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Biliary atresia in Brazil: where we are and where we are going

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Caring for children brings many joys to the day of a pediatrician: sound nutritional guidance to foster growth, immunization to prevent infectious disease, timely use of antibiotics for an acute illness. But the encounter with an infant with jaundice and pale stools breaks a smooth day and heightens the fear of danger: does the infant have biliary atresia? Often, these clinical signs develop in otherwise asymptomatic infants and during a time when parents are enjoying the new family member. Yet, they may represent the hallmarks of a disease of devastating consequences to the infant if untreated. And even when treated, the diagnosis of biliary atresia brings challenging times for the infant, for the family, and for the pediatrician.

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As the most common cause of pathologic jaundice in infants, biliary atresia is an inflammatory cholangiopathy that destroys the epithelial lining of bile ducts, disrupts bile flow, and promotes a fibrosing obstruction of extrahepatic bile ducts. The etiology of biliary atresia is yet to be defined, but the pathogenic mechanisms of the disease are tightly linked to a robust response of the immune system that targets the bile ducts.[1,2] Among the elements of the system, CD8+ and natural killer (NK) lymphocytes have been shown to be key regulators of the biliary atresia phenotype in a mouse model of disease.[3,4]

The clinical and laboratory hallmarks of the disease are jaundice secondary to direct (conjugated) hyperbilirubinemia, pale stools, variable hepatosplenomegaly, high gamma-glutamyl transpeptidase, and a liver histopathology suggestive of biliary obstruction. The final diagnosis is obtained at the time of exploratory cholangiography, which demonstrates obstruction of the extrahepatic bile duct. The only hope to restore bile flow is the resection of biliary remnants and the creation of an intestinal conduit that is anastomosed to the hilum in a roux-en-Y fashion as originally designed by Kasai & Suzuki.[5] Clinical course and treatment response obey the basic principles of illnesses: earlier diagnosis is associated with better response and outcome. The reproducibility of this paradigm across patient populations suggests that the biological basis of clinical phenotype and response to treatment are less influenced by geographical boundaries. If this statement is correct, is it worth studying biliary atresia in individual countries? The article by Carvalho et al.[6] in this issue of Jornal de Pediatria shows that the answer is yes. The article reports the current state of diagnosis and treatment of infants with biliary atresia in Brazil and identifies goals for the future that are tailored to the national clinical practice.

Carvalho et al. reviewed the clinical presentation, treatment, and outcome of 513 children with biliary atresia. The data were obtained from large clinical centers in different geographical regions of Brazil. In general, the clinical presentation with direct hyperbilirubinemia, high gamma-glutamyl transpeptidase, and a histopathology with ductal proliferation and plugs was typical in the cohort. The mean age at diagnosis and portoenterostomy was 82.6±32.8

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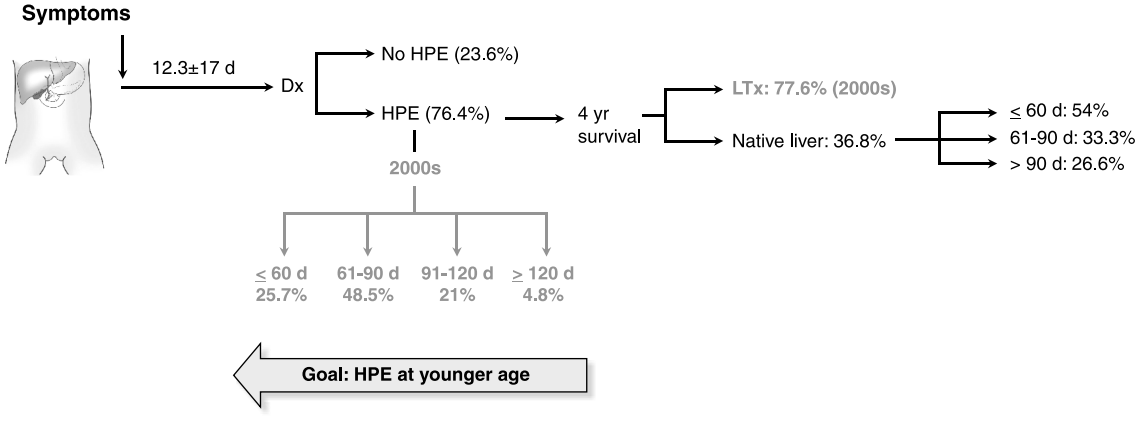
days, with surgery performed in 76.4% of the infants. In those infants treated with portoenterostomy, the 4-year survival with the native liver was 36.8%, with higher survival at 54% if the portoenterostomy was performed in infants ≤ 60 days of age. The combination of portoenterostomy and liver transplantation increased the overall survival to 73.4%. However, only 46.6% of all patients underwent transplantation – a low rate compared to other countries, in which access to transplantation increases to ≥ 60% of children.[7,8]

How do the findings help understand the continuum of care (diagnosis, treatment options, outcome) for infants with biliary atresia in Brazil? First, it is true that the mean age at portoenterostomy at 82.6±32.8 days exceeds the practice in other nations, which is around 60 days.[7,9-11] However, an analysis of the data for the most recent decade (2000 to 2010) in Brazil shows a shift of diagnosis to younger ages, with a greater percentage of infants diagnosed between 61-90 days (48.5 vs. 35% in the 80s) and a lower percentage of diagnosis beyond 120 days (4.8 vs. 20% in the 80s). In agreement with this concept, although a 4-year survival with the native liver for those infants treated with portoenterostomy was reported at 36.8%, survival improved to a robust 54% if the infants were ≤ 60 days at the time of surgery. Thus, there is a real trend to earlier diagnosis during the current decade, which is already translated into a greater number of children surviving with the native liver beyond 4 years.

The study also identifies two areas for future improvement. First, there is almost 2 weeks separating the age at onset of symptoms (12.3±17 days) and the age at portoenterostomy (82.6±32.8 days). While the reasons for such delay in diagnosis and surgical intervention were not obvious, they may have been related to community awareness of the disease, recognition by primary care physicians, and access to specialized care. Pediatric hepatologists have partnered with the Brazilian Society of Pediatrics and the Brazilian Health Ministry to increase community awareness by the incorporation of a stool color card in the Childhealth Booklet distributed by the Ministry to the parents of every neonate. The goal is to aid parents realize that acholic stools (pale, clay-colored stools) is abnormal and seek medical help as soon as the abnormal color is noted – hopefully at early stages of the disease. These are the infants that are presumed to benefit the most from current treatment modalities.

The second area for improvement relates to the use of liver transplantation to improve survival when the child develops advanced liver disease. In the centers participating in the study, survival of children treated with portoenterostomy and later with liver transplantation increased in the 2000s to 77.6%. Despite this success, only 46.6% of the patients underwent liver transplantation. The simple answer is to increase the access of children with progressive liver disease to liver transplant centers. While simple, this solution is largely dependent on an expansion in the number of accredited transplant centers, support for transplant-related cost, and appropriate follow-up care. To become a reality, these factors must become priorities for the field of pediatrics and for the society as a whole.

The data reported by Carvalho et al. portrait the current state of diagnosis, treatment and outcome of children with biliary atresia – or "where were are" today (Figure 1). They also identify potential areas for improvement – or "where we



d = days; Dx = diagnosis; HPE = hepatoportoenterostomy; LTx = liver transplantation; yr = year.

Figure 1 - Natural history of onset of symptoms, surgical intervention, and outcome with the native liver in children with biliary atresia. The figure depicts the average age at onset of symptoms, the percentage of infants undergoing hepatoportoenterostomy (HPE), and survival with the native liver by 4 years of age (overall and according to age groups at diagnosis). In gray is the percentage of infants undergoing HPE according to age groups and the survival (HPE + liver transplantation) in the last decade (2000s)

are going." It will be important for pediatric hepatologists to broaden their investigative network to include greater representation of the geographical and cultural differences in Brazil, for they are likely to influence the natural history of disease and the quality of care. It will also be important for them to continue to collect clinical data prospectively, store tissues to study the pathogenesis of the disease, and to pursue clinical trials. To be successful, their effort must be matched by an investment by the society, perhaps through funds from federal research agencies, to create a sound research infrastructure. Only then will we diagnose early and find new therapies to block disease progression and save children with their own livers.

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