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MINI REVIEW

Biliary atresia: Clinical advances and perspectives

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Summary Biliary atresia (BA) is a rare and severe inflammatory and obliterative cholangiopathy that affects both extra- and intrahepatic bile ducts. BA symptoms occur shortly after birth with jaundice, pale stools and dark urines. The prognosis of BA has dramatically changed in the last decades: before the Kasai operation most BA patients died, while nowadays with the sequential treatment with Kasai operation ± liver transplantation BA patient survival is close to 90%. Early diagnosis is very important since the chances of success of the Kasai procedure decrease with time. The causes of BA remain actually unknown but several mechanisms including genetic and immune dysregulation may probably lead to the obliterative cholangiopathy. Current research focuses on the identification of blood or liver factors linked to the pathogenesis of BA that could become therapeutic targets and avoid the need for liver transplantation. No similar disease leading to total obstruction of the biliary tree exists in older children or adults. But understanding the physiopathology of BA may highlight the mechanisms of other destructive cholangiopathies, such as sclerosing cholangitis.

Introduction

Biliary atresia (BA) is a rare disease but is the most common cause of neonatal cholestasis. BA is characterized by an inflammatory obstruction of the biliary tree leading to biliary cirrhosis and early death if untreated. Its etiology remains unclear. The current management of infants with BA combining surgical interventions and medical treatments allows long-term survival for 80—90% of patients [1,2]. The Kasai procedure (hepatoportoenterostomy (HPE) or its surgical variants) is the first surgical step aiming at restoration of the biliary flow. The earlier the Kasai operation is performed, the higher are its chances of success [3]. However, even if the Kasai operation is performed in the first month of life, 60% of children will need a liver transplantation before

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the age of 20 years [2]. When needed, liver transplantation provides an excellent second chance of long-term survival [4,5] with a close to normal quality of life. BA is the main indication for liver transplantation in children. Post-liver transplantation survival has dramatically increased in the past decades and many children with BA have now reached adulthood. However concerns remain, mainly the toxicity of the immunosuppressive therapy (including renal failure, and malignancies) that may jeopardize very long-term survival. The aim of this review is to provide an update on the current knowledge on BA, standard of care, and current directions for research.

Epidemiology

Biliary atresia is a rare disease with a variable incidence worldwide: lower in western countries (ranging from 0.5 to 0.8/10,000 live births), and higher in the Pacific Ocean area (1.1/10,000 live births in Japan and 1.5/10,000 in Taiwan) with a maximal incidence in French Polynesia (3/10,000 live births) [6]. BA is reported in all racial groups in the world, but the incidence is the highest in Polynesians [7] indicating a possible genetic predisposition. BA rarely recurs within families and twins are frequently discordant. This point indicates that if BA has a genetic component, it does not have a classic genetic inheritance. Birth seasonality was suggested for BA [8,9] and particularly in French Polynesia [10] possibly linked to an environmental effect (Fig. 1). But these environmental factors have not been identified yet. BA is likely to be a complex disease involving both genetic and environmental factors.

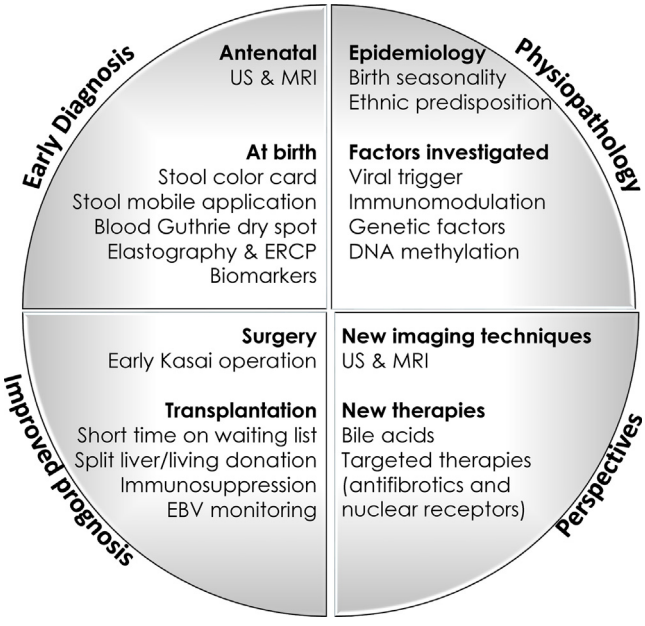

Figure 1 ''Clinical advances and perspectives in biliary atresia''. The main steps for the biliary atresia management are: early diagnosis, improvement of the prognosis by surgical and medical management, a better comprehension of the physiological mechanisms that could lead to perspectives of new treatments and prevention strategies.

Screening and diagnosis

Babies with BA are often at-term with normal birth weight and well thriving. The first symptoms appear in the first weeks of life with jaundice, permanent acholic stools and dark urines. Babies have often an increased inconsistency hepatomegaly. Blood tests demonstrate cholestasis with raised serum conjugated bilirubin (may not be very elevated) and serum bile salts. If other causes of neonatal cholestasis are ruled out (including alpha 1 antitrypsin deficiency) [11], the patient has to be referred for an emergency surgical exploration. The diagnosis of BA is established if obliteration of the extra-hepatic bile duct is observed at surgery and/or at cholangiography, and confirmed by histological analysis of the liver and the biliary remnant. Early diagnosis is a real challenge for the pediatrician. The earlier the Kasai procedure is performed, the greater are the chances of restoring the bile flow [3]. For this reason, screening strategies have been proposed to detect cholestasis and diagnose BA as soon as possible in the neonatal period (Fig. 1). Serum conjugated bilirubin or bile salt in the Guthrie dry-blood spot screening lacks specificity [12]. Urinary urobilinogen testing has been proposed in Egypt for the early detection of cholestatic babies [13]. In several countries, the wide distribution of a stool color card at birth to physicians, caregivers and parents [14—17] allowed earlier referral of infants with cholestasis and was shown to be cost-effective. Recently a mobile application for smartphones has been developed to detect acholic stools in newborns [18], which needs further evaluation. The diagnosis of BA is sometimes easy, for patients with complete cholestasis associated with ultrasonography features of syndromic form [19]. Indeed in almost 10% of cases patients have features of biliary atresia with splenic malformation syndrome (''BASM-syndrome'') associated with situs inversus, polysplenia/asplenia or other various congenital anomalies, and have worse prognosis [20]. Abdominal ultrasound (US) may also show other signs suggestive of BA, such as no visualization of the gallbladder after fasting or the absence of gallbladder empting after feeding, or a cyst at the liver hilum. The sensitivity of the triangular cord sign for the diagnosis of BA at US (echogenic fibrous tissue below the hilar plate anterior to the portal bifurcation) has shown large variations in different studies probably because the fibrosis of the biliary remnant varies among BA patients [21]. The diagnostic accuracy of MRI for BA is poor with a reported specificity of 36% and sensitivity of 99% [22]. MRI-cholangiography does not allow an accurate visualization of the biliary tree in infants younger than 3 months [23] and therefore cannot be used to rule out BA. Endoscopic retrograde cholangio pancreatography (ERCP) has proved effective with high positive and negative predictive values for the diagnosis of BA, but requires a skilled endoscopist and a specific infant endoscope (not available in many centers) [24,25] and general anesthesia. Finally, a liver biopsy maybe helpful for the diagnosis of BA when demonstrating ductular proliferation with bile plugs and portal fibrosis, but these histological changes are not specific and may be missing in very young infants [26]. Ultrasound shear wave elastography has recently been investigated as an additional tool for the diagnosis of neonatal cholestasis. The liver hardness was found more elevated in BA patients as compared