Alagille Syndrome - a case report

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Abstract
Alagille syndrome is an autosomal dominant disease that affects 1 in every 30,000 births, equally affecting both sexes. It is characterized by abnormalities in the liver, heart, eyes, face, and skeleton. The main clinical manifestation of Alagille syndrome is cholestasis, which is commonly associated with other clinical signs: heart disease, skeletal abnormalities, eye abnormalities, and facial dysmorphism. Typical facial changes include sunken eyes, broad forehead, prominent chin, bulbous nose, and small or malformed ears. It is known that a range of diseases presents with cholestasis, and differential diagnosis is a challenge for the pediatrician. Cytomegalovirus (CMV) infection should be a part of the differential diagnosis. In the present case, the diagnosis of Alagille syndrome was delayed by the presence of CMV infection. It is important to be familiar with this syndrome, so that this diagnosis is considered in patients who present some physical and morphological characteristics, in addition to jaundice. Acronyms: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; INR = international normalized ratio; PT = Prothrombin Time ; PT-INR = Partial Thromboplastin Time; DBil and TBil = Direct & Total Bilirubin.

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INTRODUCTION

Cholestasis results either from a reduction in the synthesis of bile acids or from an intra- or extra-hepatic blockage of the excretion of bile components into the small intestine. It is the main manifestation of hepatobiliary disease, which is clinically manifested by choloria, acholic or hypocholic stools, jaundice, pruritus, and xanthomas. Laboratory findings are increased blood levels of bile acids and direct bilirubin; increased transaminase, alkaline phosphatase, and gammaglutamyltransferase activities; and hypercholesterolemia. Histopathological findings are the presence of bile pigments in the cytoplasm of hepatocytes and in the lumen of bile canaliculi, ductules, and ducts, often associated with secondary cell injury.¹

Alagille syndrome is an autosomal dominant disease that affects 1 in every 30,000 live births, affecting both sexes equally. It is associated with a defect in the JAGGED1 gene.² It is characterized by abnormalities in the liver, heart, eyes, face, and skeleton. The main clinical manifestation of Alagille syndrome is cholestasis (resulting from the paucity of intrahepatic bile ducts), and it is commonly associated with other clinical signs: heart disease, skeletal abnormalities, ocular abnormalities, and facial dysmorphism. Typical facial alterations include sunken eyes, wide forehead, prominent chin, bulbous nose, and small or malformed ears.

Several diseases can present cholestasis as a symptom; therefore, differential diagnosis continues to pose a challenge for pediatricians. An example of such a disease is cytomegalovirus (CMV) infection, for which cholestasis is also the main symptom.

In this case report, we present a patient in whom the diagnosis of Alagille syndrome was delayed due to the presence of CMV infection.

Thus, the pediatrician, who is the first to see the patient, must be familiar with the various diseases that can present with cholestasis and be aware of cases in which their symptoms overlap, which can complicate the diagnosis of the underlying disease, thereby preventing timely and appropriate treatment.

It is important to be familiar with Alagille syndrome, so that its diagnosis can be suspected when a patient presents specific physical and morphological features, in addition to jaundice.

CASE REPORT

A patient from Corumbá, State of Mato Grosso do Sul, Brazil, was admitted to the Mato Grosso do Sul Regional Hospital (HRMS), in the state capital city of Campo Grande, at the age of 5 months, with a history of jaundice since birth, with progressive worsening, associated with episodes of acholic stools, choloria, and abdominal distension. The past medical history is as follows: the patient was born by cesarean delivery (indicated because his mother had undergone three previous cesarean deliveries), at term (gestational age: 38 weeks), without any complications during childbirth or pregnancy. Discharged 3 days after birth, the patient underwent phototherapy and received antibiotics for an infection. The patient was born from consanguineous parents with no familial diseases.

Upon discharge, the patient was referred for outpatient follow-up. In the first medical visit, serology tests were requested for the detection of perinatal infection. The patient presented reactive CMV IgM and IgG results and was referred to Campo Grande for treatment. Upon admittance to HRMS, the patient presented jaundice (zone 4), xanthomas, hepatomegaly, and systolic murmur on auscultation.
Admission laboratory testing showed the following results: hemoglobin: 9.5 g/dL, hematocrit: 31%, leukocytes: 11,600/mm³, band cells: 1%, segmented cells: 11%, lymphocytes: 80%, monocytes: 7%, eosinophils: 1%, platelets: 358,000/mm³, AST: 370 U/L, ALT: 324 U/L, PT-INR: 0.99, Tbil: 7.28 mg/dL, DBil: 6.06 mg/dL, GGT: 1,208 U/L, total protein: 6.9 g/dL, albumin: 3.7 g/dL, and globulin: 3.2 g/dL. Abdominal ultrasound showed mild hepatomegaly, and an echocardiogram showed a perimembranous ventricular septal defect without considerable significance at that time. New samples for serology were collected and sent for detecting CMV through the polymerase chain reaction technique. The blood sample was CMV reactive, and urine was CMV positive. Given these results, treatment for CMV infection was initiated with ganciclovir, after evaluation by the infectious disease specialist. During treatment, the patient developed a neutropenic episode, which resulted in discontinuation of the treatment for 5 days until normalization. The full treatment lasted for 42 days.

Once the treatment was established, the patient had an overall health status improvement, but a persistent increase in transaminase and bilirubin levels. Laboratory testing showed the following results: hemoglobin: 10 g/dL, hematocrit: 31.20%, leukocytes: 12,000 mm³, band cells: 0%, segmented cells: 22%, lymphocytes: 72%, monocytes: 2%, eosinophils: 4%, platelets: 602,000/mm³, AST: 299 U/L, ALT: 229 U/L, INR: 0.89, Tbil: 6.65 mg/dL, and DBil: 5.57 mg/dL. With these results and the presence of a few signs, the previously raised hypothesis of Alagille syndrome became more consistent. The patient presented dysmorphic facies (protruding forehead, sunken eyes with slight hypertelorism, pointed chin, and flat nose with a bulb-shaped tip) and cardiovascular abnormalities (ventricular septal defect and pulmonary branch stenosis). The patient resumed the treatment with ganciclovir and was later referred to another institution for further investigation. In Menino Jesus Hospital, in São Paulo, the patient was diagnosed with Alagille syndrome and is being regularly monitored, with continuous administration of ursodeoxycholic acid to control the symptoms of cholestasis. A liver transplant has been scheduled due to difficulty in controlling the symptoms, as the patient had persistent jaundice associated with intense pruritus and drug-resistant hypercholesterolemia, with pending cardiac stabilization.

**DISCUSSION**

The diagnostic challenge in newborns and infants with cholestasis is explained by the number of extra- and intrahepatic conditions clinically manifested by jaundice via direct hyperbilirubinemia, mostly without evidence indicating a specific diagnosis.

The differentiation between intrahepatic and extrahepatic causes is of great importance because extra-hepatic disorders can be surgically treated, which, if done early, can prevent permanent liver damage and improve patient survival.

Intrahepatic cholestasis may be of viral, metabolic, or toxic etiology. It can also be secondary to bile secretion abnormalities as a result of hepatocyte dysfunction or abnormal excretion due to an anatomical anomaly of the biliary tract. The latter, referred to as paucity of intrahepatic bile ducts, accounts for approximately 6.7% of the causes for intrahepatic cholestasis.

Interlobular bile duct hypoplasia exists in two forms: syndromic (Alagille syndrome or arteriohepatic dysplasia) and non-syndromic. The two forms are primarily distinguished by the best prognosis of the former in comparison to the latter, as well as by typical clinical findings in the case of Alagille syndrome. From a histopathological viewpoint, bile duct hypoplasia is characterized by a ratio between the number of interlobular bile ducts and the number of portal spaces less than 0.5; however, it is important to remember that in approximately 20% of cases, hypoplasia is only defined after 6 to 12 months of life.

Alagille Syndrome is a rare condition (1:40,000 to 1:100,000 live births) of autosomal dominant genetic transmission, with a reduced penetrance and variable expressivity, related to microdeletions of the short arm of chromosome 20. A large number of patients have no family history of the disease, which reflects the incomplete penetrance of this syndrome, in addition to the possibility of a new genetic mutation. It is characterized by five major signs: chronic cholestasis (temporary, persistent, or intermittent jaundice; pruritus starting at 6 months of age; and xanthomas in friction areas), dysmorphic facies (protruding forehead, sunken eyes with slight hypertelorism, pointed chin, and flat nose with a bulb-shaped tip), cardiovascular anomalies (peripheral pulmonary artery stenosis, present in 90% of cases, associated or not associated with complex anomalies), vertebral defects (buttock vertebrae), and posterior embryotoxon (present in 10% of the general population; it is the thickening of the line formed by Descemet’s membrane and the angle of the anterior chamber of the eyeball, visible with a slit lamp or through gonioscopy). Facial dysmorphism and butterfly vertebrae can be better characterized in older patients. The syndrome is considered complete when at least four signs coexist, whereas the presence of only three of them characterizes the syndrome as incomplete. The levels of the enzymes alkaline phosphatase and gamma-glutamyltransferase are very high in most cases. Cholesterol levels can be up to 3,000 mg/dL in 10% of patients with Alagille syndrome. The course of cholestasis is variable and often exacerbated during a viral infection. Pruritus, xanthomas, and neuromuscular symptoms resulting from vitamin E deficiency are responsible for morbidity.

CMV infection also features cholestasis, and CMV is described as the most frequent viral etiologic agent of maternal–fetal transmission. Most infections occur by maternal prime infection during pregnancy, but they can also occur in previously immune pregnant women by reinfection or viral infection.
reactivation. The child may be contaminated by the virus transplacentally or intracervically during childbirth and through breast milk. Only 10% of children present the symptomatic form of the disease. The clinical picture includes hepatomegaly, jaundice, anemia, chorioretinitis, and strabismus. Laboratory tests show increased transaminase and bilirubin levels. Diagnostic tools include polymerase chain reaction, in which the viral nucleic acid is identified and amplified; detection of specific antibodies; and viral isolation, immunohistochemistry, and immunocytology.

In the present case, given the positive results for both the presence of IgM antibodies and the detection of viral nucleic acid, the treatment for CMV infection was instituted. Even after proper treatment, the patient’s laboratory tests remained abnormal. This, associated with the patient’s physical characteristics and the presence of cardiac impairment, led to the suspicion of a diagnosis of Alagille syndrome, which was later confirmed. In this syndrome, indication for transplant is generally based on the need to improve the child’s quality of life, which is undermined by cholestasis, pruritus, frequent fractures, malnutrition, and hyperlipidemia. The timing of the transplant must be individualized; if the child shows no signs of liver failure or portal hypertension complications, he/she can wait until over 3 years of age to achieve better transplant tolerance. In the present case, a liver transplant was indicated to improve the patient’s quality of life.

For the procedure to take place, the patient awaits cardiac stabilization. In the meantime, the patient has been administered ursodeoxycholic acid and antihistamines to control the symptoms.

In this case, the presence of CMV infection delayed the diagnosis of Alagille syndrome.

CONCLUSION

Cholestatic syndrome in infancy is one of the biggest diagnostic challenges faced by pediatricians. Pediatricians, who first see the patient, must be familiar with the several diseases involved to facilitate an early diagnosis.

Overlapping conditions can often complicate the diagnosis of the underlying disease, as in the case described herein. Alagille syndrome must be part of the differential diagnosis in patients who, in addition to jaundice, present physical and morphological characteristics that characterize the syndrome. The patient’s partial improvement, even with proper treatment, drew attention to the syndrome again. Treatment is most often based on the control of signs and symptoms, and liver transplants will be required for some patients for controlling symptoms. In the present case, a liver transplant was indicated due to the difficulty in controlling the symptoms.

REFERENCES
