the increase in bilirubin at the expense of direct bilirubin nor the increase in liver transaminases. Lykavieris et al. demonstrated that the main site of these bleeds is the central nervous system, but hemorrhages in other locations can occur and are an important cause of morbidity and mortality[6]. There are no reports in the literature of bleeding in the gastrointestinal tract as an initial and in the neonatal period in the Alagille syndrome. The present report is an unusual form of presentation and shows the importance of diagnostic suspicion in cases of neonatal cholestasis, especially in association with other findings, enabling adequate treatment, with improved prognosis.

Table 1. Complementary tests.

Test	Upon admission	2 days after	Reference value for the age range
Total bilirubin (TB)	7.01 mg/dL	--	Up to 1.2 mg/dL
Direct bilirubin (DB)	3.79 mg/dL	--	Up to 0.2 mg/dL
Alanine aminotransferase (ALT)	54 U/L	51 U/L	0-50 U/L
Aspartate aminotransferase (AST)	96 U/L	82 U/L	15-60 U/L
Creatinine	0.52 mg/dL	0.38 mg/dL	0.4-0.7 mg/dL
Gama Glutamyl transferase (GGT)	184 U/L	146 U/L	1-39 U/L
Prothrombin time (PT) INR Activated partial thromboplastin time (aPTT)/ratio	Uncoagulable	12,1 seg 1,04 0,78	Up to 1.25 Up to 1.30
Hemoglobin / Hematocrit	4.70 g/dL / 14.3 %	7.1 g/dL / 21.1 %	12-16 g/dL / 36-48 %
Leukocytes / Platelets	28.730 / 505.000	16.570 / 593.000	4-10 / 150.000-400.000
Alpha-fetoprotein	1334 ng/mL	--	Up to 7.0 ng/mL
Alpha-1-antitripsin	1.23 d/L	--	0.9-2.0 g/L
25-OH-Vitamin D	17.5 ng/mL	--	Higher than 20 ng/dL
Vitamin B12	551.6 pg/mL	--	197-771 pg/mL
Abdomen ultrasound	Liver of normal size, regular contours, thin edges, normal echogenicity and homogeneous echotexture, without focal lesions detectable by the method. Portal and hepatic veins with preserved calibers and walls, without evidence of thrombi. Anechoic image in the gallbladder fossa that may correspond to a partially contracted gallbladder due to the short period of fasting, and the possibility of a finding related to the condition/ clinically informed suspicion cannot be excluded. There is no dilatation of intra- or extrahepatic bile ducts evident with the method. Preserved spleen size, contour and echotexture, without focal lesions.		

Table 2. Serologies

Serology	Result
Syphilis (Treponema test)	Non-reactant
Hepatitis A (Anti-HAV)	Reactant IgG / Non-reactant IgM
Hepatitis B (HbsAg and Anti-HBC)	Not reactant
Hepatitis C (Anti-HCV)	Not reactant
Cytomegalovirus	Reactant IgG / Not reactant IgM
Rubella	Not reactant IgG / Not reactant IgM
Toxoplasmosis	Reactant IgG / Not reactant IgM

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