



Independent case reports

# Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (Omega-3 fatty acids)

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Received 21 November 2007; revised 3 January 2008; accepted 4 January 2008

## Key words:

Parenteral nutrition-  
associated cholestasis  
(PNAC);  
Short bowel syndrome;  
Omega-3 fatty acids

**Abstract** Total parenteral nutrition is an important adjunct in the care of neonates with surgical disorders. Cholestasis is at present the most worrisome complication of this technique; it is difficult to treat and may progress to eventual cirrhosis and liver failure. This article reviews the pertinent clinical and nutritional data in a surgical patient with short bowel syndrome who developed parenteral nutrition-associated liver disease successfully treated with fish-oil based lipids.

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## 1. Purpose

Total parenteral nutrition (TPN) is an important adjunct in the care of neonates with surgical disorders. It becomes a lifesaving therapy for patients with gastrointestinal insufficiency or anatomical short bowel syndrome. These patients are dependent on TPN for long-term survival. Long-term TPN can however be associated with mechanical, septic, and metabolic complications all of which are potentially life-threatening. Mechanical and septic complications have been consistently reduced by improvement in catheter design, aseptic catheter placement techniques, and use of trained

personnel. The major part of metabolic complications has been reduced by improvements in parenteral solutions. The most serious and significant life-threatening complication today continues to be parenteral nutrition-associated cholestasis (PNAC). Parenteral nutrition-associated cholestasis is indeed the most worrisome complication because it is difficult to treat and may progress to eventual cirrhosis and liver failure namely parenteral nutrition-associated liver disease (PNALD). The etiology of PNAC although elusive is thought to be multifactorial, and proposed theories also include problems arising from lipid emulsions that are our interest in this case report. The article reviews the pertinent clinical and nutritional data in a surgical patient with short bowel syndrome who developed PNALD that was successfully treated with fish oil-based lipids and adds further evidence on the role of fish oil-based lipids as a potential therapeutic remedy for PNALD as suggested by a recent preliminary case report [1].

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## 2. Method

RJ is a baby boy at term, weighing 3.450 kg, who was referred to our surgical unit at the age of 60 days for short bowel syndrome secondary to a midgut volvulus. The child developed conjugated hyperbilirubinemia 4 months after institution of TPN (11 mg/kg per minute of dextrose, 3 g/kg per day of crystalline aminoacids, 3g/kg per day of fat emulsion). Surgical reasons delayed enteral feedings that started late, on postoperative day 45. Because enteral feedings were only minimally tolerated, TPN was continued despite his jaundice. Congenital and acquired infectious etiologies for the jaundice were ruled out by means of serologic tests for toxoplasmosis, rubella, cytomegalovirus, and herpes virus as well as multiple bacterial cultures of blood and urine. Abdominal sonography ruled out extrahepatic biliary obstruction. Choleric therapy with ursodeoxycholic acid, reduction of parenteral glucose, protein and lipid loads, interval intestinal decontamination with metronidazole and kanamycin, synbiotic therapy with prebiotics and probiotics, and parenteral nutrition cycling were initiated. When these medical methods of managing the problem failed, surgical exploration was considered. Intraoperative cholangiography, irrigation of the biliary tree with normal saline solution, and liver biopsy were performed. Jaundice did not ameliorate but became progressive and ingravescens. Clinical deterioration was manifested by increasing serum bilirubin levels, clotting dysfunction, enzyme elevations, and reduced liver synthetic activity. Repeat abdominal sonography revealed inspissated bile and biliary sludge in a very distended gallbladder. The child was again surgically explored and cholecystectomy and repeat irrigation of the biliary tree were performed. In the light of his worsening clinical conditions and on the basis of a recent preliminary report suggesting that fish oil-based lipids could reverse PNALD [1], therapy with these lipids was considered. Total parenteral nutrition with Omega-6 lipids

(Lipofundin, B. Braun, Melsungen AG, Germany) was discontinued. Ursodeoxycholic acid was also stopped before initiating therapy with parenteral fish oil because of increased cytotoxic activity as expressed by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The child was given the Omega-3-based emulsion Omegaven (Fresenius Kabi AG, Bad Homburg, Germany). Because omegaven is indicated as a supplement with conventional lipids because of the concern for developing essential fatty acid deficiency and because only 2 clinical reports have indicated that when provided alone, fish oil lipid emulsions provide sufficient arachidonic acid to prevent essential fatty acid deficiency [1,2], informed concern from the child's parents to use the product as monotherapy was obtained. Omegaven was then initiated at a dose of 0.2 g/kg per day intravenously and advanced by 0.2 g/kg per day increments to a goal dose of 1.5 g/kg per day. Hepatic function and systemic inflammation were monitored monthly by means of blood chemistries. The child continues to have 1.5 g/kg per day of omegaven till date.

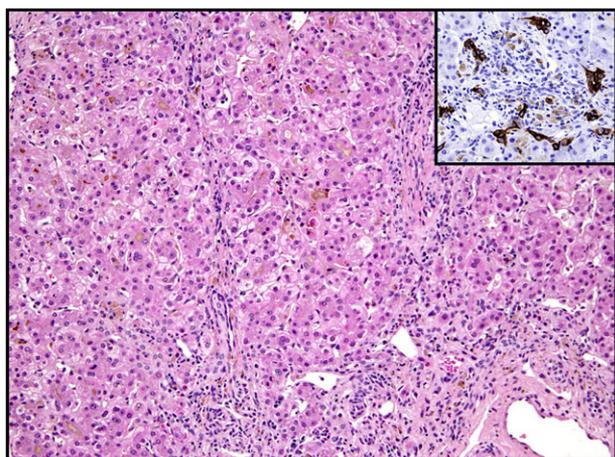
## 3. Results

Intraoperative cholangiography showed normal biliary anatomy. The bile aspirated through the cholangiographic catheter from the gallbladder was inspissated and hyperviscous. The gentle irrigation of the biliary tree with several milliliters of normal saline solution to wash out both the radiographic dye and the hyperviscid bile did not eventually resolve cholestasis, which on the contrary became progressive and ingravescens. Peak total bilirubin values and peak direct bilirubin levels doubled, and all other functional tests worsened at 40 days after lavage of the biliary tract (Table 1). There was a slight decrease of bilirubin values after cholecystectomy and repeat lavage of the biliary tract, but glutamic-oxaloacetic transaminase and glutamic-pyruvic

**Table 1** Treatment and control periods and serum liver function tests and treatment modalities of PNALD

Treatment and control periods	Treatment modalities	Total bilirubin nv 0.3-1.2	Direct bilirubin nv <0.30	$\gamma$ -glutamyl transpeptidase nv 5-50	AST nv 5-50	ALT nv 5-50	Cholinesterase nv 6400-16,000	C-reactive protein nv <5
At age 5 mo	Biliary tree irrigation	10.71	7.57	173	403	680	4998	34.9
At 40 d after biliary irrigation	Cholecystectomy	20.80	17.02	99	295	385	2340	66.3
At 40 d after cholecystectomy	Starts treatment with Omega-3	16.49	11.34	96	560	958	2533	18.34
2 mo after Omega-3 treatment		9.27	6.93	96	126	295	2575	
At 4 mo		6.79	4.78	142	122	219	3979	5.40
At 6 mo		2.26	1.44	204	65	81	4779	11.43
At 8 mo		0.52	0.24	86	57	65	5560	1.46
At 10 mo		0.43	0.15	82	55	94	6067	1.69
At 12 mo		0.44	0.13	45	65	86	6441	1.07

nv, normal value.



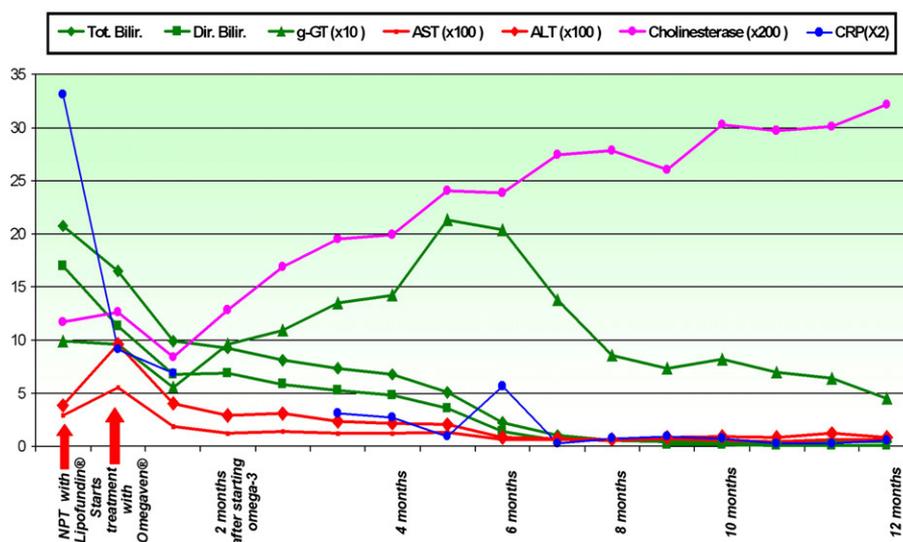
**Fig. 1** Liver specimen shows fibrous enlargement of portal tracts with short fibrous septa; in the lobule there are pseudoacini and diffuse cholestasis (H&E, original magnification  $\times 4$ ). Note the ductular metaplasia in portal tracts (inset, immunoperoxidase for anticytokeratin-AE1, original magnification  $\times 20$ ).

transaminase tripled (Table 1), and clinical deterioration was evident. Liver biopsy was consistent with PNALD—moderate distortion of hepatic architecture with initial arrangement of hepatocytes in pseudoacini trapped by fine fibrous tissue in the midst of regular cords. Bile duct proliferation and bile plugs in canaliculi were other features of the histologic picture. Portal triades showed inflammatory infiltration with granulocytes and fibrosis (Fig. 1). Omegaven initiated 40 days after cholecystectomy was well tolerated. Hepatic indexes monitored at the initiation of therapy with omegaven are shown in Table 1. There was a constant and progressive amelioration of all functional hepatic indexes monitored (Fig. 2). *Cholestasis*, defined as

a direct bilirubin level more than 2 mg/dL, resolved after 8 months of therapy despite continuing cyclic PN requirements. The child is still on omegaven therapy, and at present, there are no clinical signs of fatty acid deficiency or evidence of bleeding. C-reactive protein levels that were elevated when omegaven was started decreased concomitantly with the other hepatic functional indexes (Table 1).

### 4. Discussion

Cholestatic jaundice is a major complication of TPN in infants and small children. Peden et al [3] first described the association between parenteral nutrition (PN) and jaundice in 1971; subsequent reports confirmed the link between TPN and liver dysfunction [4,5]. The complication is considered a common problem in neonatal surgical patients, and the incidence has been reported to be from 7.4% to 70% [6-9]. The pathogenesis of hepatic dysfunction associated with TPN in children is still unclear. The basic and clinical studies performed till date suggest multifactorial risk factors such as prematurity [10-13], lack of enteral feeding [14-17], systemic or portal endotoxemia [18-20], reduced levels of gastrointestinal hormones [16], major abdominal surgery or multiple laparotomies [21,22], toxic bile acids such as lithocholic acid [23,24], carbohydrate overloading, aminoacid excess or imbalance [25-27], abnormal metabolism of fat [28], and presence of phytosterols in intravenous fat emulsions [29], as possible contributing factors. None of the theories on the etiology of PNAC in infants has so far led to a reliable means of treating or preventing it apart from stopping the TPN after a few weeks that is not always possible. Therapeutic modalities suggested for PNAC are



**Fig. 2** Baseline values during treatment with Lipofundin. Baseline and follow-up values for total bilirubin, direct bilirubin,  $\gamma$ -glutamyl transpeptidase, AST, ALT, cholinesterase, and C-reactive protein during treatment with parenteral fish oil.

limited and include cessation of TPN with provision of full nutritional support orally [30], partial enteral feeding even when continued TPN is necessary for full energy support [31], use of cholagogues [32], intestinal decontamination [33], synbiotic therapy with prebiotics and probiotics [34], and surgical irrigation of the biliary tree [35,36]. Each of these therapeutic modalities has succeeded or contributed to success in certain occasions in the treatment of PNAC and failed in others, leaving the child to progress toward PNALD. Parenteral nutrition-associated liver disease is a condition associated with relatively high mortality [37]. Commercially available intravenous fat emulsions are soy-based preparations containing phytosterols such as sitosterol, campesterol, and stigmasterol. The observation of high plasma levels of phytosterols in patients with PNALD receiving intravenous fat emulsions led to the hypothesis that accumulation of these substances contributes to cholestasis [38]. Their intravenous route of administration can lead to accumulation in hepatocytes because they are inefficiently metabolized by the liver [38]. Incorporation into hepatocyte membranes can then affect membrane fluidity and membrane-bound transport proteins such as the canalicular adenosine triphosphate-dependent bile acid transporters and sodium potassium-adenosine triphosphate [38,39]. This view of the problem although very pertinent did not completely explain several aspects of PNALD such as fibrosis and portal triade infiltration. Only recently, a convincing association between plant sterols and cholestasis has emerged; attention is now directed to the inflammatory aspects of PNALD and the role of omega-3 fatty acid supplementation in modifying the hepatic biochemical environment. Growing evidence from both animal and clinical studies indicate that Omega-3 polyunsaturated fatty acids (n-3PUFA) and their specific lipid mediators can reduce not only the activity of inflammatory processes but might also lower inflammatory susceptibility in general. Hence, they could also dampen the inflammatory response in liver tissue probably by regulating Kupffer cell activation and suppressing cytokine production. In experimental studies, Schmöcker et al [40] explored this latter possibility in a well-established model of lipopolysaccharide/galactosamine-induced hepatitis. The authors demonstrated amelioration of both ALT and histologic hepatotoxicity after administration of omega-3 fatty acids and suggested that these effects may be attributable to inflammatory cytokine downregulation via Omega-3 fatty acid content. The injury that results from ischemia and subsequent reperfusion of tissue has long been known to be the source of significantly morbid and often mortal insults in cases of acute embolic/thrombotic events, traumatic wounds, and organ transplantation.

El-Badry et al [41] studied these events namely liver ischemia/reperfusion and examined Omega-3 fatty acid supplementation effects on the hepatic biochemical environment. Some important results of Omega-3 fatty acids in this model were decreased microvascular dysfunction, biochem-

ical hepatitis (AST), and inflammatory activity. These 2 important articles describe a singular phenomenon where hepatitis, generically liver inflammation, is preventable with Omega-3 fatty acids. This phenomenon has been borne out in the recent literature, both in basic science and clinical arenas, with evidence of protective Omega-3 fatty acid derivatives (docosahexaenoic acid [DHA]) [42] and treatment of neonatal liver injury with parenteral formulation [1]. Sepsis induces cholestasis via endotoxin-mediated release of inflammatory cytotoxins that negatively affect cellular biliary transport. The clinical findings of progressive and consensual decrease of C-reactive protein and cholestasis in the experience of Gura et al [1], and our experience directly links with the laboratory data describing cytokine modulation via Omega-3 fatty acid content. Although the infectious focus cannot always be prevented, the sequelae namely cholestasis can be prevented by treatment with Omega-3 fatty acids. The inflammatory process seems to be the unifying principle that is pervasively involved in the pathophysiology of cholestasis and liver disease. The biologically active essential fatty acids of most interest are arachidonic acid (AA) in the Omega-6 family and eicosapentaenoic acid (EPA) and DHA in the Omega-3 family. These fatty acids play an important role in cell membrane composition that in turn influences fluidity and cell surface biochemical signaling and transport. Arachidonic acid and EPA/DHA are important eicosanoid and prostanoid precursors, whereas those of AA are proinflammatory and prothrombotic, those of EPA/DHA that are significantly less biologically active are usually labeled as antiinflammatory and antithrombotic. This makes their interaction critical, especially considering that AA and EPA/DHA are competitive substrates. Converting cellular membranes to an Omega-6/Omega-3 ratio close to 1:1 would decrease the substrate availability necessary for production of inflammatory cytokines and replace them with antiinflammatory mediators.

The previously established timeline for normalization of direct bilirubin levels was 3 to 4 months and only after full enteral nutrition was achieved and PN discontinued [43]. Gura et al [1] were able to diminish this course to 2 months and sometimes even shorter despite less than 100% enteral nutrition and continuation of PN. Our case required 8 months to normalize cholestatic jaundice while on 50% enteral nutrition and 50% of PN. Most probably Omega-3 fatty acids were engaged in a more severe form of PNALD. A pediatric histologic liver damage scale might be useful to explain these differences in the timeline of recovery. The child has so far not been proposed for a liver/intestinal transplant but is awaiting for an intestinal lengthening procedure. Liver biopsy will be obtained during the intestinal lengthening procedure to see if there has also been a histologic resolution of PNALD. In the light of accumulating evidence, it is hoped that in the future, Omega-3 fatty acids will gradually gain credit not only in the cure of PNAC but also as a novel protective strategy of the liver during TPN.

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