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Biliary Atresia screening: why, when and how?

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Biliary atresia is one of the most important liver diseases in childhood. At an incidence of 1 in 13,000 live births in the United States, it is considered a rare disease; however it is the indication for 40–50% of all liver transplants performed in children (1). It uniquely presents only during the first few months of life, and appears to be a phenotype caused by at least several etiologies, including a proposed perinatal insult which initiates an immune-mediated obliteration of the extrahepatic bile duct lumen and a proposed embryonic or fetal defect in the normal morphogenesis of the biliary tree (2). Outcome is uniformly poor unless a hepatic portoenterostomy (HPE; the Kasai operation) re-establishes bile drainage from the liver into the jejunum and leads to resolution of jaundice. If HPE is not successful or not performed, liver transplantation is the only life-saving alternative. Even with successful HPE, the majority of children will progress to cirrhosis, leaving survival without liver transplantation at only 20% by age 20 years (1). Thus, there is a great need to improve outcomes.

One proposed approach has been to screen infants for biliary atresia at an early age with the goal of instituting the HPE earlier in life. Why this approach? The report by Serinet et al. (3) in this issue of the Journal extends prior reports and shows that HPE in the first month of life (vs. older age) provides the best surgical outcomes and chance of avoiding, or significantly delaying, a liver transplant. Based on this new analysis of data from France, efforts should now be directed towards making the diagnosis of biliary atresia before 30–45 days. However, this is not easily achieved in the United States since most infants are not routinely seen by health care providers between 2 weeks and 2 months of age. HPE results are progressively worse if performed after 60–90 days of age. Moreover, the jaundice of biliary atresia is frequently overlooked in favor of a probable, but incorrect, diagnosis of breast milk-associated jaundice, despite recommendations to check for conjugated (direct) hyperbilirubinemia in infants with jaundice beyond 2 weeks of age (1). Unfortunately, average age at diagnosis of biliary atresia and HPE in the U.S. has not changed over the past 15 years (4). Thus, some form of screening for biliary atresia may be the most effective means to identify infants earlier than the current U.S. average of 60–70 days of life (5). This screening would clearly need to be performed prior to 30–40 days of life so that infants could be further evaluated and undergo HPE by 45 days of life to achieve best results.

The most promising screening method for biliary atresia has been the use of stool color cards to identify lack of stool pigmentation (acholic stools) that typically are present by age 30 days in biliary atresia. In Taiwan, in which a screening program infrastructure is now in place, this has been effective in reducing the average age at diagnosis and age at HPE and increasing the rate of post-operative resolution of jaundice (6), setting the stage for better long-term outcomes. It is important to note that infants in Taiwan have a routine visit to a caregiver at 1 month of age at which time the stool color card is examined, leaving sufficient

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time to initiate the evaluation and HPE for biliary atresia. In the U.S., use of stool color cards at the typical 2 month visit may not significantly bring about earlier diagnosis, however late diagnosis (beyond 90 days of age) could potentially be avoided. Thus, it would be important to determine the cost-benefit and effectiveness of a stool color card screening program in the U.S. in a pilot study in several states. In addition, continued emphasis needs to be placed on obtaining a fractionated bilirubin in all infants jaundiced at 2 weeks of age. The current recommendation of the American Academy of Pediatrics (7) to evaluate for conjugated hyperbilirubinemia if an infant remains jaundiced *at 3 weeks* or beyond will, unfortunately, miss the opportunity for early diagnosis of biliary atresia in most cases because this falls between the routine caregiver visit schedule. Finally, employing modern biotechnology to analyze neonatal samples may lead to identification of new diagnostic biomarkers for biliary atresia, with the potential to develop novel newborn blood spot screening methodologies. Other strategies to improve outcomes should simultaneously be explored. For example, a randomized controlled trial of post-operative corticosteroids is currently underway in the NIH-supported Biliary Atresia Research Consortium (8). Confining and concentrating biliary atresia surgery to the most experienced centers may also improve outcomes, as demonstrated in the United Kingdom (9).

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