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Original article

Hypercholesterolemia and hypertriglyceridemia as risk factors of liver dysfunction in children with inflammation receiving total parenteral nutrition

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SUMMARY

Background and aims: Hepatic dysfunction, due to parenteral nutrition, may become severe and lead to cirrhosis and hepatic failure, especially in newborns and infants. This study aimed to evaluate the association between the exclusive use of total parenteral nutrition (TPN) and changes in the hepatic profile, and to investigate the relationship between age, hypertriglyceridemia, and hypercholesterolemia, and the occurrence of laboratory liver dysfunction.

Methods: A descriptive and historical cohort study was conducted, evaluating 195 pediatric patients (age: 1 month to 19 years) who received TPN. The following hepatic and lipid profiles were assessed: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), bilirubin, triglycerides (TGs), cholesterol, high-density lipoprotein (HDL), albumin, and transthyretin. High C-reactive protein and/or low HDL were considered indicative of inflammatory process.

Results: The majority of patients presented normal values of AST (79.2%), ALT (74.9%), GGT (56.4%), and alkaline phosphatase (68.1%). Total bilirubin changed in 68.5% of patients, and transthyretin and albumin were low in 87.3% and 65.1% of the patients, respectively. Incidences of high GGT values were related to age (odds ratio [OR], 2.46; confidence interval [CI] 1.28–4.76; $p = 0.007$), hypercholesterolemia (OR, 3.00; 95% CI, 1.24–7.25; $p = 0.015$), and hypertriglyceridemia (OR, 2.39; 95% CI, 1.02–5.60; $p = 0.046$). Incidences of elevated ALT values were associated with hypercholesterolemia (OR, 4.57; 95% CI, 2.03–10.30; $p < 0.001$).

Conclusion: Monitoring the hepatic profile from the early stage of TPN is necessary. Changes in the plasma lipid and hepatic profiles were frequently observed during the infusion of TPN, in patients with inflammation. Patients >2 years old and those with high TG and HDL levels were more likely to have elevated GGT levels. Hypercholesterolemia was associated with ALT alterations. Strategies to attenuate these issues should be considered in the early stages, in patients with TPN.

1. Introduction

Hepatic changes related to parenteral nutrition (PN) are commonly observed in patients undergoing total PN (TPN) [1]. Although frequently observed, their etiology is multifactorial, and they may be a consequence of some risk factors, such as altered intestinal function, absence of enteral stimulation, PN components acting as toxic substances, absence of essential nutrients in the PN solution, presence of an underlying disease (short bowel syndrome, gastroschisis, jejunal atresia, necrotizing enterocolitis, etc.), premature birth, low birth weight, duration of PN, and presence of sepsis [2].

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Parenteral nutrition-associated liver disease (PNALD) has been studied in depth, and encompasses a spectrum of hepatobiliary disorders, such as steatosis, steatohepatitis, fibrosis, cirrhosis, biliary clay, cholestasis, and acalculous cholecystitis [2,3]. Its prevalence varies between 8% and 90%, and this variation is due to differences in the populations studied, the definition of liver dysfunction used (based on biochemical or histological values), the composition of the PN solutions, and the medical or surgical conditions [4]. PNALD is generally related to the prolonged use of PN. However, elevated hepatic enzyme concentrations may be observed at the onset of PN therapy [3]. Early intervention is one way to attenuate hepatic damage and minimize liver dysfunction [3]. In this context, this article aimed to study the associations between the use of TPN and changes in the plasma lipid and hepatic profiles, and to investigate the relationship of age and the presence of hypertriglyceridemia and hypercholesterolemia with the occurrence of laboratory liver dysfunction.

Data on the changes in the onset of PN, particularly in those cases in which enteral or oral nutrition is not possible, are limited. In fact, although most patients can receive enteral or oral nutrition, some cannot. Thus, the consequences, in terms of lipid and liver profiles, in patients receiving exclusive PN have not been well-elucidated thus far.

2. Materials and methods

A historical cohort study was conducted in pediatric patients who received TPN while hospitalized at the University of Campinas (UNICAMP) Hospital, from 2012 to 2016. All pediatric patients who were administered TPN were selected. The study was approved by the Ethics and Research Committee of the Hospital (#1304/2011).

Patients without complete laboratory evaluations, and those with a history of liver disease or dyslipidemia were excluded. Those who were fed oral and enteral nutrition concomitantly with PN were also excluded. Patient search records were completed during the 8 days of treatment, and filed after discharge.

The age of the patients studied ranged from 1 month to 19 years. For the analysis, patients were divided into 2 age groups (>2 and ≤2 years) due to the high possibility of the rapid development of liver disease in neonates and infants [5].

2.1. Nutritional assessment

All patients' nutritional statuses were assessed at the time of PN prescription, comprising anthropometric data and the evaluation of plasma levels of albumin, transthyretin, and cholesterol. Patients with albumin and cholesterol levels <3.5 g/dL and <100 mg/dL, respectively, were considered malnourished [6]. Although there are more elaborate markers of malnutrition, in clinical practice, tests for albumin and cholesterol are the most easily available.

2.2. Inflammatory assessment

High C-reactive protein (CRP) (≥3.0 mg/dL) and/or low high-density lipoprotein (HDL) cholesterol (<45 mg/dL) levels were considered to be indicative of inflammation [7].

2.3. PN prescription routine

Before the prescription, all patients' nutritional statuses were assessed. The amount of energy incorporated in the PN was computed based on the grams of each macronutrient, multiplying the amount in grams of amino acids by 4, carbohydrate by 3.4, and lipid (TCL/TCM at 20%) by 10. The PN composition was individually modified according to weight, clinical conditions, and laboratory parameters. The multidisciplinary nutritional therapy team, in this study, comprised a nutritionist, physician, nurse, and pharmacist who calculated the PN daily. The PN prescriptions were based on the norms recommended in the literature [8]. The composition of the parenterals used is shown in Fig. 1.

2.4. Laboratory monitoring

A complete laboratory test was performed on each patient before the first PN treatment, and during the entire period of PN use. For this study, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), bilirubin, triglycerides (TGs), cholesterol, and HDL cholesterol were considered. All the cut-off values adopted in this study are shown in Fig. 2. The laboratory monitoring was performed in 3 periods: up to 48 h before the start of the infusion of PN, from the first day to the fourth day, and from the fifth day to the eighth day of PN infusion.

ALT and GGT values that were at least twice as high as those established as the reference values were considered altered. To determine the levels of albumin, CRP, transthyretin, cholesterol, HDL, and TG, the blood was collected in a vial without anticoagulant, and the methods used were colorimetric method (bromocresol green), nephelometry, enzymatic colorimetric method, enzymatic direct colorimetric method, and enzymatic colorimetric method, respectively. To determine the ALT and AST levels, the IFCC-UV-kinetic method (with pyridoxal phosphate) was used; for the GGT level, the kinetic colorimetric enzymatic method; for the alkaline phosphatase level, the colorimetric kinetic; and for the bilirubin level, the Diazo colorimetric method. The dosages and procedures were administered and standardized, respectively, in the Laboratory of Clinical Pathology of the Hospital.

2.5. Statistical analysis

The SPSS software version 16.0 was used for statistical analysis.

The prevalence of high ALT and GGT levels was determined based on the following predictive variables: sex, age, malnutrition, total and HDL cholesterol levels, TG levels, and the presence of inflammatory process. To evaluate the association between the qualitative variables, a chi-square test or Fisher's exact test was used when indicated. The odds ratios (ORs), adjusted using the multivariate logistic regression and the forward stepwise method (Wald) (with inclusion and exclusion p-values of 0.05 and 0.10, respectively), were determined. p-Values <0.200 of the predictor variables that presented in the bivariate analysis were selected to compose the model.

3. Results

A total of 207 patients were selected for the study, 12 of whom were excluded based on the exclusion criteria. Of the 195 patients admitted to the study, 112 were male (57.4%), and most of the participants were >15 years old (24.6%) (Table 1).

With regards to the laboratory profile, the transthyretin and albumin levels in 87.3% and 65.1% of the patients, respectively, were below the reference values.

The HDL cholesterol level was low in 94.4% of the patients, and the CRP levels were high in 92.7% of them (Table 2).

The ALT level was twice as high as normal in 30.1% of the women, and 33.8% of those who were <2 years old.

Among the patients who were classified as malnourished, based on the laboratory tests, ALT alterations were observed in 24.3%. The highest proportion of ALT alterations (40%) were observed in patients with chronic malnutrition (based on the anthropometric data

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