Pattern of Diagnostic Evaluation for the Causes of Pediatric Acute Liver Failure: An Opportunity for Quality Improvement

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Objective To describe the frequency of diagnostic testing for the 4 most common causes of pediatric acute liver failure (PALF) (drugs, metabolic disease, autoimmune process, and infections) in indeterminate PALF within the PALF Study Group Database.

Study design PALF was defined by severe hepatic dysfunction within 8 weeks of onset of illness, with no known underlying chronic liver disease in patients from birth through 17 years of age.

Results Of the 703 patients in the database, 329 (47%) had indeterminate PALF. In this group, a drug history was obtained in 325 (99%) urine toxicology screenings performed in 118 (36%) and acetaminophen level measured in 124 (38%) patients. No testing for common metabolic diseases was done in 179 (54%) patients. Anti-nuclear antibody, anti-smooth muscle antibody, and anti-liver kidney microsomal autoantibodies associated with autoimmunity were determined in 239 (73%), 233 (71%), and 208 (63%) patients, and no tests were obtained in 70 (21%). Testing was performed for hepatitis A virus, hepatitis B virus, and Epstein Barr virus in 80%, 86%, and 68%, respectively.

Conclusions Current practice indicates that investigation for metabolic and autoimmune causes of PALF are infrequent in patients ultimately given a diagnosis of indeterminate acute liver failure. This offers an opportunity to improve diagnosis and potential treatment options in children with acute liver failure. *(J Pediatr 2009;155:801-6)*.

See editorial, p 769 and related article, p 812

Acute liver failure (ALF) is a rare, life-threatening disorder that leads to death or liver transplantation in up to 45% of patients.[1-4] The diagnostic evaluation of these critically ill patients is challenging and is often hampered by many factors, including the blood volume required for some tests, a short time interval between presentation, and outcome such as death or liver transplantation, an incomplete differential diagnosis, the lack of consensus on an age-appropriate evaluation, or clinical improvement mitigating ongoing diagnostic curiosity. Several studies have demonstrated that a cause is not determined in up to 40% to 50% of the pediatric patients.[1,2,4] In comparison, adults with liver failure do not have a specific diagnosis 17% of the time.[5,6] Given the rarity of pediatric ALF (PALF), there is likely to be variability in the diagnostic approach to this entity. Regarding the nearly half of patients who are left with an indeterminate diagnosis, the question of what constitutes a complete, but ultimately nondiagnostic, evaluation is a serious and complex concern that is not uniformly agreed on among pediatric hepatologists and thus may be amenable to a systematic approach.

With these background issues, we hypothesized that the indeterminate PALF cohort would consist of a high proportion of patients whose diagnostic evaluation would be incomplete and that opportunities exist to improve the diagnostic approach to PALF. Thus the goal of this study is to describe the frequency of spe-

AIH	Autoimmune hepatitis
ALF	Acute liver failure
ANA	Anti-nuclear antibody
ASMA	Anti-smooth muscle antibody
EBV	Epstein Barr virus
FAO	Fatty acid oxidation
Gal-1-PUT	Galactose-1-phosphate uridyltransferase
HBV	Hepatitis B virus
HSV	Herpes simplex virus
LKM	Liver kidney microsomal antibody
PALF	Pediatric acute liver failure

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cific screening evaluations for the common causes of PALF in those patients with a final diagnosis of indeterminate ALF.

Methods

The PALF Study group began as an Ancillary Study of the National Institutes of Health (NIH)–funded Adult Acute Liver Failure Study in 1999 and received independent NIH-NIDDK funding in 2005 (UO1 DK072146). Currently, the consortium consists of 20 active pediatric liver transplantation centers, 17 in the United States, 1 in Canada, and 2 in the United Kingdom. The study was approved by the Institutional Review Boards of all of the institutions, and written informed consent was obtained from the parents or guardians of the children who were subjects in this study. After enrollment, demographic, clinical, and diagnostic data are recorded daily for up to 7 days with telephone or face-to-face follow-up for vital and transplantation status at 6 months and 1 year. The diagnostic and clinical evaluation performed is under the direction of the attending physician at the clinical site and constitutes the local standard of care. For purposes of the PALF study, ALF was defined as the presence of severe hepatic dysfunction occurring within 8 weeks of onset of illness, with no known underlying chronic liver disease in patients from birth through 17 years of age with a liver-based coagulopathy (not corrected with vitamin K) with an international normalized ratio ≥1.5 or prothrombin time ≥15 seconds in patients with encephalopathy or an international normalized ratio ≥2.0 or prothrombin time ≥ 20 seconds in patients without encephalopathy. A final diagnosis was assigned by the primary investigator at the clinical site.

The data set of those patients with a final diagnosis of indeterminate ALF was examined for the diagnostic tests that would screen for the most commonly identified causes of PALF. Data were further analyzed for all subjects and for subjects <7 months of age and ≥7 months of age. Evidence for a complete, partial, or absent screening evaluation was obtained from the case report forms, which were submitted to the Data Coordinating Center. Evidence of screening for drug exposure, including acetaminophen, included a completed drug exposure history, a specific history of acetaminophen exposure, acetaminophen serum level in patients with a history of acetaminophen exposure, and urine toxicology screen. Evidence for screening for autoimmune hepatitis included ANA, anti-smooth muscle antibody (ASMA), and anti-liver kidney microsomal antibody (LKM). Evidence screening for metabolic causes of ALF included screening for (1) fatty acid oxidation defects: urine organic acids and a plasma acylcarnitine profile, (2) mitochondrial disorders: serum or plasma lactate and pyruvate level, (3) tyrosinemia, (restricted to patients <7 months old): urine succinyl acetone, (4) Wilson disease (restricted to patients ≥ 3 years of age): ceruloplasmin or 24-hour urine for copper, and (5) neonatal iron storage liver disease (restricted to patients ≤3 months of age): ferritin. Evidence of screening for common specific infectious causes in patients under 7 months of age included the following: (1) herpes simplex virus (HSV): either serum or plasma HSV PCR, or anti HSV immunoglobulin M (IgM), or viral culture of blood or cerebral spinal fluid, or testing of liver biopsy for HSV, (2) hepatitis B virus (HBV): either HBsAg, or anti-HBc IgM or HBV DNA PCR. Evidence of screening for the most common infections in patients at least 7 months of age included the following: (1) hepatitis A virus: anti-HAV IgM, (2) HBV: either HBsAg, or anti HBc IgM or HBV DNA PCR, (3) Epstein Barr virus (EBV): either EBV VCA IgM or EBV PCR.

Statistical Analysis

The statistical significance of differences in baseline demographic and clinical characteristics of participants with indeterminate diagnosis versus those with a specified diagnosis was assessed with the Pearson χ^2 test for difference in proportions. The nonparametric Wilcoxon rank-sum test was used for significance testing of distributions of continuous variables. Pearson χ^2 testing was also used for differences in completeness of autoimmune hepatitis (AIH) and fatty acid oxidation (FAO) tests by center size. All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

There were 703 patients in the PALF database on February 7, 2008; the final diagnoses are listed in Table I. There were 329 (46.8%) patients with a final diagnosis of indeterminate acute liver failure. Compared with patients with a specific diagnosis, the indeterminate patients were younger at enrollment, more likely to be male, and had higher total bilirubin at presentation (Table II). Indeterminate patients had a much greater probability (44.4%) to undergo liver transplantation within 3 weeks of enrollment compared with non-indeterminate patients. Excluding patients with a diagnosis of acetaminophen from the group of patients with a specific diagnosis, the indeterminate patients still had significantly higher total bilirubin and AST at presentation. The likelihood of undergoing transplantation within 3 weeks after enrollment into the study remained significantly higher in the indeterminate group compared with the group of patients with a specific diagnosis, even with acetaminophen excluded.

Screening for Commonly Diagnosed Causes of PALF in Patients Categorized as Indeterminate Drug Toxicity

Virtually all of the patients with an indeterminate diagnosis (325/329, 99%: 100% (61/61) for those <7 months old versus 98.5% [264/268] for those ≥7 months old) had a drug history taken at the time of evaluation for PALF. Twenty-nine (8.8%: 6.6% (4/61) of those <7 months old and 9.3% (25/268) of those ≥7 months old; $P = .49$) had a history of acetaminophen exposure. Of these 29 patients, 21 (72%) had an acetaminophen level (all of which were ≤302 mg/L). Of the 300 children with indeterminate PALF who did not have a history of acetaminophen exposure, 103 (34%: 11% [6/57] of