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Prevalence of Liver Complications in Children Receiving Long-Term Parenteral Nutrition.

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Short title: Liver disease and parenteral nutrition

Abbreviations: CIPO: chronic intestinal pseudo-obstruction; GA: gestational age; TPN: total parenteral nutrition; IBD: inflammatory bowel disease; IUGR: intrauterine growth retardation; LB: liver biopsy, , SBS: short bowel syndrome;

Keywords: parenteral nutrition; liver disease; chronic disease; infant; child; adolescent; biopsy; fibrosis.

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ABSTRACT

BACKGROUND:

The hepatic prognosis of long-term home total parenteral nutrition (TPN)-dependent children is poorly documented.

OBJECTIVE:

To study outcome data in home TPN-dependent children and to describe precisely their liver biopsies in the attempt to analyze risk factors for biochemical and histological hepatic abnormalities.

PATIENTS AND METHODS:

Medical records of 42 children receiving home TPN for more than 2 years between January 1998 and December 2007 in a single approved home total parenteral center were reviewed. Hepatic biochemical abnormalities were analyzed. Hepatic biopsies were classified by two independent pathologists.

RESULTS:

Duration of TPN was 7.9 ± 0.8 years (mean \pm SEM), with an average age at onset of 1.5 ± 0.5 years. Twenty four patients (57%) developed biochemical liver abnormalities in an average of 2.9 ± 0.4 years after starting TPN. Risk factors for biochemical abnormalities were younger age at TPN commencement, longer duration of TPN, higher rate of catheter-related infections, and higher volume and energy content of TPN.

Liver biopsies were performed in 43% of patients (mean age 3.2 ± 0.9 years). Almost all patients had fibrosis (94%). Risk factors were dependent on each histological abnormality: fibrosis was significantly associated with a shorter length of bowel and a longer duration of TPN; cholestasis correlated with a lower percentage of total parenteral energy intake due to lipids; and steatosis had no risk factor identified.

CONCLUSION:

Our study reports a high rate of histological liver abnormalities and analyzes risk factors in children who underwent very long-term home TPN.

INTRODUCTION

For children depending on total parenteral nutrition (TPN), home TPN is an alternative to prolonged hospitalization. However, a long period of TPN can lead to severe complications. Among them, chronic abnormalities in liver biochemistries are frequent in adult and children, ranging from 15% to 85% (Quigley *et al.*, 1993; Clarke *et al.*, 1991; Messing *et al.*, 1992; Kelly, 2006; Knafelz *et al.*, 2003; Colomb *et al.*, 1992; Angelico and Della Guardia, 2000; Colomb *et al.*, 2007)). Chronic PN associated liver disease (PNALD) can lead to cholestasis and steatosis, as well as fibrosis and cirrhosis, as well as cholestasis and steatosis. However, the lack of an accurate and standardized histologic classification is an obstacle to compare studies. Many risk factors of PNALD have been identified (Beath, *et al.*, 1996; Ito and Shils, 1991; Colomb *et al.*, 2000, Fitzgibbons *et al.*, 2010). However, in children, data are fewer than in large adult cohorts and risk factors may be different. Furthermore, the duration of TPN varies widely among patients, confusing the impact of different factors. In addition, data on very long-term TPN in children are lacking. Finally, the relation between risk factors and specific histologic abnormalities (i.e. fibrosis, cholestasis and steatosis) are poorly documented. Therefore, the aims of this study were to analyze retrospectively outcome data in children receiving home TPN for more than 2 years and to describe accurately the liver lesions in an attempt to analyze risk factors for PNALD hepatic biochemical and histological abnormalities.

PATIENTS AND METHODS

Data were aggregated retrospectively from medical records over a 10-year period, from January 1998 to December 2007. We included children depending on TPN for more than 2 years, enrolled in long-term TPN programs of a single approved pediatric home TPN center in a French university teaching hospital. Children with liver disease diagnosed before initiation

of TPN or identified as unrelated to TPN (i.e. inborn liver disease, acquired toxic or viral liver disease) were excluded.

If TPN was essential to maintain growth and nutritional status, then home TPN was prescribed. Parents were taught home infusion during an average of 2 to 3 weeks, as previously described (Puntis, 1995). Follow-up included a 24-hour telephone hotline number for emergencies and regular outpatient follow-up visits to adapt the composition and volume of the nutrient solution to meet the child's requirement and to detect the occurrence of PN associated liver disease complications. The goal was to progressively decrease the number of nightly infusions if intestinal function improved. The composition of the TPN (i.e. amino acids, lipid emulsion, trace elements and vitamins) varied during the 10 years of the study.

Variables contributing to the development of PNALD were collected from the medical charts and included: demographic characteristics (age, sex, length of gestation, birth weight and height); the primary diagnosis including the etiology of short bowel syndrome (SBS); the length of remaining small bowel and conservation of ileocecal valve and/or colon; the age at TPN commencement and duration of TPN; the reason for TPN discontinuation; the numbers of days per week of TPN infusion and the duration in hours per day. Other factors evaluated included; the type of bacteria and the number of catheter-related infections defined as episodes of fever with clinical and biological parameters of infection (i.e. increased plasma concentration of C-reactive protein and polynuclear); positive blood cultures from the catheter and peripheral vein for the same pathogen or >1 positive blood culture for the same pathogen, effectiveness of antibiotic therapy; the presence of oral or enteral nutrition; and the cause of death. Furthermore, the home TPN regimen was analyzed to assess the mean daily volume and parenteral energy intake, the amounts of lipid, dextrose and protein expressed in g/kg of body weight per day, and the proportion of lipid and dextrose expressed as percentage of parenteral energy intake.

Criteria for PNALD were abnormalities in liver biochemistries lasting longer than 2 months including: hepatocellular injury (plasma alanine transaminase concentrations 1.5 times above the upper limit of normal) and cholestasis (bilirubin or alkaline phosphatase and γ -glutamyl transpeptidase plasma concentrations 1.5 times above the upper limit of normal). Biochemical abnormalities were classified as cytolysis alone, cholestasis alone or both if both cytolysis and cholestasis were present.

The first liver biopsy (LB) was performed if liver biochemistries or clinical hepatic abnormalities persisted for more than 6 months; or rarely, if abdominal surgery was necessary (cholectomy, for example). **Another biopsy was cared out if abnormalities on liver biochemistries worsened and latter from any sepsis or further risk factor.** Formalin-fixed LB specimens were stained with hematoxylin-eosin-saffron, trichrome, periodic acid-Schiff, and Perls. In addition, oil red staining was performed on frozen biopsy specimens when they were available. All LBs were analyzed and scored retrospectively and independently by two pathologists using 5 criteria as described in Table 1 in attempt to quantify fibrosis, cholestasis and steatosis. If disagreements existed between the two analyses, the final reported result was based on a third analysis done by both pathologists together.

Statistical analysis

First, we described the patients' characteristics and their biochemical and histological hepatic abnormalities. Then, in order to analyze risk factors of home PNALD abnormalities, patients were divided into two groups depending on biochemical and histological abnormalities. For biochemical abnormalities, children with cytolysis and/or cholestasis were compared with children without these conditions. For histological abnormalities at any biopsy, children without or having only mild abnormalities were compared with those with severe abnormalities for each kind of histological abnormality (fibrosis, cholestasis or steatosis).

For quantitative data, results were expressed as mean \pm SEM. For qualitative data, results were expressed as effective number and percentage. The non-parametric Kruskal-Wallis test was used to compare two or more independent groups of cases on one variable. χ^2 or Fisher exact tests were performed to compare the observed frequencies between the independently defined groups. Statistical significance was defined as a *P* value < 0.05 .

RESULTS

Description of population

Forty-two patients with very long-term TPN (> 2 years) were included (see Table 2). The male/female sex ratio was 1.2. Half were premature (< 37 weeks GA) and 25% were less than 31 weeks GA. Indications for home TPN were mainly primary digestive disease ($n=38$, 90%): short bowel syndrome (SBS), chronic intestinal pseudo-obstruction (CIPO), intractable diarrhea or inflammatory bowel disease (IBD). The largest subgroup included children with SBS, primarily neonatal in origin: atresia ($n=9$, 39%), enterocolitis ($n=8$, 35%), or volvulus ($n=3$, 13%). Among the 60% of children with SBS, the length of remaining small bowel was less than 50 cm in 17 (41%), between 51cm and 100cm in 5 (12%) and between 101cm and 150cm in 3 (7%) patients. The ileocecal valve was intact in 60% of children.

Home TPN duration The overall home TPN mean duration was long, almost 8 years. **Most patients ($n=33$, 78.6%) began TPN before the age of 1 year with a median age during neonatal period.** The age at TPN beginning, as well as the duration of home TPN, depended on the indication (figure 1). Sixty-nine percent of patients ($n=29$) had TPN for longer than 4 years and 43% ($n=18$) for more than 8 years.

TPN weaning and death

By January 2008, outcome is summarized in table 2. Around half of children remained on TPN. Interestingly, 9 children (21.4%) were weaned off after 5 years; the longest one was weaned off after 11 years. Almost half of patients (n=10, 43.5%) with SBS, despite a TPN dependency longer than 2 years, were weaned off TPN; but only 14.3% (n=1) of those with CIPO or Hirschsprung's disease were weaned off. Fifteen children (35.7%) were continuing home TPN in our pediatric centre and 6 others (14.3%) in an adult centre. Three patients (7%) had died: one from his primary disease (AIDS), one just after his intestinal transplantation and the last one just after bone marrow transplantation for immune deficiency. None died from hepatic complications, nor from direct complications of TPN. Three children (7%) underwent isolated intestinal transplantation: one with SBS died in the early postoperative period, as mentioned above, one with Hirschsprung's disease lost an intestinal graft after acute transplant rejection and restarted home TPN, and one with Hirschsprung's disease was weaned off TPN.

Infectious complications

The mean frequency of catheter-related infections was 1.1 ± 0.2 infections/patient/year of TPN, which corresponded to 7.5 ± 1.2 infections/patient. Only 4 patients (10%) never had septicemia, 12% (n=5) had a single septic episode, and 14% (n=6) had two episodes. The bacteria most often identified were coagulase-negative *Staphylococcus*.

Biochemical liver abnormalities and risk factors

Twenty-four patients (57%) developed biochemical liver abnormalities after a mean TPN duration of 2.9 ± 0.4 years, as detailed in Table 3. **One-third of patients (n=14) had the first biochemical disturbance before the age of 1 year. Among patients weaned off TPN, almost all**

(14/16) normalized their hepatic biochemistry within the 5 years; 2 others normalized in the next 2 years and for the last one we have no information concerning the hepatic biochemistry.

Risk factors for biochemical abnormalities are summarized in Table 4: younger age of TPN commencement ($p=0.032$), longer duration of TPN ($p=0.001$), higher rate of catheter-related infections ($p=0.004$), higher volume and energy content of TPN ($p=0.002$ and $p=0.017$ respectively), including a higher glucose rate in TPN ($p=0.01$).

Sixteen patients (38%) had a cholecystectomy: 6 (38%) for lithiasis and the others for prevention of lithiasis.

Hepatic histological abnormalities and risk factors

The LB was done only in those children who presented with abnormal liver biochemistries for more than six months or in the rare child who required abdominal surgery. A total of 43 LBs were performed in 19 patients; 38 were percutaneous needle biopsies and 5 were surgical biopsies (15%). Only 34 were available for retrospective analysis (79%), corresponding to 18 children (43%); the 5 missing LB were either performed in other hospital or specimen were transferred to other center. LBs were performed after a median of 2.5 years and one-third of LBs were performed during the first year of TPN. Almost all patients had fibrosis (94%), 41% had cholestasis and 41% had steatosis, as detailed in Table 3. Three patients had a LB during cholecystectomy before biochemical abnormalities developed. All these patients had fibrosis (stage 2 or 3) and two also had steatosis.

Risk factors were dependent on each histological abnormality (Table 4): fibrosis was significantly associated with a shorter length of bowel ($p=0.015$) and a longer duration of home TPN ($p=0.049$); cholestasis was correlated with a lower percentage of total parenteral energy intakes from lipids ($p=0.025$). Steatosis had no risk factor identified in our cohort.

DISCUSSION

Our study describes the evolution of home PNALD in 42 children receiving very long-term parenteral nutrition (average of 9 years and 8 months). We included a series of LBs for 18 children. The histological samples were accurately analyzed retrospectively by two independent pathologists using 5 histological criteria (Table 1).

In our cohort, only 10% of patients (had home TPN for an extra digestive disease. This incidence is lower than other cohorts, in which these etiologies account for around 25% of cases (Kelly, 2006; Ito and Shils, 1991). This difference could be related to exclusion criteria, as we excluded all children with home TPN durations of less than 2 years and those with initial hepatic insufficiency. On the other hand, short bowel syndrome resulting from neonatal causes accounted for almost half of patients with digestive disease, in accordance with the other published studies (Colomb *et al.*, 1992; Colomb *et al.*, 2000; Diamanti *et al.*, 2007).

The duration of home TPN in our cohort was especially important; it was almost double the duration of previous pediatric studies (Colomb *et al.*, 1992; Colomb *et al.*, 2007; Beath *et al.*, 1996; Diamanti *et al.*, 2007, Fitzgibbons *et al.*, 2010). We decided to include only children with more than 2 years of home TPN, which correspond to the theoretical duration of intestinal adaptation. Interestingly, 17 children (40.5%) were weaned off TPN after a long duration (5.5 years), which is a crucial point for intestinal transplantation evaluation. The difficulty of weaning off TPN was dependent on the etiology: the children with SBS had a high success rate of stopping TPN after 2 years (43.5%); on the other hand, children with CIPO or Hirschsprung's disease had less chance of TPN weaning after the same duration (14%), as described in previous studies (Colomb *et al.*, 1992; Quiros-Tejeira *et al.*, 2004). The mortality in our cohort was especially low (7%) compared to similar pediatric groups (16 to 33%) (Colomb *et al.*, 1992; Angelico and Della Guardia, 2000). In our study, the long duration of TPN favored a selection of patients with digestive etiologies which have a better

survival rate compared to systemic disease (congenital and acquired immune deficiencies, for example).

Catheter-related septicemia is one of the most frequent complications of TPN. In our study, the incidence of septic episodes was similar to the other studies: 1.1 versus 0.4 to 1.5 septicemia/child/year of TPN in the previously published data (Colomb *et al.*, 1992; Beath *et al.*, 1996). Only 10% of our patients never had a catheter-related infection. Negative-coagulase *Staphylococcus* was the main pathogen responsible for infection (43%), which is also in accordance with previous studies (Beath *et al.*, 1996; Hermans *et al.*, 2007)).

PNALD is another classical complication of TPN. Prevalence of this complication varies from 7.4 to 84% in the literature, depending on the pathology and the criteria used to define the liver complication (Colomb *et al.*, 1992; Kelly, 1998; Kumpf, 2006). For this reason, we described precise biochemical and histological hepatic abnormalities. **Biochemical impairments were especially frequent in our cohort (57%) compared to the other pediatric studies (15-23%) (Angelico and Della Guardia, 2000; Colomb *et al.*, 2007; Diamanti *et al.*, 2007); Diamanti *et al.*, 2003); despite oral nutrition for all patients of our cohort, which is a well known protective factor against PNALD.** Again, the double duration of TPN in our cohort compared to previous published studies may explain this difference. Furthermore, a substantial number of LBs were performed (43% of children), demonstrating a high rate of histological complications: fibrosis was present in almost all children who underwent LB, while both cholestasis and steatosis was found in 41% of patients (Table 3). This high frequency of fibrosis is in agreement with a recent study: in a cohort of 6.1 month old children, Fitzgibbons described 89% of hepatic biopsies with fibrosis and 9.6% with cirrhosis despite a shorter duration of TPN (4.7 month vs 2 years) (Fitzgibbons *et al.*, 2010)). **In our study, the follow-up of histological abnormalities indicated that steatosis was stable or decreased during the 10-year study period for the majority of patients; cholestasis varied**

widely depending on the patients, and fibrosis was stable or increased but never decreased (data not shown). Five years after TPN discontinuation, almost all patients normalized their hepatic biochemistry, however we have no histological analysis to confirm a complete normalization. Interestingly, 3 patients without any biochemical abnormality underwent a systematic LB during cholecystectomy. All three had fibrosis (stage 2 to 3), and two of them had associated steatosis. The same association of fibrosis with normal hepatic biochemical parameters was reported in youngest children: 55% of biopsies with fibrosis and 37% (3/8 patients) with cirrhosis were obtained in patients without evidence of biochemical cholestasis (Fitzgibbons *et al.*, 2010). These results raise the issue of systematic LB and the place of new techniques such as Fibroscan® (de Ledinghen *et al.*, 2007) to monitor very long-term TPN in the attempt to detect infra-biochemical liver complications. Further multicenter trials are needed to answer to this important clinical question.

The pathophysiology of PNALD complications is not yet fully understood. Many risk factors are involved. To our knowledge, this study is the first to analyze independent risk factors for biochemical or histological abnormalities in very long term TPN and to propose an accurate classification of histological abnormalities (Table 1). Interestingly, risk factors were different depending on the kind of complication (Table 4). For biochemical impairment as reflected by abnormal liver biochemistries, we confirmed some risk factors previously described, such as a young age of TPN initiation, a long duration of TPN, a higher rate of catheter-related infections, a higher volume and energy content of TPN, and a high glucose rate in TPN (expressed as absolute intake g/kg/d or as in relative amount of % caloric intake) (Beath *et al.*, 1996; Puntis, 1995; Quiros-Tejiera *et al.*, 2004; Candusso, *et al.*, 1995; Kelly, 1998; Kumpf, 2006). Surprisingly, the lipid rate in TPN was not statistically significantly related to biochemical abnormalities as previously described (Diamanti, *et al.*, 2007; Hermans *et al.*, 2007; Kumpf, 2006; Kaufman *et al.*, 2003; Cavicchi *et al.*, 2000). We can argue, first,

that during management of our cohort, a high rate of lipids was avoided in accordance with international recommendations (Koletzko *et al.*, 2005); second, that a high glucose rate leading to increasing biochemical abnormalities indicates that the carbohydrate-to-lipid ratio is important for preventing hepatic disturbances, as previously reported (Bresson *et al.*, 1989). With respect to histological risk factors: for steatosis, we didn't find any significant risk factors among those analyzed. In contrast, a more severe fibrosis was associated with a shorter intestinal length, a longer duration of TPN and a higher rate of lipid infusion ($p=0.05$). Recently, gestational age at birth was reported to be significantly associated with the degree of liver fibrosis (Fitzgibbons *et al.*, 2010). Cholestasis was only associated with lipid intake as percentage of total energy. Other classical risk factors, such as prematurity (Quiros-Tejeira *et al.*, 2004; Kelly, 1998; Kumpf, 2006; Kaufman *et al.*, 2003; Robinson and Ehrenkranz, 2008), intrauterine growth retardation (Robinson and Ehrenkranz, 2008) and resection of the ileocecal valve, were not found in our cohort.

CONCLUSION

Our study describes a cohort of children with the longest duration of home TPN in the literature and indicates that late weaning off of TPN is possible in almost half of patients. To our knowledge, this is the first study that uses standardized criteria for histological biopsies to analyze the deleterious effect of long-term home TPN in children. It demonstrates a high rate of PN associated liver disease hepatic complications. However, in our study, even if these children were at high risk, none died of hepatic complications. For the first time, we showed that histological liver injuries were dependent on specific risk factors and we reported their evolution over time. **Our study highlights the importance of preventing catheter-related infections and adaptation of the lipid-glucose ratio to decrease hepatic damage.** Finally, we raise the issue of systematic LBs to monitor hepatic complications in very long-term TPN.

BIBLIOGRAPHY

- Angelico M, Della Guardia P (2000). Review article: hepatobiliary complications associated with total parenteral nutrition. *Aliment Pharmacol Ther* **14**, S54-S57.
- Beath SV, Davies P, Papadopoulou A, Khan AR, Buick RG, Corkery JJ *et al.* (1996). Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. *J Pediatr Surg* **31**, 604-606.
- Bresson JL, Narcy P, Putet G, Ricour C, Sachs C, Rey J (1989). Energy substrate utilization in infants receiving total parenteral nutrition with different glucose to fat ratios. *Pediatr Res* **25**, 645-648.
- Candusso M, Giglio L, Faraguna D (1995). Long-term home parenteral nutrition in children. *Clin Nutr* **14**, S28-S32.
- Cavicchi M, Beau P, Crenn P, Degott C, Messing B (2000). Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* **132**, 525-532.
- Clarke PJ, Ball MJ, Kettlewell MG (1991). Liver function tests in patients receiving parenteral nutrition. *J Parenter Enteral Nutr* **5**, 54-59.
- Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Revillon Y, Jan D *et al.* (2007). Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. *J Pediatr Gastroenterol Nutr* **44**, 347-353.
- Colomb V, Fabeiro M, Dabbas M, Goulet O, Merckx J, Ricour C (2000). Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. *Clin Nutr* **19**, 355-359.
- Colomb V, Goulet O, Rambaud C, De Potter S, Sadoun E, Ben Hariz M *et al.* (1992). Long-term parenteral nutrition in children: liver and gallbladder disease. *Transplant Proc* **24**, 1054-1055.
- de Ledinghen, V., B. Le Bail, Rebouissoux L, Fournier C, Foucher J, Miette V *et al.* (2007). Liver stiffness measurement in children using FibroScan: feasibility study and comparison with Fibrotest, aspartate transaminase to platelets ratio index, and liver biopsy. *J Pediatr Gastroenterol Nutr* **45**, 443-450.
- Diamanti A, Basso MS, Castro M, Calce A, Pietrobattista A, Gambarara M (2007). Prevalence of life-threatening complications in pediatric patients affected by intestinal failure. *Transplant Proc* **39**, 1632-1633.
- Diamanti A, Gambarara M, Knafelz D, Marcellini M, Boldrini R, Ferretti F *et al.* (2003). Prevalence of liver complications in pediatric patients on home parenteral nutrition: indications for intestinal or combined liver-intestinal transplantation. *Transplant Proc* **35**, 3047-3049.
- Fitzgibbons SC, Jones BA, Hull MA, Zurakowski D, Duro D, Duggan C, *et al* (2010). Relationship between biopsy-proven parenteralnutrition-associated liver fibrosis and biochemical cholestasis in children with short bowel syndrome. *J Pediatr Surg* **45**, 95-99.
- Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V (2007). Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* **44**, 459-463.
- Ito Y, Shils ME (1991). Liver dysfunction associated with long-term total parenteral nutrition in patients with massive bowel resection. *J Parenter Enteral Nutr* **15**, 271-276.
- Kaufman SS, Gondolesi GE, Fishbein TM (2003). Parenteral nutrition associated liver disease. *Semin Neonatol* **8**, 375-381.
- Kelly DA (1998). Liver complications of pediatric parenteral nutrition--epidemiology. *Nutrition* **14**, 153-157.

- Kelly DA (2006). Intestinal failure-associated liver disease: what do we know today? *Gastroenterology* **130**, S70-S77.
- Knafelz D, Gambarara M, Diamanti A, Papadatou B, Feretti F, Tarissi De Iacobis I *et al.* (2003). Complications of home parenteral nutrition in a large pediatric series. *Transplant Proc* **35**, 3050-3051.
- Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R (2005). 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* **41**, S1-S87.
- Kumpf VJ (2006). Parenteral nutrition-associated liver disease in adult and pediatric patients. *Nutr Clin Pract* **21**, 279-290.
- Messing B, Colombel JF, Heresbach D, Chazouilleres O, Galian A (1992). Chronic cholestasis and macronutrient excess in patients treated with prolonged parenteral nutrition. *Nutrition* **8**, 30-36.
- Puntis JW (1995). Home parenteral nutrition. *Arch Dis Child* **72**, 186-190.
- Quigley EM, Marsh MN, Shaffer JL, Markin RS (1993). Hepatobiliary complications of total parenteral nutrition. *Gastroenterology* **104**, 286-301.
- Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N *et al.* (2004). Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. *J Pediatr* **145**, 157-163.
- Robinson DT, Ehrenkranz RA (2008). Parenteral nutrition-associated cholestasis in small for gestational age infants. *J Pediatr* **152**, 59-62.

LEGENDS

Figure 1-a: Age at TPN commencement based on indications (mean \pm SEM).

Figure 1-b: TPN duration based on indications (mean \pm SEM).

CIPO: chronic intestinal pseudo obstruction, IBD: inflammatory bowel disease, TPN: total parenteral nutrition.

Table 1: Scoring used for microscopic analysis

Scoring	0	1	2	3	4
Portal fibrosis	None	One or more enlarged portal tracts	One or more septa	One or more portal-portal bridges	Cirrhosis
Centrilobular fibrosis	None	One or more centrilobular veins with thick wall	One or more septa	One or more central-portal or central-central bridges	Cirrhosis
Perisinusoidal fibrosis	None	Focal	Diffuse		
Steatosis (% of hepatocytes)	None	< 25%	25 to 50%	51 to 75%	> 75%
Cholestasis	None	Hepatocellular granules	Few intercellular (canalicular) bile plugs	Several intercellular (canalicular) bile plugs	Ductular bile plugs

This table is a description of histological scoring using 5 criteria in attempt to quantify fibrosis, cholestasis and steatosis. ND: not done

Table 2: Patient characteristics

Patients, n	42
Male n (%)	23 (54.8)
Term, GA (weeks) (mean±SEM)	35.6 ± 0.7
IUGR, n (%)	10 (25)
Parenteral nutrition	
Age of TPN commencement, years (mean±SEM)	1.5 ± 0.5
Duration of TPN, years (mean±SEM)	7.9 ± 0.8
Indications for TPN, n (%)	
Short Bowel Syndrome	23 (54.8)
CIPO and Hirschsprung's disease	7 (16.7)
Intractable Diarrhea	4 (9.5)
Inflammatory Bowel Disease	2 (4.8)
Lymphangiectasia	2 (4.8)
Immune Deficiency	2 (4.8)
Colic Resection	2 (4.8)
Outcome, n (%)	
Weaning off home TPN	17 (40.5)
Continuing home TPN	22 (52.5)
Death	3 (7.1)
Intestinal Transplantation (IT)	3 (7.1)
-IT weaning off home TPN, n	1
-IT continuing home TPN, n	1
-IT death, n	1

TPN content at time of biochemical hepatic abnormality	
Proteins, g/kg/d (mean±SEM)	0.32 ± 0.11
Dextrose, g/kg/d (mean±SEM)	14.4 ± 0.6
Lipids, g/kg/d (mean±SEM)	1.8 ± 0.08
Hepatic biopsies	
Total hepatic biopsies, n	34
Patients with biopsies, n (%)	18 (42.9)
Age at first biopsy, months (mean± SEM)	29.5 ± 6.6
Infection history	
Total incidence, sepsis per TPN year (mean±SEM)	1.1 ± 0.2
Staphylococcus, coag-neg per child (%)	44.0
Enterobacteria, sepsis per child (%)	33.3
Staphylococcus aureus per child (%)	8.0

This table describes the patients and pathologies; the characteristics of total parenteral nutrition duration and composition at time of biochemical hepatic abnormalities; the number of hepatic biopsies and the catheter related infections.

CIPO: chronic intestinal pseudo obstruction; coag neg: coagulase negative; GA: gestational age;

TPN: total parenteral nutrition; IT: intestinal transplantation; IUGR: intra uterine growth

retardation; mo: months; PN: parenteral nutrition

Table 3: Hepatic abnormalities

Characteristics	Patients	TPN total duration
Value (mean \pm SEM)	n (%)	Months (mean \pm SEM)
Biochemical (liver function tests)		
Patients	42 (100.0)	95.0 \pm 9.6
<i>None</i>	18 (42.9)	60.0 \pm 8.7
<i>Cytolysis</i>	6 (14.3)	118.6 \pm 18.2
ALT = 108.8 \pm 13.4 (UI/L \pm SD)		
<i>Cholestasis</i>	6 (14.3)	161.2 \pm 22.6
Bilirubin = 28.4 \pm 2.1 (μ mol/L \pm SD)		
GGT = 102.9 \pm 7.6 (UI/L \pm SD)		
<i>Cytolysis+Cholestasis</i>	12 (28.6)	102.6 \pm 21.1
Histological	Biopsies	TPN duration
	n (%)	Months (mean \pm SEM)
Biopsies n	34 (100.0)	46.9 \pm 5.9
<i>Fibrosis</i>	31 (91.2)	50.0 \pm 6.2
Mild	8 (23.5)	55.6 \pm 13.6
Moderate	6 (17.6)	35.0 \pm 14.2
Severe	17 (50.0)	52.6 \pm 8.0
<i>Cholestasis</i>	14 (41.1)	31.1 \pm 7.6
Mild	7 (20.5)	43.4 \pm 13.0
Moderate	4 (11.8)	13.5 \pm 5.3
Severe	3 (8.8)	26.0 \pm 10.0
<i>Steatosis</i>	14 (41.1)	58.8 \pm 12.0

Mild	6 (17.6)	66.3 ± 18.0
Moderate	6 (17.6)	57.0 ± 22.0
Severe	2 (5.9)	41.5 ± 30.4

This table describes the number of patients and the duration of total parenteral nutrition depending on the type of hepatic abnormalities. First, the biochemical hepatic abnormalities are classified as cytolysis (ALT increased), cholestasis (bilirubin and/or GGT increased) or both so called mixt (cytolysis and cholestasis). Second, the histological abnormalities are classified as fibrosis, cholestasis and steatosis. The intensity of histological abnormalities is expressed as mild, moderate or severe.

Table 4: Factors contributing to home total parenteral nutrition-related liver abnormalities

Factor	Biochemical Abnormalities			Histological Abnormalities								
	Cytolysis and/or Cholestasis			Fibrosis			Cholestasis			Steatosis		
	None	Present	p (%)	None or Mild	Severe	p (%)	None or Mild	Severe	p (%)	None or Mild	Severe	p (%)
Indications for TPN												
Type of etiology, n	18	24	NS	2	16	NS	12	6	NS	13	5	NS
Small-bowel <100cm, n/total	5/18	17/24	NS	0/2	13/16	0.015	9/12	4/6	NS	10/13	3/5	NS
TPN characteristics												
Age of TPN commencement, mo (mean±SEM)	27.2±10.9	11.8±6.7	0.032	0.5±0.5	6.2±5.5	NS	7.5±7.4	1.9±1.2	NS	7.2±6.8	1.4±1.4	NS
Duration of TPN, mo (mean±SEM)	60.0±8.7	121.0±13.3	0.001	39.6±8.7	106.2±13.0	0.049	101.0±16.6	94.5±20.0	NS	97.2±15.6	103.1± 22.6	NS
Oral nutrition, n/total	13/14	21/23	NS	1/2	14/16	NS	10/12	5/6	NS	11/13	4/13	NS
Enteral nutrition, n/total	0/14	4/21	NS	0/2	3/14	NS	2/10	1/6	NS	2/13	1/5	NS
Parenteral volume, ml/kg/d (mean±SEM)	76.4±29.0	107.3±29.0	0.002	112.5±67.2	111.7±29.7	NS	11.3±10.0	112.8±30.2	NS	117.4±34.7	98.2±24.1	NS
Parenteral energy intake,	65.7±15.4	80.3±18.2	0.017	64.3±10.2	82.5±16.6	NS	79.5±19.4	82.4±10.3	NS	64.2±10.2	83.5±16.6	NS

kCal/kg/d (mean±SEM)												
Parenteral Gluc intake, g/kg/d (mean±SEM)	12.6±3.2	15.6±3.6	0.01	13.3±1.8	16.1±3.6	NS	15.1±3.9	16.4±2.6	NS	15.4±3.9	16.4±2.6	NS
Parenteral Lipid intake, g/kg/d (mean±SEM)	1.7±0.5	1.9±0.5	NS	1.3±0.4	1.9±0.5	0.05	1.9±0.5	1.6±0.4	NS	1.8±0.6	2.0±0.0	NS
Parenteral Lipid intake, % energy intake (mean±SEM)	30.7±10.5	29.0±8.7	NS	21.0±3.0	28.9±10.2	NS	30.5±10.0	20.2±3.8	0.025	27.4±11.2	28.9±5.9	NS
Parenteral infusions, d/w (mean±SEM)	4.6±0.8	4.8±0.9	NS	4.5±0.7	4.8±0.6	NS	4.7±0.7	5.0±0.0	NS	4.8±0.4	4.6±0.9	NS
Parenteral cyclisation, h/d (mean±SEM)	12.4±0.9	14.3±4.2	NS	13.5±2.1	15.0±4.8	NS	13.6±3.6	17.6±5.6	NS	14.7±4.5	15.3±5.8	NS
Infections n/patient (mean±SEM)	3.9±4.9	10.1±8.7	0.004	7.0±9.9	8.5±5.6	NS	8.7±6.0	7.7±5.8	NS	8.5±6.3	7.8±5.0	NS
Gram-negative infection, n/patient (mean±SEM)	1.2±2.0	3.6±4.8	NS	4.0±5.7	2.9±3.5	NS	3.2±3.7	2.8±3.8	NS	3.4±3.9	2.0±2.8	NS

This table details the factors associated with biochemical or histological hepatic abnormalities among the pathology, the parenteral nutrition characteristics, and catheter related infection. NS: no significant; mo: month.



