PARENTERAL NUTRITION-ASSOCIATED LIVER DISEASE IN CHILDREN

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Parenteral Nutrition-Associated Liver Disease (PNALD)

- Epidemiology
- Diagnosis
- Natural history
- Management
EPIDEMIOLOGY
Incidence

- The incidence of PNALD in children has ranged from 7-84%

- PNALD in long-term PN patients
  - 40-60% of children
  - 15-40% of adults

Kelly. Gastroenterology 2006; 130:S70
Incidence of hyperbilirubinemia in neonates receiving PN

Prematurity

- Prematurity and/or low birth weight represent risk factors for PNALD
  - Infants born less than 32 weeks' gestation had a significantly higher rate of cholestasis (13.7%) and a higher peak direct bilirubin than those born at more than 36 weeks (1.4%)
- Some reports have not found as clear an association
- Prematurity may influence the development of PNALD far less than the duration of PN

Sepsis

- Sepsis has been consistently associated with PNALD
  - Episodes of sepsis, including catheter-related sepsis, are associated with the severity of liver disease in PNALD
  - Bacterial overgrowth may contribute to PNALD

Intestinal failure

- Infants with extensive small bowel resections (residual length ≤10% of expected) are more likely to develop PNALD as compared with those with less extensive bowel resections or intestinal dysmotility

Enteral feeding

- PNALD is more likely to develop in those children who are unable to tolerate any enteral feeding compared with those who are partially enterally fed

Benjamin et al.. Am J Clin Pathol 1981;76:276
Hodes et al. J Pediatr Surg 1982; 17:463
Colomb et al. Transplant Proc 1992;24:1054
Predictors of PNALD

• In a prospective trial, necrotizing enterocolitis was identified as being a significant predictor in the development of PNALD

• In the first days of life, certain NICU patients can be identified as being at very high risk for developing PNALD
  • Patients <750 g birth weight
  • Gastroschisis
  • Jejunal atresia

Spencer et al. JPEN J Parenter Enteral Nutr 2005;29:337-43
DEFINITION
Definition

- **Cholestasis**
  - elevated serum conjugated bilirubin $\geq 2$ mg/dL (34.2 micromol/L)

- **Duration of parenteral nutrition**
  - At least 2 weeks to 2 months

- **Rule out other causes of liver disease**
  - Infectious hepatitis, inborn errors of metabolism, cystic fibrosis
Earliest indicator of PNALD

• The most sensitive indicator of early cholestatic liver disease
  • rise in serum bile acid concentrations, particularly sulfated lithocholate

• Neonates receiving PN had significantly increased levels of glycocholic acid, taurocholic acid, and combined taurochenodeoxycholic + taurodeoxycholic + tauroursodeoxycholic acids

Farrell et al. JPEN J Parenter Enteral Nutr. 1982;6:30
D’Apolito et al. JPEN J Parenter Enteral Nutr. 2010;34:538-541
Is hyperbilirubinemia alone enough for a diagnosis?

- In children who had PN for > 2 months
  - 66 children underwent 83 liver biopsies
  - Median age at biopsy = 6.1 month; median duration of PN = 4.7 months
  - 70.3% had a history of exposure to parenteral omega-3 lipid emulsion
  - 89% of liver biopsies demonstrated some degree of fibrosis including 9.6% with evidence of cirrhosis
    - 55% of biopsies with fibrosis were obtained in patients without evidence of biochemical cholestasis
    - 3 / 8 patients (37%) with cirrhosis on liver biopsy had no evidence of biochemical cholestasis

CLINICAL COURSE
Hepatic dysfunction secondary to PN

- Three clinical syndromes
  - Cholestasis
    - more common in infants
  - Steatosis
    - more common in adults
  - Biliary sludge and cholelithiasis
    - occur in both adults and children
Clinical course of PNALD

- ~40–60% of children on long-term TPN will develop hepatic dysfunction

- The earliest clinical sign is a rise in conjugated bilirubin
  - may occur as early as within 2 weeks of starting PN
  - will rise during episodes of intercurrent sepsis

- May be an increase in alkaline phosphatase and amino transferases within 4–6 weeks in 34% of infants

Kelly et al. Gastroenterology 2006;130:S70–S77
Liver failure in PNALD

- PNALD progresses to end-stage liver failure in 15-50% of patients

- Persistent elevation of serum bilirubin (>12mg/dl, 200 mmol/L) is associated with a poor prognosis

Lab values that predict liver failure

Table IV. Bivariable analyses of laboratory tests in predicting liver failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference value*</th>
<th>Odds ratio(e^θ): LF versus LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>&gt;11.7 mg/dL</td>
<td>10.08 (P &lt; .0001)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≤168 x 10^3/µL</td>
<td>9.15 (P &lt; .0001)</td>
</tr>
<tr>
<td>Albumin</td>
<td>≤3.0 g/dL</td>
<td>7.71 (P &lt; .0001)</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&gt;1.3</td>
<td>6.71 (P = .06)</td>
</tr>
<tr>
<td>Gamma glutamyl transferase</td>
<td>≤121 U/L</td>
<td>1.90 (P = .08)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>&gt;182 U/L</td>
<td>1.65 (P = .15)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>≤4.0 x 10^3/µL</td>
<td>1.61 (P = .19)</td>
</tr>
</tbody>
</table>

*Means of continuous variables for the entire group of patients with LF plus LR served as differentiating points for bivariable analyses to calculate odds ratios by logistic regression for correlated data.

## Lab values that predict liver failure

**Table VI. Combinations of laboratory values that predict probability of liver failure**

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
<th>Scenario 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at tests</td>
<td>High bilirubin only</td>
<td>Very high bilirubin only</td>
<td>High bilirubin and low albumin</td>
<td>High bilirubin, low platelets, and low albumin</td>
<td>Very high bilirubin, low platelets, and low albumin</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>3 months 6 months</td>
<td>3 months 6 months</td>
<td>3 months 6 months</td>
<td>3 months 6 months</td>
<td>3 months 6 months</td>
</tr>
<tr>
<td>Platelet count</td>
<td>6 mg/dL</td>
<td>11.7 mg/dL</td>
<td>6 mg/dL</td>
<td>6 mg/dL</td>
<td>11.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>220 x 10^3/μL</td>
<td>220 x 10^3/μL</td>
<td>220 x 10^3/μL</td>
<td>168 x 10^3/μL</td>
<td>168 x 10^3/μL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5 g/dL</td>
<td>3.5 g/dL</td>
<td>3.0 g/dL</td>
<td>3.5 g/dL</td>
<td>3.0 g/dL</td>
</tr>
<tr>
<td>Probability of LF</td>
<td>.382</td>
<td>.630</td>
<td>.553</td>
<td>.490</td>
<td>.658</td>
</tr>
</tbody>
</table>

Total serum bilirubin concentration, platelet count, and serum albumin concentration independently predicted liver failure in multivariable analysis. Predicted probabilities were calculated by using estimated regression coefficients and estimated values for variables.

Reversibility of PNALD

• PN-induced hepatic dysfunction and structural changes are potentially reversible if PN can be discontinued before the development of severe fibrosis

• Cholestasis usually resolves in most patients after discontinuation of parenteral nutrition

Alanine aminotransferase level remains elevated long after normalization of direct bilirubin levels (median 35 vs 13 weeks, $P=0.001$), and 50% of patients failed to normalize ALT by 2 years.

Persistence of fibrosis

- Hepatic fibrosis persisted in two infants with intestinal failure on Omegaven, despite improvements in cholestasis

Non-invasive markers of liver fibrosis

- Assessment of liver fibrosis with multiple serum markers has been shown to be sensitive, specific, and reproducible in adults with a range of chronic liver diseases.
- Measurement of liver stiffness has shown some initial promise in cystic fibrosis.
- $^{13}$C-methionine breath test may be a measure of liver function in children with short bowel syndrome.

Rosenberg et al. Gastroenterology 2004;127:1704–1713
MANAGEMENT
Management

- Manage non-nutritional causes
  - Avoid and treat sepsis
  - Treat bacterial overgrowth
  - Avoid hepatotoxic medications
- Modify enteral and parenteral nutrition
  - Avoid overfeeding
  - Cycle parenteral nutrition
  - Maximize enteral nutrition
  - Modulate intravenous lipid
- Pharmacological treatment
  - Ursodeoxycholic acid
  - Parenteral choline
  - Parenteral taurine
- Small intestinal and/or liver transplantation

Lloyd et al. Proceedings of the Nutrition Society. 2007. 66: 530 538
Management

- Manage non-nutritional causes
  - Avoid and treat sepsis
    - Scrupulous attention to central venous line care
    - Prompt treatment of line infections
  - Treat bacterial overgrowth
    - Oral decontamination
    - Prebiotics
  - Avoid hepatotoxic medications

Management

• Modify enteral and parenteral nutrition
  • Avoid overfeeding
    • Since overfeeding → hepatic steatosis

• Cycle parenteral nutrition
  • Minimizes the adverse effects of prolonged insulin hypersecretion
  • Allows a break from PN
  • Has been shown to improve liver function tests

• Maximize enteral nutrition

• Modulate intravenous lipid

Lipid modulation

• Two primary strategies
  
  • Use of alternate lipids
    • Fish oil-based lipid emulsion (Omegaven)
  
  • Decreased provision of soybean-based lipid
Proposed beneficial effects of omega-3 fatty acids

- Improve Bile Flow
  - Decrease lithogenicity of bile
  - Eicosanoid mediated mechanism

- Decreased
  - Cholestasis
  - Hepatitis
  - Fibrosis

- Immunomodulatory
  - Shift from arachidonic acid derived eicosanoids to those derived from docosohexanoic acid and eicosapentaenoic acid
  - related to n6:n3 ratio

- Decreased Steatosis
  - Stimulate β-oxidation of fatty acids
  - Reduction in denovo lipogenesis
  - Suboptimal substrates for glycerol esterification
  - Reduced oxidative stress by modulating superoxide dismutase and glutathione peroxidase

Omega-3 fatty acids

- Prospective study of Omegaven (1 g/kg per day) in 18 neonates with short-bowel syndrome who developed cholestasis
- Historical cohort of 21 infants with short-bowel syndrome who also developed cholestasis while receiving soybean emulsions (3 gm/kg per day)
- Primary end point was time to reversal of cholestasis
- Median time to reversal was 9.4 weeks in the fish oil group and 44.1 weeks in the historical cohort
- The fish oil cohort experienced reversal of cholestasis 4.8 times than the historical cohort
- A total of 2 deaths and 0 liver transplantations were seen in the fish-oil cohort and 7 deaths and 2 transplantations in the historical cohort
- Fish-oil–based fat emulsion was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, infections, or growth delay

Gura et al. Pediatrics 2008;121;e678
Restriction of soybean-based lipid

- Prospective study of intravenous lipid reduction in PN to 1 g/kg per day 2 times per week in neonates with PNALD.
- Historical matched controls who received 3 g/kg per day of intravenous lipids
- Intravenous lipid reduction resulted in a significant decline in total bilirubin levels compared with controls
  - Similar growth in the 2 groups
  - Mild essential fatty acid deficiency in 8/31 infants which was reversed with additional days of lipid infusion

Pharmacological Options

• Ursodeoxycholic acid
  • Several small studies in neonates with parenteral nutrition-associated cholestasis
  • Generally have shown a beneficial effect

• Taurine and Choline
  • More research is needed

Levine et al. J Pediatr Endocrinol Metab. 1999. 12:549–553