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Persistent alanine aminotransferase elevations in children with parenteral nutrition-associated liver disease

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Abstract

Background: Parenteral nutrition-associated liver disease (PNALD) is a serious condition affecting many children with short bowel syndrome. The aim of this study was to longitudinally assess serum alanine aminotransferase (ALT), a marker for hepatocyte injury, in enterally fed children with PNALD.

Methods: Retrospective chart review of 31 patients treated from 1999 to 2006 by the Center for Advanced Intestinal Rehabilitation at Children's Hospital Boston (Mass). Inclusion criteria included PN duration of greater than 3 months with subsequent tolerance of full enteral nutrition and evidence of PN-associated liver injury. Time to normalize ALT and direct bilirubin were estimated using Kaplan-Meier and Cox proportional hazards methods.

Results: Mean age PN cessation was 6 months (range, 2-14 months). Median PN duration was 18 weeks (interquartile range [IQR], 13-33 weeks), and median follow-up was 24 weeks (IQR, 14-48 weeks). After transition to full enteral nutrition, 74% of children normalized direct bilirubin, whereas only 50% normalized ALT. Kaplan-Meier median time to direct bilirubin and ALT normalization were 13 weeks and 35 weeks, respectively ($P = .001$).

Conclusion: Children with PNALD who have achieved PN independence have persistent ALT elevation despite normal direct bilirubin levels. This implies that hepatic injury may be ongoing beyond the time of bilirubin normalization in this cohort of patients.

Parenteral nutrition (PN) is a lifesaving intervention in children with short bowel syndrome [1]. Unfortunately, up to 65% of these children experience some liver dysfunction,

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which may manifest histologically as cholestasis or cirrhosis, and/or biochemically as hyperbilirubinemia and elevated serum aminotransferases [2,3]. Parenteral nutrition-associated liver disease (PNALD) progresses to end-stage liver failure in 15% to 50% of patients [4,5], and together with sepsis is the most common cause of death in patients with short bowel syndrome [6-8].

Once PNALD develops, treatment options are limited. By far the most successful strategy for reversing PNALD is a transition to full enteral feeding [9,10] with most patients normalizing direct bilirubin 3 to 4 months after discontinuing PN [11]. Intravenous ω-3 fatty acid supplementation has also shown promise in the reversal of PN-associated hyperbilirubinemia within a similar time frame [12].

The aim of this study was to assess the pattern of serum alanine aminotransferase (ALT) normalization in a cohort of patients with short bowel syndrome and PNALD who were successfully rehabilitated to full enteral nutrition. Specifically, we evaluated the time to normalization of serum ALT vs normalization of direct bilirubin. We chose to focus on ALT because it is primarily concentrated in the liver, whereas aspartate aminotransferase and alkaline phosphatase are found in multiple tissues [13,14], thus ALT may be a more sensitive marker for ongoing hepatocyte injury [15].

1. Methods

1.1. Study population

After obtaining approval from the Institutional Review Board at Children's Hospital Boston (protocol no. M06010049), data were retrospectively collected from the medical records of all eligible patients who attended the Center for Advanced Intestinal Rehabilitation Clinic, a multidisciplinary intestinal rehabilitation program, between May 1999 and January 2006. Inclusion criteria included age of 0 to 18 years, severe short bowel syndrome as defined by history of PN of more than 90 days, subsequent tolerance of full enteral nutrition (100% of nutrient and energy requirement via the gastrointestinal tract for >3 weeks), and follow-up in Center for Advanced Intestinal Rehabilitation Clinic after reaching full enteral nutrition. Exclusion criteria included hemodynamic instability, renal failure, suspected congenital obstruction of the hepatobiliary system (eg, biliary atresia or choledochal cyst), or diagnosis of hepatitis, α-1-antitrypsin deficiency, copper deficiency, or human immunodeficiency virus infection.

1.2. Data collection and follow-up

Thirty-one eligible patients were identified, and data were abstracted from this group. All available serum liver function tests before and after transitioning to full enteral nutrition were recorded. Patients were observed from PN cessation until normalization of both serum ALT (≤30 U/L) and direct bilirubin (≤0.4 mg/dL) or until lost to follow-up (no recorded liver function tests for >6 months).

1.3. Statistical methods

Demographic and clinical characteristics of patients who had normal and abnormal serum ALT at time of PN cessation were compared. If no ALT level was available at the date of PN cessation, the closest date prior to cessation of PN was used. Numerical variables were described using means with standard deviations (SDs) or medians with interquartile ranges (IQRs), and categorical variables were described using proportions. Numerical variables across groups were compared using appropriate parametric and nonparametric tests.

When analyzing time to normalization of serum ALT or direct bilirubin, only participants with abnormal ALT or direct bilirubin at the time of PN cessation were included. McNemar's test was used to evaluate the difference between the proportion of patients who normalized ALT vs direct bilirubin, and the Wilcoxon rank-sum test was used to assess the difference between times to normalize the two tests. The median times to normalization of serum ALT and direct bilirubin were determined by Kaplan-Meier analysis and based on the Aalen estimator in separate Cox proportional hazard models. The trajectories of ALT and direct bilirubin over time were plotted over biweekly medians beginning at time of cessation of PN. Adjustments for potential confounding factors (gestational age, primary diagnosis, bowel length, presence of ileocecal valve, duration of PN and age at PN cessation, sepsis, and peak liver function tests at PN cessation) were considered in this analysis.

All analyses were performed in SAS 9.1 (SAS Institute Inc, Cary, NC) and S-plus 8.0 (Insightful, Seattle, Wash). Statistical tests were considered significant if $P \leq .05$.

2. Results

2.1. Population description

We analyzed data from 31 patients (mean age, 6 months, range 2-14 months) with short bowel syndrome and suspected PNALD. The most common etiology of short bowel syndrome was necrotizing enterocolitis (41.9% of patients), followed by volvulus (25.8% of patients). Most patients (59.3%) had an intact ileocecal valve. Table 1 shows demographic and clinical characteristics of all patients. Patients were observed for a median of 24 weeks (IQR 14-48 weeks) after transition to full enteral nutrition. Of the 31 patients, 24 had abnormal ALT (ALT >30 U/L) and 19 patients had abnormal direct bilirubin (>0.4 mg/dL) at time of cessation of PN.