Stool Color Card Screening for Early Detection of Biliary Atresia and Long-Term Native Liver Survival: A 19-Year Cohort Study in Japan

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Objective To evaluate the sensitivity and specificity of a stool color card used for a mass screening of biliary atresia conducted over 19 years. In addition, the age at Kasai procedure and the long-term probabilities of native liver survival were investigated.

Study design From 1994 to 2011, the stool color card was distributed to all pregnant women in Tochigi Prefecture, Japan. Before or during the postnatal 1-month health checkup, the mothers returned the completed stool color card to the attending pediatrician or obstetrician. All suspected cases of biliary atresia were referred for further examination. Diagnosis was confirmed by laparotomy or operative cholangiography for high-risk cases before the Kasai procedure. Patients with biliary atresia were followed from the date of their Kasai procedure until liver transplantation, death, or October 31, 2013, whichever comes sooner.

Results A total of 313 230 live born infants were screened; 34 patients with biliary atresia were diagnosed. The sensitivity and specificity of stool color card screening at the 1-month check-up was 76.5% (95% CI 62.2-90.7) and 99.9% (95% CI 99.9-100.0), respectively. Mean age at the time of Kasai procedure was 59.7 days. According to Kaplan-Meier analysis, the native liver survival probability at 5, 10, and 15 years was 87.6%, 76.9%, and 48.5%, respectively.

Conclusions The sensitivity and specificity of the stool color card have been demonstrated by our 19-year cohort study. We found that the timing of Kasai procedure and long-term native liver survival probabilities were improved, suggesting the beneficial effect of stool color card screening. *(J Pediatr 2015;166:897-902)*.

Biliary atresia is the most frequent hepatic cause of death in early childhood, with an incidence of 0.7 in 10 000, 0.6 in 10 000, and 0.5 in 10 000 live births in the US, UK, and France, respectively.[1-3] In Japan, the incidence is greater, affecting approximately 1.0 in 10 000 live births.[4] Biliary atresia is characterized by a complete inability to excrete bile as a result of sclerosing inflammation of the extra, and possibly intra, hepatic bile ducts.[5] Patients with biliary atresia have 3 main clinical features: pale-pigmented stools, prolonged jaundice, and dark urine. Pale-pigmented stools appears within the first month after birth for most patients, and 2-5 months for others.[4,6] Although there is strong evidence that biliary atresia develops before birth and progresses after birth, its etiology remains unclear. The Kasai procedure[7] commonly is used as a first-line treatment for all types of biliary atresia.[8,9]

Prognosis for patients with biliary atresia is primarily related to the patient's age at the time of Kasai procedure and the anatomy of the bile duct remnant.[8-10] It is generally acknowledged that a Kasai procedure performed early, especially one that is performed before the patient reaches 60 days of age, can improve the long-term native liver survival and reduces likelihood of liver transplantations.[10,11] In Japan, 66.1% of living-donor liver transplantations performed for recipients younger than 18 years of age were attributable to biliary atresia.[12]

Serinet et al[10] highlighted the importance of screening for biliary atresia. The concept of a stool color card for mass screening was introduced for the first time to the local population in Tochigi Prefecture by Matsui and Dodoriki in early 1994, which resulted in early Kasai procedure (<60 days of age) in 2 of 3 patients with biliary atresia.[13] Since then, the stool color card had been distributed in the prefecture until March 2011. Subsequently, the concept of stool color card for mass screening was adopted and used in Taiwan in 2002 and resulted in earlier referral of patients with biliary atresia nationwide.[14]

In this present study, we aimed to determine the sensitivity and specificity of stool color card screening during the 19-year period, as well as its effect on the

JBAR Japanese Biliary Atresia Registry

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timing of Kasai procedure and long-term native liver survival in the Tochigi cohort.

Methods

Participants were all infants born to mothers living in Tochigi Prefecture, situated about 100 km north of Tokyo (Figure 1; available at www.jpeds.com), from August 1994 to March 2011. Infants born in Tochigi Prefecture to mothers who lived outside of the prefecture before giving birth were not included. Under the Maternal and Child Health Law in Japan acted since 1965, all children in the country go through the same postnatal health management.

The stool color card (3rd edition; Figure 2) was placed within the Maternal and Child Health Handbook that was given to all pregnant women by their respective local government according to the Maternal and Child Health Law in Japan. Before or during the infant's 1-month health checkup, the mothers were asked to fill in the corresponding number of the image on the stool color card (Figure 2) that most resembled the color of her infant's stool. The card was then submitted to the attending pediatrician or obstetrician. A positive result was defined as a stool color determined by the guardian that matched either image 1, 2, or 3 before or during the infant's 1-month health checkup.

The Department of Pediatrics at the Jichi Medical University in Tochigi Prefecture (as the stool color card office), Japan was notified of all positive cases as soon as possible by telephone or fax. All stool color cards were collected and sent to the stool color card office at Jichi Medical University on a weekly basis. At the office, the cards were rechecked to confirm whether all corresponding numbers were properly recorded and that positive cases had been properly attended to. At the initial phase (first 3 years), all staff was trained on how to manage positive cases detected by the stool color card.

Verbal informed consent was obtained from all participants. The study protocol was reviewed and approved by the Ethics Board of the National Center for Child Health and Development.

Patients with Biliary Atresia and Long-Term Follow-Up

For patients with positive stool color card results, the possibility of other types of infantile cholestasis was eliminated by a pediatric specialist or pediatric hepatologist through clinical, biochemical, radiologic, histologic, and genetic investigations when necessary. A final diagnosis for high-risk cases was determined by laparotomy and/or by operative cholangiography prior to Kasai procedure by a pediatric hepatologist or surgeon. None of the false positive cases underwent any invasive procedures. All patients with biliary atresia received Kasai procedure at the soonest possibility performed in accordance with the Japanese Society of Pediatric Surgeons classification.[15]

Patients with biliary atresia in Tochigi Prefecture received Kasai procedure and were followed up regularly by their respective hospital (across 8 medical centers). Long-term follow-up was possible because all Japanese residents are covered by at least 1 health insurance plan that allows access to any necessary procedures post-Kasai procedure.[16] In addition, pediatric patients with any of the 514 intractable chronic diseases (including biliary atresia), defined by Ministry of Health, Labour and Welfare of Japan, are supported by a medical aid program.[16] Postsurgical procedures in Tochigi Prefecture are consistent with those in other areas of Japan. To ensure that no patient with biliary atresia in Tochigi Prefecture was overlooked, the patient list in our study was compared with that of the medical aid program covering the 514 intractable chronic diseases.

For the investigation of native liver survival probabilities, patients with biliary atresia in this study were observed from the date of Kasai procedure until liver transplantations, death, or October 31, 2013, whichever occurred sooner.

Statistical Analyses

Four reference data sets were used: nationwide data during stool color card screening between 1994 and 2011 from the Japanese Biliary Atresia Registry (JBAR), nationwide data before stool color card screening between 1989 and 1994 from JBAR,[17] Tochigi Prefecture data before stool color card screening between 1987 and 1992,[4] and Tochigi Prefecture data before stool color card screening between 1989 and 1991[18] (Table I). To quantify uncertainty, 95% CIs were used. The records of approximately 80%-90% of nationwide patients with biliary atresia diagnosed in hospitals that are part of the Japanese Society of Pediatric Surgeons were documented in JBAR. All patients with biliary atresia in our study were registered in JBAR. According to the Act on the Protection of Personal Information, only statistical data and not individual data can be used. Student t test or one-sample t test was performed to compare age at Kasai procedure. Kaplan-Meier analysis and the log-rank test were used to estimate the native liver survival probabilities with age (in months) as the time scale. IBM SPSS Statistics 21 (IBM Corporation, Armonk, New York) was used for statistical analysis. $P < .05$ was considered statistically significant.

For analytical purposes, all 34 patients with biliary atresia were first considered as a whole (termed "all cases"), and then as 2 separate groups: patients identified using stool color chart and referred promptly (Table I).

Results

There were 313 230 live births in Tochigi Prefecture from August 1994 to March 2011 (Figure 1). We collected the stool color cards of 264 071 infants, yielding a return rate of 84.3% at the 1-month health check-up; 2014 showed a positive result, and 26 of them were diagnosed with biliary atresia. Finally, a total of 34 patients were diagnosed with biliary atresia in Tochigi prefecture during the study period. A patient with Alagille syndrome detected by the stool color card (stool color corresponding to image 2) at