Alagille Syndrome

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KEYWORDS

• *JAG1* • *NOTCH2* • Pediatric • Cholestasis • Liver transplant

KEY POINTS

- Alagille syndrome (ALGS) is a multisystem disorder with variable phenotypic penetrance caused by heterozygous mutations in 1 of 2 genes that are fundamental components of the Notch signaling pathway, *JAGGED1* (*JAG1*) and *NOTCH2*.
- Features of the syndrome include characteristic facies, bile duct paucity, chronic cholestasis, and abnormalities in cardiac, renal, vascular, skeletal, and ocular systems.
- Indications for transplantation include severe pruritus, liver synthetic dysfunction, portal hypertension, bone fractures, and growth failure.
- Genotype-phenotype correlation studies have not shown a link between mutation type and clinical manifestation or severity, leading to the hypothesis that a second gene could function to modify the effects of a *JAG1* or *NOTCH2* mutation. Several candidate genetic modifiers have been identified in animal and human studies.
- Current therapies for ALGS patients are supportive and focus on clinical manifestations. 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.

INTRODUCTION

Alagille syndrome (ALGS) is an autosomal dominant, multisystem disorder with variable phenotypic penetrance that was first described in 1969 by Daniel Alagille. 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, skeletal abnormalities, and characteristic facial features. Although not currently included in the diagnostic criteria, patients also have a high prevalence of renal and

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vascular disease. Early approximations based on the diagnosis of cholestasis in infants estimated the frequency as 1 in 70,000 live births. Molecular diagnosis, however, has increased the number of cases detected and the true incidence is probably closer to 1 in 30,000.[1]

ALGS is caused by various mutations in JAGGED1 (*JAG1*), which encodes the ligand Jagged1 in the Notch signaling pathway.[2,3] A majority of patients have a detectable mutation in JAG1 (more than 90%), but there is also a smaller percentage with mutations in *NOTCH2*.[4,5] The same genetic mutation often has different phenotypic characteristics within the same family. There is ongoing investigation into the genetic modifiers of this disease to further elucidate the relationship between genotype and phenotype.

CLINICAL FEATURES

Hepatic

Initial reports of ALGS identified patients based on bile duct paucity. As more has been learned about the disease, it has been shown that although hepatic involvement is common, it is not always present. More recent reports found cholestasis in only 89% of patients and bile duct paucity in 75%.[6] Cholestasis can vary from mild to severe. Hepatitis, if present, is usually mild and synthetic dysfunction is rare. Bile salt levels can be elevated even with normal bilirubin. Bile ducts are also damaged with elevations in alkaline phosphatase and gamma glutamyltransferase. 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.[7,8] Because the mechanism for resolution is poorly understood, it can be difficult to predict which children will improve and which will go on to develop cirrhosis. Total bilirubin above 6.5 mg/dL, conjugated bilirubin above 4.5 mg/dL, and cholesterol above 520 mg/dL under the age of 5 are predictors for sustained and more severe liver disease.[9]

In a recent prospective study of liver disease outcomes in ALGS, the morbidity was much higher than previously reported.[7,10] The cohort was limited to those patients presenting with cholestasis, but 50% had ascites, 25% had at least 1 episode of variceal bleeding, and only 20% survived childhood with their native liver.[11]

There are many complications of chronic cholestasis and some of the most bothersome to children include pruritus and xanthomas. Pruritus also develops early and is often more severe than the degree of cholestasis as measured by laboratory indicators. Intractable itching can be 1 of the most debilitating symptoms of this disease. Patients with impaired bile secretion also have reduced secretion of cholesterol. Cholesterol levels can be more than 1000 mg/dL to 2000 mg/dL, often resulting in the formation of xanthomas. These lesions typically develop over the first few years of life and resolve as cholestasis improves.

Histopathology

Bile duct paucity is the most consistent feature of ALGS (**Fig. 1**C). The normal bile duct to portal space ratio ranges from 0.9 to 1.8. Alagille based his original definition of bile duct paucity as a bile duct to portal tract ratio less than 0.5. It is recommended to examine at least 6 portal tracts to make an accurate diagnosis, but many pathologists require 10 to 20 portal tracts.[12] In 1 large clinical study, bile duct paucity was present in only 60% of liver biopsies done prior to 6 months of age and in 95% of those done after 6 months of age.[7] Ductular proliferation and giant cell hepatitis can also been seen in infancy and have led to misdiagnosis of biliary atresia (**Fig. 1**A, B). The mechanism for the progression of bile duct paucity over the first months of life is unknown but may be