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Original Articles

A screening algorithm for the efficient exclusion of biliary atresia in infants with cholestatic jaundice

Tim Jancelewicz [a,e,*], Rebecca Barmherzig [a,e], Catherine T.-S. Chung [b,f], Simon C. Ling [c,f], Binita M. Kamath [c,f], Vicky L. Ng [c,f], Joao Amaral [d], Constance O'Connor [c,f], Annie Fecteau [a,e], Jacob C. Langer [a,e]

[a] Division of Pediatric Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada
[b] Division of Pathology and Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada
[c] Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada
[d] Department of Diagnostic Imaging, Division of Image Guided Therapy, The Hospital for Sick Children, Toronto, Ontario, Canada
[e] Department of Surgery, University of Toronto, Toronto, Ontario, Canada
[f] Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Background: Neonates with cholestasis may undergo many tests before biliary atresia (BA) or an alternative diagnosis is reached, and delayed intervention may worsen outcomes. An optimal diagnostic approach to reduce risk, cost, and delay has yet to be defined. The purpose of this study was to develop an algorithm that rapidly and accurately excludes BA for infants with cholestatic jaundice.
Methods: A single-center retrospective comparison of diagnostic workup was made between cholestatic infants with BA, and those without BA who underwent hepatobiliary iminodiacetic acid (HIDA) scan during admission. Patients were born between 2000 and 2010 and those older than 100 days at assessment were excluded. Sensitivity and specificity analysis of predictive variables was performed and an algorithm constructed.
Results: There were 45 BA and 167 non-BA patients. Some variables were 100% sensitive for the exclusion of BA: conjugated bilirubin <2.5 mg/dL, gamma-glutamyl transpeptidase <150 U/L, excretion on HIDA, or a normal percutaneous cholangiogram. Clinical variables and ultrasound were less useful as screening tests owing to low specificity and sensitivity, respectively. Liver biopsy was 98% sensitive and 84% specific in the diagnosis of BA. An algorithm was constructed that rules out BA with a negative laparotomy rate of 3–22%.
Conclusion: We propose a screening algorithm for infants with conjugated hyperbilirubinemia that permits efficient exclusion of BA with minimal invasive testing and with a low risk of negative laparotomy. This algorithm now requires prospective evaluation to determine its diagnostic accuracy and its ability to reduce hospital costs, patient morbidity, and time to Kasai portoenterostomy in patients with BA.

Biliary atresia (BA) is a common cause of neonatal conjugated hyperbilirubinemia. Patients may undergo a wide range of tests before BA or an alternative diagnosis is reached, and delay in diagnosis beyond 60–100 days of age may reduce longevity of the native liver and increase morbidity in infants with BA, although the ideal surgical timing remains controversial [1–3]. Late diagnosis also worsens outcomes in other conditions associated with neonatal cholestasis, such as hypopituitarism, galactosemia, and tyrosinemia [4,5]. The optimal diagnostic approach to reduce risk, unnecessary testing, and delay prior to definitive diagnosis or surgery has yet to be completely defined.

The purpose of this study was to compare the diagnostic evaluation of infants with BA to that of infants with both non–BA-associated cholestasis and an unclear diagnosis at presentation, in order to develop an efficient approach for the exclusion of BA. We hypothesized that for some patients there is superfluous workup performed prior to surgical intervention, and our goal was to develop a streamlined algorithm that allows rapid, objective, and accurate clinical assessment for infants with cholestatic jaundice, and reduced time to operation for patients with BA.

1. Patients and methods

This study was approved by the Research Ethics Board of The Hospital for Sick Children, University of Toronto (1000017943).

1.1. Patient selection and endpoints

A retrospective review was performed of all infants born between January 1, 2000 and June 1, 2010 who underwent a Kasai portoenterostomy for BA (confirmed at operation and by pathology) and who were ≤100 days of age at time of initiation of workup. The comparison cohort consisted of patients born during the same time

* Corresponding author at: Le Bonheur Children's Hospital, 51 North Dunlap St. Suite 230, Memphis, TN, 38112. Tel.: +1 901 545 9973.
E-mail address: tjancele@uthsc.edu (T. Jancelewicz).

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period who did not have BA, who presented with cholestatic jaundice at ≤100 days of age, and who underwent hepatobiliary iminodiacetic acid (HIDA) scan during their workup. As a selection criterion, HIDA scan was considered a marker of clinician concern for a possible diagnosis of BA, and was chosen to identify a subset of infants whose presentation was clinically suspicious for extrahepatic obstruction.

Patients were excluded if records were incomplete (e.g. study reports or laboratory values not available) or if they died before a diagnosis was reached. The primary endpoints were diagnostic operative exploration with confirmation of BA, diagnosis of and/or treatment for a non-BA cholestatic condition, or resolution of cholestasis without targeted therapy or definitive diagnosis.

1.2. Data acquisition

Clinical data were gathered including patient demographics, birth data, concomitant conditions, ultimate diagnosis, operative data, and relevant medical history (age of onset of jaundice, age at time of workup for cholestasis, and stool color as assessed by a physician at time of workup).

For serum laboratory measurements, the lowest levels seen within the first 24 hours of initial admission (or, if already admitted, at time of workup for cholestasis) were recorded, in order to subsequently generate stringent cutoff values; variables were conjugated bilirubin (CB), unconjugated bilirubin (UB), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), and albumin.

Abdominal ultrasound (AUS) reports were reviewed and the following findings, if noted, were documented: presence or absence of gallbladder (GB), size and shape of GB, intrahepatic or extrahepatic duct dilation, liver echogenicity, triangular cord sign, size and number of spleen(s), and any other salient diagnostic feature (e.g. presence of a choledochal cyst).

HIDA scan reports were reviewed and results were recorded as either “draining” or “non-draining”, in reference to the presence or absence of radiolabeled tracer in the small intestine within 24 hours of injection. Number of days of pre-HIDA phenobarbital treatment was also recorded. At our institution, HIDA scans were considered complete by the radiologist only if radiotracer uptake was sufficient for interpretation within 24 hours.

Percutaneous transhepatic cholecysto-cholangiogram (PC) reports were recorded as “diagnostic of BA” (adequate cannulation with contrast injection, and absent extrahepatic biliary drainage), “not BA” (patent extrahepatic and intrahepatic bile ducts), or “inconclusive” if the biliary tree could not be cannulated, or if a study could not be performed to the radiologist's satisfaction and/or images could not be definitively interpreted by the radiologist. Studies were performed using gallbladder cannulation with a standard technique [6]. Intraoperative cholangiogram findings were also reviewed but only used for endpoint determination.

For percutaneous core liver biopsy findings, the contemporaneous pathologist's interpretation was categorized as “consistent with large duct obstruction”, “not consistent with large duct obstruction”, or “indeterminate or cannot exclude BA.” Also recorded were degree of bile duct proliferation (none, mild, moderate, or severe), stage of portal fibrosis (stage 0–4), and the presence or absence of bile duct plugs, giant cell transformation, hepatocellular ballooning, and portal inflammation [7]. Intraoperative biopsy findings obtained at time of open cholangiogram and/or Kasai were also documented for endpoint determination, but were not used as outcomes predictors.

1.3. Statistical analysis

For univariate comparison between cohorts and subgroups, Fisher's exact test was used for categorical variables and the Wilcoxon rank-sum test for continuous variables. Some laboratory values were dichotomized into normal and abnormal values using cutoff thresholds generated by us to enable use of these continuous variables as predictors in subsequent analysis.

In order to generate a diagnostic algorithm, sensitivity and specificity and positive and negative predictive values (PPV and NPV) were used to generate some steps in the pathway. To assess for independent predictors, multivariate logistic regression analysis was performed on relevant significant variables using stepwise forward selection.

Statistics and graphing functions were performed using Stata (StataCorp LP, College Station, Texas). A P value of <0.05 was considered significant.

2. Results

2.1. Cohort characteristics

There were 45 BA and 167 non-BA patients, after exclusions for missing information (2 BA and 9 non-BA patients). All BA patients underwent Kasai portoenterostomy with diagnosis confirmed by intraoperative findings and final pathology. In the non-BA group, seven (4%) underwent diagnostic laparotomy with operative cholangiogram. Ultimate diagnoses are shown in Table 1 and clinical characteristics at presentation are in Table 2. Among clinical features, by logistic regression, presence of acholic stools yielded the highest odds ratio (OR) for BA. With the exception of malrotation, heterotaxy, and polyspenia, the presence of major concomitant diagnoses and comorbidities such as prematurity was more common in non-BA patients (Tables 2 and 3).

2.2. Laboratory values

Laboratory values that were significantly different between groups included UB, albumin, and GGT (Table 4). Several patients in the non-BA group had low CB levels because the CB decreased within the first 24 hours after presentation, and the lowest value was taken for analysis (as per our methods). Among BA patients, the lowest CB level seen was 2.7 mg/dL. BA patients had CB levels that fell within a relatively narrow range as compared with the non-BA group (Fig. 1A), irrespective of age at presentation (Fig. 1B). GGT levels were consistently higher among BA patients, and increased with time (Fig. 1C and D). However, a few BA patients had only mildly elevated GGT levels; the lowest level seen in the BA cohort was 150 international units (U) per liter (L) (normal 0–45 U/L).

2.3. Imaging studies

Among all patients who underwent AUS (Table 5), 64% had an abnormally “small”, “contracted”, or “absent” GB. One non-BA patient had an ultrasound report that described the GB as “absent”. Other ultrasound features, including the triangular cord sign, were inconsistently mentioned in radiologist reports and therefore were not useful as independent predictors.

Table 1
Ultimate diagnoses in the non-BA cohort.

	Non-BA patients (N = 167)
Idiopathic neonatal hepatitis – INH (%)	97 (58)
Parenteral nutrition (PN) cholestasis	38 (23)
Alagille syndrome	8 (5)
Cytomegalovirus (CMV) hepatitis	6 (4)
Alpha-1 antitrypsin (A1AT) deficiency	5 (3)
Progressive familial intrahepatic cholestasis	3 (2)
Niemann–Pick type C	2 (1)
Congenital portosystemic shunt	2 (1)
Other [arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome, Budd–Chiari syndrome, neonatal sclerosing cholangitis, citrin deficiency, choledochal cyst, unspecified mitochondrial cytopathy]	6 (4)

BA – biliary atresia.