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BILIARY TRACT ATRESIA ASSOCIATED WITH ALAGILLE SYNDROME AT THE PAEDIATRICS DEPARTEMENT OF RABAT: CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT
Biliary atresia is a frequent cause of neonatal cholestasis, characterized by intra- and extra-hepatic bile duct obstruction. Alagille syndrome, an autosomal dominant multisystemic disorder, may be clinically indistinguishable from biliary atresia in the neonatal period. We report the case of a child with Alagille syndrome, with a history of biliary atresia. and confirmation of Alagille syndrome on the basis of clinical, paraclinical and genetic criteria, including a missense mutation of the JAG1 gene. Confirmation of the clinical diagnosis of Alagille syndrome in patients without biliary atresia by the discovery of new pathogenic mutations in the JAG1 gene is not surprising. However, the role of JAG1 mutations in the etiology of biliary atresia remains unclear. Our results do not confirm the association of biliary atresia with JAG1 mutations. In conclusion, mutational analysis of JAG1, in addition to liver histology, could be useful in diagnosing the "grey zone" of patients with Alagille syndrome initially presenting as biliary atresia in early childhood. Early molecular diagnostics should be considered in selected cases of overlapping Alagille syndrome and biliary atresia.

KEYWORDS: Biliary atresia, Neonatal cholestasis, Alagille syndrome, JAG1 gene mutation.

INTRODUCTION

Alagille syndrome is a complex autosomal dominant multisystemic disease with incomplete penetrance, clinically defined by the association of at least three of five main features: chronic cholestasis, congenital heart disease, skeletal anomalies (typically butterfly-wing vertebrae), ocular anomalies (mainly posterior embryotoxon) and peculiar face. Genetically, it is characterized by heterozygous mutations in the JAG1 gene.[1,2] or, more rarely, in the NOTCH2 gene.[3]

Biliary atresia is a frequent cause of neonatal cholestasis, defined as an occlusive panductular cholangiopathy affecting both the intra- and extra-hepatic bile ducts.[4] The etiology of biliary atresia remains unknown, although genetic background may play a role in some cases.[5-8] Prompt diagnosis and treatment are essential, as the effectiveness of surgical reconstruction of the extrahepatic bile ducts by porto-enterostomy (Kasai procedure) decreases with patient age.[9] Most patients require liver transplantation at an older age.

Alagille syndrome can sometimes be difficult to distinguish from biliary atresia in the neonatal period, due to the variability of the syndrome's clinical expression, which can result in minimal or subclinical disease. Mutations in JAG1 have been identified in a subgroup of patients with biliary atresia.[6,7] although their specific contribution to clinical symptoms and disease course remains to be clarified. Moreover, some patients with Alagille syndrome are probably misdiagnosed as suffering from biliary atresia because of this variability.[10]

In this study, we report the case of a patient with both biliary atresia and Alagille syndrome, confirmed by clinical and paraclinical criteria. Our aim is to discuss the diagnostic and therapeutic challenges associated with this rare clinical presentation, as well as to highlight the importance of early and accurate recognition of both conditions to improve patient outcomes.

PATIENT AND OBSERVATION

This is a 2-year-old child admitted for hepatic cholestasis, with a history of biliary atresia operated on at the age of 3 months. She had no family history of liver disease or neonatal cholestasis, and no notion of consanguinity. Clinical examination revealed diffuse mucocutaneous jaundice, a distinctive facies with a rounded forehead, sunken eyes and pointed chin, and a 3-standard-deviation delay in staturo-ponderal development. The child was in

good hemodynamic condition, with hepatomegaly (14 cm liver arrow) and splenomegaly measuring 2 finger-breadths. Cardiovascular examination revealed a systolic murmur radiating to all four foci, with no straight signs, gallop sounds or pericardial friction, and pleuropulmonary examination was normal. Paraclinical examinations showed hemoglobin at 11 g/dl, WBCs at 8,000 e/mm³, thrombocytopenia at 124,000 e/mm³, and a disturbed hepatic workup with AST at 351 IU/l, ALT at 245 IU/l, PAL at 350 IU/l, GGT at 200 IU/l, total bilirubin at 245 mg/l, conjugated bilirubin at 240 mg/l, albumin at 41 g/l, PT at 72%, APTT at 1. 4, factor V 48%, alpha-fetoprotein 1583 IU/ml, gamma-globulins 16.6 g/l, IgG 12 g/l, TG 3.6 g/l, and cholesterol 2.36 g/l. Renal function tests were normal, with urea at 0.23 g/l and creatinine at 2.5 mgl. Abdominal ultrasound and Doppler revealed a cirrhotic liver with splenomegaly and copious abdominal effusion. Cardiac ultrasonography showed pulmonary stenosis, tricuspid insufficiency and aortic dextroposition, and ophthalmological examination revealed a 360-degree posterior embryotoxon... Genetic testing favored a missense mutation in the JAG1 gene. The diagnosis of Alagille syndrome was made on the basis of clinical and paraclinical criteria.

The patient was put on liposoluble vitamin supplementation (ADEK), ursodeoxycholic acid and rifampicin.

DISCUSSION

The confirmation of the clinical diagnosis of Alagille syndrome in patients without biliary atresia by the discovery of new pathogenic mutations in the JAG1 gene is not surprising. However, the role of JAG1 mutations in the etiology of biliary atresia remains unclear. Given that a defect in Jagged1/Notch-2 signaling is responsible for the transdifferentiation of hepatoblasts into biliary epithelia[11] and that mutations in JAG1 or NOTCH2 are known to cause Alagille syndrome type 1 and 2, respectively, the association of JAG1 with biliary atresia reported by Kohsaka et al.[4] would be plausible. These authors found 9 missense mutations present in 11 of 102 patients with biliary atresia, 28 of whom underwent liver transplantation before the age of 5. None of the mutation carriers developed the typical clinical features of Alagille syndrome before the age of 5. According to the first hypothesis presented in[4], patients with biliary atresia and JAG1 deficiency could represent an atypical Alagille syndrome whose clinical features are not fully expressed. Furthermore, the mutated Jagged1 protein could affect inflammatory processes in the liver through the regulation of cytokine expression mediated by the Jagged1/Notch-2 pathway.

The association of these missense mutations with Alagille syndrome has also not been reported. This discrepancy may be attributed to differences in the ethnicity of biliary atresia patients studied in Japan, Europe and the USA. Similarly, the role of JAG1 mutations in the genetic etiology of biliary atresia may be questioned. Eight of the 9 mutations reported by Kohsaka et al[4] were identified in sporadic cases. As the JAG1 gene is not a strong candidate gene for biliary atresia due to the sporadic incidence of the disease, the reported presence of rare missense mutations in the JAG1 gene does not unequivocally prove the genotype-phenotype correlation.

One of the main diagnostic features of Alagille syndrome is biliary ductular sparseness, which is more common in late infancy and childhood.[12-13] Ductular proliferation is present in a small number of infants with Alagille syndrome, leading to significant diagnostic confusion. Due to the variability of early liver histopathology in Alagille syndrome, a number of patients have been misdiagnosed as having biliary atresia.[12, 14, 15] Surgical reconstruction of the extrahepatic biliary system in patients with Alagille syndrome does not correct the loss of bile ducts within the liver, and liver transplantation is preferred. Therefore, early molecular diagnostics could be considered in selected cases of Alagille syndrome and overlapping bile duct atresia.

CONCLUSION

In our cases do not confirm the association of biliary atresia with JAG1 mutations. In addition to liver histology, mutational analysis of JAG1 could be useful in diagnosing the "grey zone" of patients with Alagille syndrome presenting initially as biliary atresia in early childhood.

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