COMMENTARY

Biliary Atresia: The Timing Needs a Changin'

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ABSTRACT

Biliary atresia (BA), a uniquely pediatric liver disease, is the leading cause of liver-related death in children and the most frequent indication for liver transplantation in the pediatric population. Early intervention with a Kasai procedure (KP) is the current standard of care for this condition. The single most important and well-established prognostic factor for the KP outcome is the patient's age at the time of the KP. The older the infant, the less successful the operation and the less favourable is the post-KP survival with native liver. There remains in Canada, and throughout the world, a problem of late referral, delayed diagnosis and older age at surgery. Early disease detection and intervention has been hampered by the lack of an effective screening strategy for BA. Recently, however, novel programs for the early identification of BA in the first month of life, but after two weeks of age, have been successfully implemented and evaluated in some countries, with significantly improved outcomes for affected infants. Whether any of these programs should be adopted to improve the timing of referral and treatment for Canadian infants affected with this devastating liver disease deserves consideration and study.

Key words: Pediatric liver disease; neonatal cholestasis; newborn screening

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Integral to comprehensive pediatric public health policy are screening programs aimed towards timely disease recognition and early intervention. In Canada, universal newborn screening for metabolic diseases, including rare disorders such as phenylketonuria, hearing deficit and endocrine conditions, is now routine in pediatric care in most provincial jurisdictions and has proven highly beneficial to the health and social well-being of Canadian children.[1]

The World Health Organization established several criteria to be considered for the development of a disease screening program: the disease is recognized as an important health problem; there is a latent or early symptomatic stage; reliable and inexpensive screening examinations are available; and effective treatments, when applied early, are beneficial.[2] Biliary atresia (BA) is a uniquely pediatric liver disease characterized by an idiopathic, progressive, fibrosclerosing obliteration of large bile ducts.[3,4] Delay in its diagnosis, with corresponding late intervention and treatment, results in high morbidity and mortality. While timely diagnosis is the most important prognostic factor for BA, early detection has been hampered by the lack of an effective screening strategy. Recently, novel programs for early identification of BA have been implemented in several countries. Whether any of these programs should be adopted in Canada deserves careful evaluation.

BA is the most frequent cause of liver-related death in children and the leading indication for liver transplantation in the pediatric population.[3,4] It is manifest exclusively during the neonatal period, in the first two to four weeks of life, with persistent jaundice due to a conjugated hyperbilirubinemia and pale acholic stools. BA incidence in Canada is estimated at 1:19,000 live births (18-22 cases annually), similar to rates reported in western Europe but lower than in Asia (1:5,500).[5,6] The current standard of care for BA is sequential surgical management with an initial Kasai procedure (KP), in which the obstructed extrahepatic bile duct is resected and a loop of bowel is brought to the porta of the liver in an effort to restore bile flow, followed by liver transplantation (LT) for those cases that progress to liver failure.[3,4] Infants without the initial KP require semi-urgent LT and have a worse prognosis.[5] Left untreated, all BA infants die by three years of age.[4,5]

The survival of BA patients with their own native liver depends largely on the success of the initial KP. A successful KP re-establishes bile drainage with return of bile pigmented stools, clearance of jaundice and normalization of serum bilirubin by three months of age.[3,4,7] It obviates the need for early LT. Conversely, a failed KP requires LT in early infancy at a time when both the patient age and the marked growth failure associated with end-stage cholestatic liver disease are immutable risk factors for wait list mortality and poor transplant outcome.

Several strategies to improve the KP prognosis are related to postoperative patient management: the use of antibiotics as prophylaxis for recurrent ascending cholangitis; ursodeoxycholic acid to stimulate bile flow; and aggressive nutritional support to enhance growth.[3,4,8] The impact of short-term adjuvant corticosteroid therapy is under investigation.[9] Caseload experience and the expertise of the site and surgeon may also influence the KP outcome.[10,11]

The most important prognostic factor for the KP is the patient age at the time of the procedure.[3,4,7,11,12] The older the infant at the time of KP, the less successful the outcome and less favourable is the post-KP native liver survival. We recently completed the largest and

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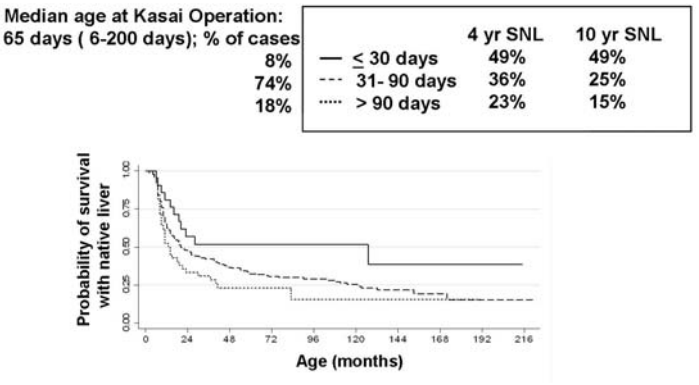
longest follow-up study of North American children with BA in the era of LT.[5] Of 349 BA infants born in Canada between 1985 and 2002, the median age of referral to a tertiary centre was 55 days and the median age at KP was 65 days. The 10-year post-KP native liver survival was 49% for those undergoing KP at age ≤30 days, as compared with 15% for those having their KP at age >90 days. (p<0.0001, Figure 1). Only 8% of Canadian BA cases had their KP at the most favourable prognostic age, ≤30 days old. In contrast, almost 20% of cases had a "late" KP after 90 days of age, at a time when the prognosis for native liver survival is poor. There was no significant difference in referral age, patient age at KP or the post-KP native liver survival between 1985-1995 and 1995-2002 cohorts, confirming that in the last several decades, Canada has not seen any improvements in these outcome parameters.[5]

Late referral, delayed diagnosis and older age at KP remain a worldwide challenge.[5] In Canada, several major obstacles exist to establishing an early BA diagnosis. BA is a rare condition, and few health care providers will see any BA cases during their career. In contrast, neonatal jaundice is the most common clinical problem among newborns, in approximately two thirds of whom it develops during the first week of life.[7] Jaundice at this age is almost always a benign, self-limited condition due to an unconjugated hyperbilirubinemia. Even the vast majority of neonates with prolonged jaundice persisting beyond two weeks are healthy breastfed infants with benign "breast milk jaundice".[7] Thus, it is not surprising that the jaundice of BA, due to a conjugated hyperbilirubinemia, is often considered inconsequential, and no further investigations are undertaken. Indeed, most parents and health care providers do not seek further investigation for infants with prolonged jaundice, despite the recommendations of the Canadian Pediatric Society (CPS) that infants who are jaundiced beyond two weeks of age should have a measurement of total and conjugated bilirubin.[13]

The presence of clay-coloured stools has been shown to be a valuable indicator of BA with a sensitivity of 95.2%.[14] Yet the assessment of stool colour is not routine to well-baby-care practice, and pale stools are not recognized as being abnormal in jaundiced infants. Another barrier to timely BA diagnosis in Canada is the schedule for the routine care visit, which calls for infant visits by two weeks and then at eight weeks of age. Since most parents are unaware of the issues regarding prolonged jaundice and pale stools, and BA newborns are usually otherwise healthy, these symptoms do not prompt an unscheduled office visit. Consequently, the jaundiced infant with BA may not be seen by a health care provider until 8 weeks of age, affording a limited "window of opportunity" for evaluation and intervention.

Efforts have been made worldwide towards earlier diagnosis and more timely KP intervention to improve the native liver survival. The UK introduced a "yellow alert" public education campaign, but its impact remains unknown.[15] Attempts to develop a BA diagnostic biochemical screening test have been hampered by the lack of a known disease-specific serum or urine biomarker.[3,7] More promising has been the recent introduction of a stool colour card to screen for BA. In a one-year study of 147,337 children screened in Japan, mothers were asked to match the colour of their infant's stool according to photographs of different stool colours. Use of the stool colour card yielded a sensitivity of 67% and specificity of 99.9% for BA.[7] Recently, Taiwan initiated a BA universal screening program using the infant stool colour cards.[16] The rate of surgery

Figure 1. Biliary atresia in Canada: Influence of age at Kasai on survival with native liver



Post-Kasai procedure (KP) survival with native liver rates (SNL) at 4 and 10 years for the groups that had their KP at ≤30, 31-90 and >90 days of age, respectively. The post-KP SNL was significantly different between each of the age groups through 10 years (all comparisons p<0.0001). Of the patients having a KP in Canada, 8% had the operation at ≤30 days whereas 18% had their KP at >90 days. (Adapted from Schreiber et al.[5])

before 45 days of age was increased from 62.4% in 2004 to 82.9% in 2005, and no infants underwent a KP at >90 days of age. A successful KP was achieved in 60% of the cases overall, significantly higher than the 37% in a historical control group (p<0.002).

What approaches should we consider to prompt earlier BA detection in Canada and shift the current timing of the KP to an earlier age? First, we need to raise awareness among parents and health care providers about prolonged newborn jaundice and inform them that jaundice with pale stools is highly indicative of an obstructive type pathologic jaundice. Second, health care providers should be better informed about the current CPS recommendations for bilirubin testing in newborns with prolonged jaundice. In most provinces, requisition for a serum bilirubin level in infants does not automatically report both conjugated and unconjugated bilirubin fractions, therefore limiting the utility of the test. Provincial laboratory policy should implement the reporting of both the conjugated fraction and the total serum bilirubin on all requests for serum bilirubin levels in infants aged 7 days to 4 months, regardless of whether the conjugated fraction was specifically ordered. When the measured conjugated bilirubin fraction is >20% of the total bilirubin, the report should include a comment recommending "prompt evaluation to assess for biliary atresia". Finally, introduction of a stool card screening program in Canada has the potential to be an effective and inexpensive method to educate families and health care providers about BA and to prompt earlier intervention to eliminate late referral groups. Yet the feasibility of implementing this screening program in Canada and its cost-effectiveness are uncertain and require careful investigation. Each of these approaches may bring about timely BA detection and improve outcome. Each deserves further study. Yes, the timing for biliary atresia needs a changin'.

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RÉSUMÉ

L'atrésie des voies biliaires (AVB), une maladie du foie qui n'atteint que les enfants, est la principale cause de décès par maladie du foie chez l'enfant et l'indication la plus fréquente de transplantation hépatique dans la population pédiatrique. Une intervention de Kasaï (IK) précoce est la norme actuelle de traitement pour cette maladie. L'âge du patient au moment de l'intervention est le facteur le plus important et le mieux attesté pour un pronostic favorable. Plus le nourrisson est vieux, moins l'intervention est couronnée de succès et moins les chances de survie après l'IK sont bonnes avec le foie d'origine. Au Canada comme dans le reste du monde, il y a encore des retards dans l'aiguillage et le diagnostic des patients, ce qui fait que les nourrissons sont trop âgés au moment de la chirurgie. La détection et l'intervention précoces sont compliquées par l'absence d'une stratégie de dépistage efficace de l'AVB. Mais récemment, certains pays ont mis en œuvre et évalué avec succès des programmes novateurs de détection rapide de l'AVB entre deux semaines et un mois de vie; ces programmes ont significativement amélioré les résultats cliniques des nourrissons atteints. Faudrait-il les adopter afin d'accélérer l'aiguillage et le traitement des nourrissons canadiens qui présentent cette atteinte hépatique dévastatrice? La question mérite d'être étudiée.

Mots clés : maladies du foie de l'enfant; cholestase néonatale; dépistage chez le nouveau-né