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

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Abstract

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.

*A list of Pediatric Acute Liver Failure Study Group members is available at www.jpeds.com (Appendix).

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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.

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 specific 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 those < 7 months old and 40% [97/243] of those ≥7 months old; $P < .0001$) had serum acetaminophen level measured, all of which were less than 63 mg/L. Of the 124 participants in the indeterminate group with a known acetaminophen level, 22 (18%; 7/21 with a positive history of exposure, and 15/103 with a negative history) had an acetaminophen level of at least 10 mg/L. Further screening for drug exposure with a urine toxicologic screening was performed in 118 (36%: 15% (9/61) of those <7 months and 41% (109/268) of those ≥7 months old; $P < .0001$).

Screening for Metabolic Liver Disease

Among all patients with indeterminate PALF, only 52% had at least 1 screening test for FAO defects. Because this disorder may be more common in younger children, we analyzed the testing pattern in children less than 3, 3 to 5, and 6 to 8 years of age, respectively, to determine whether there was age-dependent variability in testing for FAO. The percentage of children screened with a plasma acylcarnitine profile or urine organic acids was higher in children younger than 3 years of age (44% and 66%) than in the older age groups (3-5 years old: 29% and 43% and 6-8: 13% and 48%; Table III). Only 19% (62/329: 23% (14/61) among those <7 months and 18% (48/268) of those ≥7 months $P = .36$) of subjects had lactate and pyruvate levels determined.

Ceruloplasmin levels were determined in 78% of patients ≥3 years of age. Urine copper determination was performed in 60 patients, but in only 3.3% (6/184) of patients who did not have ceruloplasmin determination, such that 81% of patients at least 3 years of age were screened for Wilson disease. There was a significant difference in the prevalence of screening for Wilson disease with a 24-hour urine copper level in patients older than 5 years of age compared with those 3 to 5 years of age (41% of 126 patients more than 5 years vs 16% of 58 patients 3 to 5 years of age; $P = .002$).

Because metabolic liver disease may be a more common, identifiable cause of PALF in very young infants, we examined screening for FAO (urine organic acids, acylcarnitine profile), galactosemia (urine reducing substances, Gal-1-PUT assay), tyrosinemia (urine succinyl acetone), and neonatal iron storage liver disease (ferritin) in infants 3 months old and younger. In these 53 infants with indeterminate PALF, 57% had screening for tyrosinemia, 52% had screening for galactosemia, 70% had screening for neonatal iron storage liver disease, and 77% had screening for FAO.

Screening for Autoimmune Hepatitis

The number of patients with determination of the autoantibodies ANA, ASMA, and LKM are shown in Table IV; only 79% (39% of those <7 months vs 88% of those ≥7 months; $P < .0001$) had any testing performed, and only 55% (30% of those <7 months vs 61% of those ≥7 months old; $P < .0001$) had all 3 autoantibodies determined. Some tests may not be performed because of concerns about the reliability of the available assays. LKM autoantibodies may represent an example of this, although there was a fair amount of agreement between whether an ANA or ASMA was done and whether LKM was examined, indicating that many times the entire panel was done. However, it was much more common to have an ANA or ASMA measurement without LKM measurement than to have LKM without ANA or ASMA.

Screening for Infections

Screening was performed for hepatitis A in 80%, hepatitis B in 86% and EBV in 68% of patients. Although there was relatively frequent testing for hepatitis A and B, these diagnoses accounted for only 7 (1.9%) of the cases among the 374 with a specific diagnosis. HBV serologic studies were obtained in 52 (85%) of the 61 children <7 months old, and the most common viral cause in this age group, herpes virus, was screened for in 29 (47%) cases.

Center Variability

To further understand potential underlying factors in the variability in diagnostic evaluations we examined the variability in screening for AIH and FAO among centers. There was a larger percentage of patients ($P = .0002$) undergoing testing for ANA in the centers in the top one-third tier of enrollment (80%) than the remaining centers (62%). A similar result was obtained for ASMA (78% tested in centers in the top one-third tier of enrollment vs 61% tested in the remaining centers [$P = .001$]). Among patients who ultimately underwent liver transplantation, 83% had an ANA result, compared with 55% of those who died or survived at least 21 days with their native liver (67% [$P = .0004$]). Similarly for ASMA, 83% were tested for the group who underwent liver transplantation, 55% were tested for those who died, and 63% were tested for those who survived with their native liver ($P < .0001$). Indeed there was a significantly higher rate of testing for ASMA in patients who were ever listed for liver transplantation (76% tested) compared with those who were never listed for a liver transplant (62% [$P = .01$]). However, a lower percentage of patients who either died or underwent liver transplantation were screened for FAO (urine organic acids tested: 42%, acylcarnitine profile 21%) compared with those who survived with their native liver (urine organic acids tested 58% [$P = .004$]; acylcarnitine profile 39% [$P = .0004$]).

Discussion

As part of the PALF study, we assessed the diagnostic testing for each patient. There was no mandated evaluation as part of this observational study because there is currently no consensus on the evaluation of PALF. Somewhat surprisingly, a large number of patients with an indeterminate diagnosis were not screened for the 4 leading causes of PALF. Indeed,

only 4.9% (13 of 268) of patients at least 7 months of age underwent screening for AIH, drug exposure, hepatitis A, and FAO defects.

There are a variety of potential reasons why the evaluations may be incomplete. Some of the patients may have recovered quickly or had a very rapid progression leading to less urgency or time for a search for a cause. However, these data suggest that evaluations were equally complete or incomplete independent of the rapidity of progression. Indeed there was a higher rate of testing for some causes like AIH in patients who were ever listed for liver transplantation, suggesting that testing was pursued more aggressively in patients who were perceived to be more ill. In small ill infants, blood volume issues may also preclude some testing. Some testing such as hepatitis A and B may not have been performed in children who had been previously vaccinated. Some disorders such as neonatal iron storage liver disease (coagulopathy with minimally to moderately elevated transaminases) or galactosemia (global illness with vomiting after galactose exposure) have been reported to have characteristic clinical presentations, and testing may not have been performed in the absence of those presentations.

PALF is a rare entity even in large centers. The average number of cases per participating center year in this study was only 5 (range 0 to 21) from 2003 to 2007. With multiple caregivers involved in the care of patients with a rare disease, it is not surprising that there is considerable variability in the diagnostic testing for this disorder.

Screening drug histories and testing for common infectious causes were fairly consistently performed. Urine toxicology screening was less frequently performed, but this may be related to the fact that many drugs that can cause acute hepatic toxicity are not detected by standard urine toxicology screening.

The major opportunity for improved diagnoses suggested by our data is in the area of AIH and metabolic liver disease. Previous work from the PALF group suggested that there were underlying abnormalities in FAO even in patients with another diagnosis.[7] Because many of the metabolic diseases affect the newborn, some centers may rely on the newborn screening for young infants. However, even though newborn screening looks for galactosemia and in many areas there is extended newborn screening for FAO, the percent who were not screened for tyrosinemia, which is less reliably detected on the extended newborn screen, was similar to the 2 disorders for which one might reasonably assume that there was newborn screening. In addition, many older children can present with FAO, and they were not screened for FAO defects any more frequently than younger patients who may have undergone extended newborn screening. Although the significance of positive titers of AIH autoantibodies may be debated, approximately 10% of patients with AIH will have an acute presentation with PALF.[8–10] These patients cannot be identified if the diagnosis is not pursued.

On the basis of the commonly known causes for PALF, there are missed opportunities for potential treatment such as steroid therapy for AIH, antiviral treatment for HSV and HBV infections, NTBC therapy for tyrosinemia, and NAC for acetaminophen overdose. In

addition, there are emerging new therapies for entities such as neonatal iron storage liver disease[11] and mitochondrial disorders.[12]

Even if there is not a specific therapy, establishing a diagnosis may have important ramifications for the decision to proceed with liver transplantation: (eg, muscle and cardiac involvement in FAO defects, muscle and CNS involvement in mitochondrial disorders), potential genetic implications for family counseling (ie, FAO defects, mitochondrial disorders, Wilson disease, tyrosinemia) or in the management/prevention of a disorder in subsequent pregnancies (neonatal iron storage liver disease).[13]

PALF represents a rare entity with a large differential diagnosis, which indicates the need to prioritize evaluation. This is an ideal setting for a systematic quality improvement approach and standardized evaluations. This study demonstrated that current practice in major centers in the United States, Canada, and the United Kingdom suggests that there are opportunities to systematize the evaluation of PALF. Specifically we recommend that patients without a readily identifiable cause of PALF be considered for further screening for drug-induced PALF, metabolic, AIH, and infectious causes of PALF on the basis of age and clinical presentation.

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Glossary

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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Appendix

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Table I

Final diagnoses in 703 patients with PALF

Final diagnosis	Number of patients (%) (n = 703)	Number of patients younger than 7 months (%) (n = 149)	Number of patients at least 7 months (%) (n = 554)
Indeterminant	329 (46.8%)	61 (40.9%)	268 (48.4%)
Drug toxicity	111 (15.8%)	3 (2.0%)	108 (19.5%)
Acetaminophen overdose	88 (12.5%)	2 (1.3%)	86 (15.5%)
Other drugs	23 (3.3%)	1 (0.7%)	22 (4.0%)
Autoimmune hepatitis	48 (6.8%)	0 (0.0%)	48 (8.7%)
Metabolic disease	68 (9.7%)	27 (18.1%)	41 (7.4%)
Fatty acid oxidation defect	2 (0.3%)	0 (0.0%)	2 (0.4%)
Tyrosinemia	8 (1.1%)	5 (3.4%)	3 (0.5%)
Wilson disease	23 (3.3%)	0 (0.0%)	23 (4.2%)
Other	35 (5.0%)	22 (14.7%)	13 (2.3%)
Infections	45 (6.4%)	20 (13.4%)	25 (4.5%)
Hepatitis A	5 (0.7%)	0 (0.0%)	5 (0.9%)
Hepatitis B	2 (0.3%)	0 (0.0%)	2 (0.4%)
EBV	8 (1.1%)	0 (0.0%)	8 (1.4%)
Other	30 (4.3%)	20 (13.4%)	10 (1.8%)
Other diagnosis	102 (14.5%)	38 (25.5%)	64 (11.6%)

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Table II

Comparative demographics

	Indeterminate (n = 329)	Non-indeterminate (n = 374)	*P* value*	Non-indeterminate Non-APAP (n = 286)	*P* value†
Age (years)			.0005‡		.90‡
Median	3.7	8.2		3.9	
25%, 75%	1.0, 9.5	0.7, 14.7		0.2, 12.9	
Min, max	0.0, 18.0	0.0, 18.0		0.0, 18.0	
Male	180 (54.7%)	176 (47.1%)	.04§	158 (55.2%)	.89§
Total bilirubin at presentation (mg/dL)			.001‡		<.0001‡
No.	306	343		257	
Median	14.2	5.0		8.1	
25%, 75%	6.1, 20.2	2.3, 13.7		3.2, 15.7	
Min, max	0.2, 43.1	0.2, 59.5		0.2, 59.5	
AST at presentation (IU/L)			.19‡		.001‡
No.	315	356		269	
Median	1716	1611		866	
25%, 75%	519, 3321	334, 4171		215, 2956	
Min, max	17, 710 000	11, 27 312		11, 14 312	
Encephalopathy 3 or 4 at presentation‖	40 (13.0%)	49 (13.9%)	.73§	37 (14.0%)	.73§
Outcome for the first 21 days			<.0001§		<.0001§
Died	31 (9.4%)	57 (15.2%)		54 (18.9%)	
Transplantation	146 (44.4%)	69 (18.5%)		64 (22.4%)	
Alive	152 (46.2%)	248 (66.3%)		168 (58.7%)	

*P value to compare indeterminate group with non-indeterminate group.

†P value to compare indeterminate group with non-indeterminate non-APAP group.

‡From Wilcoxon rank-sum test.

§From Pearson χ^2 test.

‖Number of patients missing coma scores at presentation: indeterminate, 21, non-indeterminate 22 APAP 1.

Table III

Screening for fatty acid oxidation defects in patients <9 years old (n = 243)

	<3 years old (n = 145)	3–5 years old (n = 58)	6–8 years old (n = 40)	*P* value
Acylcarnitine profile				.0006*
Not done or missing result†	81 (55.9)	41 (70.7)	35 (87.5)	
Abnormal (diagnostic)‡	0 (0.0)	0 (0.0)	0 (0.0)	
Abnormal (nonspecific)‡	5 (7.8)	1 (5.9)	0 (0.0)	
Abnormal (not otherwise specified)‡	11 (17.2)	2 (11.8)	2 (40.0)	
Normal‡	48 (75.0)	14 (82.4)	3 (60.0)	
Urine organic acids				.004*
Not done or missing result†	49 (33.8)	33 (56.9)	21 (52.5)	
Abnormal (diagnostic)‡	0 (0.0)	0 (0.0)	0 (0.0)	
Abnormal (nonspecific)‡	22 (22.9)	0 (0.0)	0 (0.0)	
Abnormal (not otherwise specified)‡	36 (37.5)	6 (24.0)	7 (36.8)	
Normal‡	38 (39.6)	19 (76.0)	12 (63.2)	

*P value from χ^2 test of comparison of the probability of test not done or missing result versus the probability of test done (combining abnormal (diagnostic), abnormal (nonspecific), abnormal (not otherwise specified), and normal) by age.

†Percentage “Not done” is the number not done divided by the total sample.

‡Percentage of “Abnormal (Normal)” is the number of Abnormal (Normal) divided by the number of tests done.

Table IV

Frequency of diagnostic testing for autoimmune hepatitis autoantibodies

Testing	Number of subjects tested
ANA	239 (72.6%)
SMA	233 (70.8%)
LKM	208 (63.2%)
No testing	69 (21.0%)
1 autoantibody	21 (6.8%)
2 autoantibodies	58 (17.6%)
3 autoantibodies	181 (55.0%)

SMA, Smooth muscle antibody.