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Review Article

Pediatric parenteral nutrition-associated liver disease and cholestasis: Novel advances in pathomechanisms-based prevention and treatment

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ABSTRACT

Parenteral nutrition constitutes a life-saving therapeutic tool in patients unable to ingest/absorb oral or enteral delivered nutrients. Liver function tests abnormalities are a common therapy-related complication, thus configuring the so-called Parenteral Nutrition Associated Liver Disease (PNALD) or cholestasis (PNAC). Although the damage is frequently mild, and resolves after discontinuation of parenteral nutrition, in some cases it progresses into cirrhotic changes, especially in neonates and infants.

We present a literature review focusing on the pathogenetic mechanisms-driven prevention and therapies for the cases where parenteral nutrition cannot be discontinued.

Ursodeoxycholic acid has been proposed in patients with cholestatic hepatopathy, but its efficacy needs to be better established. Little evidence is available on efficacy of anti-oxidants, antibiotics, probiotics and anti TNFα. Lipid emulsions based on fish oil with a high content of long-chain polyunsaturated fatty acids ω-3 appear effective both in decreasing intrahepatic inflammation and in improving biliary flow. Most recent promising variations such as soybean/MCT/olive/fish oil emulsion [third generation lipid emulsion (SMOFlipid)] are under investigation.

In conclusion, we remark the emergence of a number of novel pathomechanisms underlying the severe liver impairment damage (PNALD and PNAC) in patients treated with parenteral nutrition. Only few traditional and innovative therapeutic strategies have hitherto been shown promising.

1. Introduction

Parenteral nutrition (PN) is a "life-saving" therapy for patients unable to ingest or absorb oral or enterally delivered nutrients for a significant period [1]. Main indications to pediatric PN are summarized in Table 1.

The complex wide spectrum of PN-induced liver function alterations are named almost always interchangeably with the terms of PNALD/PNAC/PNALI (parenteral nutrition associated liver disease/cholestasis/injury) or IFALD (intestinal failure associated liver disease) when liver disease is specifically associated to intestinal failure in PN dependent infant and children. In this paper we refer to PNALD including IFALD patients, except when specifically indicated by the reference. They are characterized by cholestasis and/or hypertransaminasemia occurring during long-term parenteral nutrition after exclusion of other causes of liver disease. Asymptomatic increase of aminotransferase frequently occurs within 2–3 weeks after starting PN and is often followed by an increase of serum conjugated bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and serum bile acids. The latter seem to be an early marker of liver damage in neonatal age [2]. If mild, the biochemical abnormalities generally revert to normal after the discontinuation of PN and the starting of oral feeding. This reversal is due to the beneficial effects of the so-called "minimal enteral intake" on bile flow. The stimulation of the intestine, even with small amounts of food, is necessary for the release of hormones, in particular of cholecystokinin (CCK), which stimulates gallbladder contraction avoiding sludge and stones formation. It also maintains the integrity of the intestinal walls, and reduces bacterial translocation [3]. Reducing continuous administration of PN

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Table 1
Main indications to parenteral nutrition in infants and children.

Low birth weight
Major surgery (gastrointestinal, post-traumatic)
Chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis)
Respiratory disease (cystic fibrosis, acute respiratory distress)
Cardiovascular disease evolving to failure
Digestive illness which avoid oral feeding (pancreatitis, NEC)
Infections
Burns
Severe neurologic impairment
Severe metabolic disease
Neoplastic terminal disease
AIDS terminal disease

NEC, necrotizing enterocolitis.

for an ideal time of 8 h/day is considered beneficial on lowering insulinemia, lipogenesis and fatty liver as well [4].

As shown in Table 2, in cases where a long-term PN is necessary, a wide spectrum of hepato-biliary changes may occur [5–8]. These changes are seen particularly in the pediatric population, ranging from simple steatosis to cholestasis, cholelithiasis and liver fibrosis, progressing to cirrhosis, portal hypertension and "end stage" liver disease which may even require liver transplantation.

Steatosis is the most common finding in adults, whilst early intrahepatic cholestasis with possible rapidly evolving liver dysfunction is most often common in neonates and infants. Prematurity (gestational age <37 weeks) and low birth weight are significant risk factors for PNALD/IFALD [5]. The prevalence of PNALD varies considerably among studies: it is estimated to be approximately 15–40% in adults, 40–60% in infants [9], and up to 85% in neonates who are receiving long term PN [7]. A recent review of twenty-three articles showed an incidence of 28.2% and 49.8% of pediatric PNAC and IFALD [10]. Moreover, in a recent prospective, multicenter study the incidence of PNALD was statistically correlated with the severity of Necrotizing Enterocolitis (NEC) [9]. The incidence of PNALD was directly proportional to the duration of PN (from 15.7% for PN ≤1 month up to 60.9% for PN ≥2 months) [11]. End-stage liver disease, often leading to combined intestinal and liver transplant, develops approximately in 15% of patients receiving long-term PN, when considering both adult and pediatric patients [12–14].

A wide epidemiological study over 4 years, involving 279 hospitalized children aged 0–18 years affected by long-term intestinal failure (IF), revealed a prevalence of 22% of IFALD, and 5% of the latter progressed to end stage disease [15].

PN is administered with a complete balanced nutrients' mixture that typically provides 10–20% from aminoacids and non-proteic calories from dextrose (50–60%) and lipid emulsions (20–30%), respecting a correct non-protein calories to nitrogen ratio. The latter are provided also to prevent essential fatty acid [linoleic acid (LA) and alpha-linoleic acid (ALA)] deficiency (EFAD) [16]. Indeed, the process of conversion of ALA into docosahexaenoic (DHA) and eicosapentaenoic (EPA) (inhibited by omega 6 excess) is metabolically costly and slowed in preterms. Precise individual caloric requirement should be calculated to avoid the risk of overfeeding causing steatosis.

2. Pathogenesis

PNALD has multifactorial origin with a number of involved pathogenetic mechanisms [17–19]. Among the many factors, immaturity of the liver plays an important role in the disease's natural history, as suggested by the age-related difference of disease progression. Cholestasis can develop into irreversible inflammatory/fibro-cirrhotic liver disease if not properly recognized and treated. Whereas steatosis, may be reversible, particularly in adults [17].

Alteration of bile salt entero-hepatic circulation in addition to prematurity may also be due to ileal resection, jejunostomy or distal ileal disease (e.g. inflammatory bowel disease, IBD). Recent insight into enterohepatic circulation reports that biliary salts activate farnesoid X factor (FXF), a nuclear factor present in gut and liver. This is of interest since it is known that ursodeoxycholic acid (UDCA) and, particularly, chenodeoxycholic acid (CDCA) stimulate synthesis of fibroblast growth factor 19 (FGF 19) via FXF, which reaches hepatocytes and down regulates CYP7A1, reducing biliary salt synthesis. Oral CDCA was successfully used in reducing steatosis in a PNALD animal model treatment [20].

In case of massive intestinal resection, short bowel syndrome is a serious risk factor for PNALD due to the combination of small intestinal bacterial overgrowth (SIBO), endotoxemia and local inflammation. In this scenario, the alteration of enterohepatic circulation secondary to intestinal resection is combined with the low motility of the remaining intestine, favoring SIBO and/or dysbiosis [21]. These intestinal bacteria produce a lipopolysaccharidic (LPS) endotoxin and a peptidoglycan polysaccharide complex that "translocate" to the liver in consequence of the increased permeability of the damaged intestinal mucosa ("leaky-gut") [22]. LPS may directly trigger TLR-4 and the consequent pro-inflammatory cascade leading to inflammatory and fibrotic changes. Pro-inflammatory cytokines (e.g. TNFa and IL1B) also down regulate the transcription of bile acids transporters. Karim et al. demonstrated that soy lipid-based PN caused progressive liver injury via LPS-(TLR4) Kuppfer cell activation when administered to rats with intestinal barrier damage [23].

Trace elements supplementation in PN is a standard practice in many neonatal intensive care units. However, many of these elements are contaminants in PN solutions, and contamination levels may already be sufficient for their normal metabolic needs. Additional supplementation could lead therefore to hepatic toxicity in neonates. Recently Bonjorappa et al. reviewed well this aspect [24]. They found that individualized supplementation of trace elements in TPN treated infants may be more appropriate rather than using bundled packages [25]. Manganese, as well as copper, are eliminated via the bile and theoretically may accumulate during cholestasis. Serum manganese level was correlated to high bilirubin and AST level [26]. However, it is not clear if its high levels cause cholestasis or if they are a consequence [13].

Serum copper, is physiologically regulated by liver excretion but its level seems to be not substantially affected by cholestasis. In course of TPN, copper level must be carefully monitored in the presence of cholestasis, but it should not be withheld from PN [27].

Also parenterally infused aluminum, as a contaminant of PN solutions, results in liver injury as demonstrated by elevated bile acids and by blunting of the bile canaliculi microvilli seen in pig models [28]. Safe aluminum levels have been established at up to 2 mcg/kg/day [29].

A carnitine deficiency has also been associated to the pathogenesis of hepatic steatosis. The carnitine deficiency, which is involved in the transport of long chain tryglicerides (LCT) across the mitochondrial membrane for oxidation, has been described in preterm infants because of limited stocks and reduced synthesis. However, the opportunity of carnitine supplementation in PN remains controversial [30,31].

A very important pathogenetic role on the development of PNALD is played by the quantity and quality of fat emulsions used. However, the pathogenic mechanism is not yet well known. Lipid infusion can be detrimental as it contributes to the onset of the so-called "fat overload syndrome" when exceeding the intake of 4 g/kg/day. Proper lipids/carbohydrates ratio as an excess of carbohydrates can determine lipogenesis as well due