Alagille Syndrome and Other Hereditary Causes of Cholestasis

Jane L. Hartley, MBChB, MRCPCH, MMedSci, PhD[a], Paul Gissen, MD, PhD[b], Deirdre A. Kelly, MD, FRCPI, FRRCP, FRCPCH[a,*]

KEYWORDS

• Conjugated hyperbilirubinemia • Neonatal jaundice • Pruritus
• Hepatosplenomegaly • Fat-soluble vitamins

KEY POINTS

- Conjugated hyperbilirubinemia is always significant and must be investigated.
- Inherited disorders cause a significant proportion of cases presenting with pediatric liver disease.
- It is important to recognize the spectrum of severity in the inherited cholestatic disorders.
- Early and accurate diagnosis helps informed patient management and can prevent deterioration in some patients.
- Genetic diagnosis in all cases improves family counseling and management of future cases.

INTRODUCTION

Neonatal jaundice is common and is transient in most normal infants. Conjugated hyperbilirubinemia is always significant and caused by several diseases, of which extrahepatic biliary atresia (EHBA) is the single leading cause of morbidity and mortality in childhood liver disease.[1] However, recent advances in the understanding of the cause and pathogenesis of cholestasis highlighted the importance of genetic causes of cholestasis.

ALAGILLE SYNDROME

Alagille syndrome (AGS) (MIM118450) is a highly variable, autosomal dominant multisystem condition with an estimated frequency of 1 in 30,000.[2] It was initially described as a hepatic disease, but molecular testing has shown that the liver involvement is variable including no overt liver disease. Those who have significant liver disease present

[a] Liver Unit, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK; [b] MRC Laboratory for Molecular Cell Biology, UCL Institute of Child Health, London, UK
* Corresponding author.
E-mail address: DEIRDRE.KELLY@bch.nhs.uk

Clin Liver Dis 17 (2013) 279–300
http://dx.doi.org/10.1016/j.cld.2012.12.004 **liver.theclinics.com**
1089-3261/13/$ – see front matter

in the neonatal period with conjugated hyperbilirubinemia.[3] Overall, there is a 10% mortality rate from vascular accidents, cardiac disease, and liver disease.[4]

Approximately 95% of patients with AGS have mutations in *JAG1*, which encodes the NOTCH signaling pathway ligand Jagged-1.[5] Jagged/Notch interactions that occur at cell–cell contact points determine cell fate in early development. *NOTCH2* mutations were found to cause AGS in patients who did not have mutations in JAG1,[6] and renal disease is more common in patients with NOTCH2 than JAG1 defects.

There is a lack of genotype–phenotype correlation in AGS, and a range of phenotypes are found in affected members of the same family.[7] Thus, it is likely that additional genetic and/or environmental factors determine the final clinical phenotype. Before molecular testing, AGS was a clinical diagnosis consisting of intralobular bile duct paucity and at least 3 of 5 other major clinical features[8]: cholestasis, cardiac disease with peripheral pulmonary stenosis, skeletal anomalies with butterfly thoracic vertebrae, posterior embryotoxon seen on slit lamp examination of the eyes, and triangular facies.

Clinical Features

Hepatic features

Cholestasis in the neonatal period occurs in 95% of cases[3] but may be mild and not clinically apparent.[2,9] When the cholestasis is severe, it may be clinically difficult to distinguish from biliary atresia. It is essential to make the correct diagnosis, as a Kasai procedure performed in a child with AGS may cause deterioration of liver function.[10] The identification of other AGS clinical features may aid medical management in cases that are difficult to distinguish from biliary atresia.

The liver disease is often associated with severe pruritus, which significantly affects the child's quality of life,[11] and hypercholesterolemia with xanthoma on the extensor surfaces. Xanthoma and pruritus may improve with time.[11] Hepatocellular cancer may develop in those with cirrhosis, and patients should be screened for this condition with abdominal ultrasonography and alpha fetoprotein levels.[12]

Cardiac features

More than 90% of patients with AGS have cardiac anomalies, with the typical cardiac lesion being peripheral pulmonary stenosis (PPS), although most other congenital cardiac lesions have also been associated with AGS (eg, 16% of cases have tetralogy of Fallot).[13] Cardiac disease is an important determinant for early survival.[3]

Skeletal features

Classically, butterfly shape of the thoracic vertebrae is seen because of abnormal fusion of the spine leading to a sagittal cleft in 80% of cases.[14] Other vertebral anomalies may occur such as pointed anterior process of C1, spina bifida occulta, fusion of adjacent vertebrae, hemivertebrae, and absence of 12th ribs. There is no long-term clinical consequence of the vertebral changes. Craniosynostosis[15] and radioulnar synostosis[16] with shortening of the finger distal phalanges and a fusiform appearance may occur. Fractures have been reported in up to 28% of patients with AGS, with the majority affecting the lower limb bones.[17]

Ophthalmologic features

Posterior embryotoxon may be supportive of the diagnosis of AGS, occurring in 90% of cases,[18] but can also be found in up to 15% of the normal population and in other syndromes such as 22q11.2 deletion.[19] It has no long-term visual consequences. Other ocular findings may be iris hypoplasia, abnormalities of the optic discs, abnormal retinal vessels, and pigmentary retinopathy.