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INVITED COMMENTARY

Old habits die hard: The age at Kasai portoenterostomy in European infants with biliary atresia

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To the pediatric hepatologist working in tertiary care, few clinical presentations are as straightforward as the jaundiced infant with discolored stools. These patients are considered to have biliary atresia until proven otherwise. Within days, it is usually possible to demonstrate or exclude an alternative diagnosis and, if indicated, to proceed with an intraoperative cholangiogram, followed by Kasai portoenterostomy (KPE) if biliary atresia is indeed confirmed. Speed is of the essence, as a higher age at KPE results in lower rates of clearance of jaundice and a higher need for early liver transplantation. Traditionally, an age at KPE of less than 60 days was believed to be required for optimal outcomes, but epidemiological data dictate that this threshold is already crossed at 30–45 days of life.[1–3]

With focused diagnostic paths in specialized centers, it seems clear that the most important determinant of age at KPE is the age at time of tertiary referral. Timely referral, in turn, depends critically on the awareness of this very rare condition amongst both pediatricians as well as—and perhaps especially—first line care providers, including general practitioners, midwives and well-child screening services. To increase this awareness, many countries have adopted policies that provide stool color charts to either parents or health care providers, which has shown cost-effectiveness in meta-analysis (reviewed in[2,4]). In addition, the 2017 NASPGHAN/ESPGHAN practice guideline recommends obtaining not only total but also conjugated bilirubin levels (or if unavailable, the direct fraction) in any infant who remains jaundiced after 2-3 weeks of life to enable early detection of neonatal cholestasis.[5] However, these campaigns must compete against the epidemiological fact that jaundice in a neonate is most often harmless and transient. Since jaundice is common in breast-fed babies around this age, family members or health care providers may generally feel unperturbed by this symptom. Moreover, a provider's lenient approach towards jaundice may be reinforced every time an infant's jaundice does indeed resolve over time without any need for further medical treatment or testing. To which extent governments (usually counseled by national pediatric societies) are successful in their attempts to increase awareness and timely biochemical screening for neonatal cholestasis is largely unknown.

In this issue of *JPGN*, Lacaille et al. present the humbling conclusion that the average age at KPE in European countries has not decreased since the 1990s and 2000s.[6] By surveying pediatric hepatologists from 18 tertiary care centers in 15 countries, the authors retrieved data from a total of 772 biliary atresia patients diagnosed between 2015 and 2019. Based on an incidence of 1 in approximately 18,000 live births, this

cohort represents an estimated 55% of all biliary atresia patients that are expected to have been born within that time frame in the EU (with the UK and Switzerland). In these patients, the median age at KPE remained at 60 days, which is unchanged in comparison to the results from 10 to 30 years earlier that are available from previous studies of biliary atresia patients in several European countries.[1,7] By simultaneously showing that 75% of patients underwent KPE within 10 days of admission to tertiary care, this report supports the conclusion that biliary atresia patients still dwell too long either at home or in general care outside the view of pediatric hepatologists and pediatric (liver) surgeons. For a disease in which every day counts, there remains an awfully long gap to close to reduce the average age at KPE to below 30–45 days.

Whether the current situation in Europe is still as sobering as described in this study is unknown. All reported patients were diagnosed between 2015 and 2019. With the NASPGHAN/ESPGHAN practice guideline only released in 2017, it may be premature to conclude that its recommendations have not been successfully implemented. By now, more time has passed which may have allowed for wider dissemination of its key messages into first- and second-line layers of care, or for implementation into updated national guidelines. This consideration notwithstanding, the recommendation to obtain total and direct/conjugated bilirubin fractions in any jaundiced child at 2–3 weeks of age was neither novel nor contentious when it was adopted in the NASPGHAN/ESPGHAN guideline, but in fact reiterated a NASPGHAN recommendation that already dated back to 2004.[5] It is also conceivable that continuing distribution of stool color cards—and in particular the digital equivalents that are now available in several iterations via smartphone applications—are yet to reveal their full potential to change referral practices for European biliary atresia patients.[2] With ever increasing digitalization and popularity of life style and parenting apps, these digital tools may bring stool color awareness to parents that would have missed this information when presented via conventional formats.

While spanning a large part of the European Union, the study by Lacaille et al. only presents aggregate data and does not aim to resolve any differences in age or age distribution at KPE that may exist between countries. Nations differ in health care systems and public health policies and subanalysis at the nation level could therefore help to identify the most successful screening strategies. Furthermore, after having identified such a large cohort of unique biliary atresia patients, it would be worthwhile to attempt reconstructing individual patient's journeys from the time of first presentation to any health care professional, even if only retrospectively, to further distinguish between patient's delay and doctor's delay as the most important contributor to delay to KPE. Such information could inform additional efforts aimed at reinforcing screening recommendations.

The topic of promoting early detection remains a top priority for pediatric hepatologists worldwide and is the subject of ongoing research and innovative detection strategies. The growing realization that biliary atresia already originates in utero rather than from an elusive perinatal or neonatal trigger has opened the way for trials that use conjugated bilirubin, bile acids or metalloproteinase 7 levels in newborn blood spots as early screening tools.[8,9] While it remains to be demonstrated whether these approaches can achieve the stringent sensitivity and specificity requirements that would make this strategy feasible at the population level, addition of biliary atresia biomarkers to already established screening infrastructure would circumvent altogether the problem of unfamiliarity amongst non-specialists and therefore holds the power to truly make a difference in the average age of KPE for affected newborns. Given the persistence of old habits and preconceptions on jaundice in infants, the results presented by Lacaille et al. emphasize that the search for alternative screening tools for biliary atresia must continue unabated.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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