Original paper

Activity of aminotransferases as a marker of liver injury in home parenteral nutrition patients

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Abstract

Aim of the study: Parenteral nutrition associated liver disease (PNALD) is a frequently reported complication of long-term parenteral nutrition. Early diagnosis and treatment of PNALD can help prevent end-stage liver disease. The aim of the study was to evaluate the activity of aminotransferases as a marker of liver dysfunction in patients receiving home parenteral nutrition under the care of a reference center.

Material and methods: A comprehensive analysis of patients' medical records from a 9-year period (December 2012 – December 2021) was conducted and the following parameters were evaluated: parenteral nutrition mixture composition, total plasma bilirubin, activity of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), standardized time factor prothrombin (international normalized ratio [INR] factor) and serum albumin. The analysis covered 630,537 days of parenteral nutrition. The study included 251 patients (140 women and 111 men) included in the Home Parenteral Nutrition Program.

Results: PNALD was diagnosed in 11 parenteral fed patients, which gives the frequency of 8.3%/9 years of treatment. Two deaths were classified as cause of death related to liver disease but not related to PNALD. None of the patients included in the analysis developed end-stage liver failure.

Conclusions: The above analysis shows that individual selection of the composition of the mixture for intravenous nutrition significantly reduces the risk of PNALD and may prevent liver failure in this context.

Key words: liver disease, PNALD, home parenteral nutrition, aminotransferases.

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Introduction

Parenteral nutrition (PN) is a method of treating patients with gastrointestinal insufficiency in whom food supply through the gastrointestinal tract is impossible or ineffective [1-3]. A complete mixture used for parenteral nutrition contains amino acids, glucose, fat emulsion, electrolytes, vitamins and trace elements.

Long-term home parenteral nutrition (HPN) is used in patients with irreversible gastrointestinal insufficiency or in patients who require several months of preparation for reconstructive surgery. This treatment requires strict adherence to procedures, the progression of which may be associated with the occurrence of complications, which are divided into three groups: mechanical, metabolic, and septic. Metabolic complications include blood sugar and electrolyte disturbances, as well as complications related to the functioning of organs, especially the liver and kidneys. Septic complications include catheter-related bloodstream infections and skin infections around access to the central vein. Recurrent and chronic septic conditions exacerbate liver damage. Most complications can be avoided if procedures are strictly followed (aseptic access control, mixture preparation and storage, metabolic controls, and method and timing of mixing).
Liver dysfunction in patients on home parenteral nutrition

Parenteral nutrition-associated liver disease (PNALD) is a commonly reported complication of long-term parenteral nutrition with an incidence of 25-100%, associated with increased mortality in patients on PN [4-7]. Abnormal blood test results indicative of liver damage (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin and serum bile acids) are observed in 30-40% of patients in PN [4, 6].

Clinical studies show that the incidence of PNALD-associated liver failure is decreasing [1]. This is related to optimization of nutritional intake and comprehensive patient care, modification of dosage and introduction of new types of fat emulsions for preparation of nutritional mixtures. Early diagnosis and treatment of PNALD can help prevent end-stage liver disease. It is difficult to clearly define the PNALD risk factors – they include both the length of the remnant bowel, the possibility of enteral feeding of the patient, disorders of hepatobiliary circulation, excessive energy intake, nutritional deficiencies and incorrect composition of the parenteral admixture (usually incorrect selection of fat emulsion) [4, 6, 8]. The risk of PNALD increases when extensive bowel resection has been performed and the patient is unable to consume food [4, 6, 8]. Data also show an increase with increasing duration of parenteral therapy [1, 8, 9].

Aim of the study

The aim of the study was to evaluate the activity of aminotransferases as a marker of liver dysfunction in patients receiving home parenteral nutrition under the care of a reference center.

Material and methods

This retrospective study comprised all adult patients (N = 251, 140 women, and 111 men) included in the HPN procedure in the reference center in Poland on December 31, 2012, according to the report of the Polish National Health Fund.

Patients were divided into three groups depending on their clinical status on December 31, 2021: group 0 – patients who died, group 1 – patients weaned off parenteral nutrition due to regaining gastrointestinal autonomy, group 2 – patients still receiving home parenteral nutrition. Group 2 was additionally divided into subgroups: 2A – patients without PNALD features, 2B – patients with PNALD features.

Demographic data of individual groups are presented in Table 1.

A comprehensive analysis of patients’ medical records from the 9-year period (December 2012 – December 2021) was conducted and the following parameters were evaluated: parenteral nutrition mixture composition, total plasma bilirubin, activity of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), standardized time factor prothrombin (international normalized ratio [INR] factor) and serum albumin.

The analysis included all medical records: Home Parenteral Nutrition Procedure Qualification Cards, Hospital Discharge Cards, Hospitalization Epicries, Death Cards, Visit Entries, and Nutrition Clinic Check-Up Cards.

Patients in group 1 were not included in further analysis of the study because they had completed nutritional treatment or had changed their HPN centers. Groups 0 and 2 were analyzed in detail for identification of liver disorders.

The research was approved by the Ethics Committee of the Centre of Postgraduate Medical Education (protocol code 94/2021, date of approval November 10, 2021).

Statistical analysis

For quantitative variables, the following measure was determined: central tendency (median), mean,
min, max, standard deviation. For the categorical variables, the following measures were determined: number (n) and frequency (%).

In a situation where the dependent variable was on the quantitative/ordinal scale, and the independent variable on the qualitative scale, Mann-Whitney and Kruskal-Wallis non-parametric tests were used. The above tests are used when the conditions for using parametric tests are not met, including the condition of normal distribution.

Statistical analysis was performed using the SPSS program and all relationships are statistically significant when p < 0.05.

Results

The results were discussed based on the classification into groups.

Group 0

Sixty-three patients died during the study. In 61 patients, the cause of death was other than liver disease. The most commonly reported cause was cardiovascular failure (39%). Two deaths were classified as cause of death related to liver disease but not related to PNALD (case 1 – PBC – primary biliary hepatitis, case 2 – injury – both discussed below).

Case 1. A 63-year-old male patient was receiving parenteral nutrition due to an almost complete resection of the small intestine with an end jejunostomy (20 cm posterior to the ligament of Treitz). Blood tests showed an elevated total bilirubin concentration (mean concentration in the 4 months before death was 7 mg%, maximum concentration 12.6 mg%), elevated transaminases (ALT 96 U/l, AST 128 U/l) and an expanded INR index. An ultrasound image showed hyperechoic liver parenchyma, enlargement of its dimensions, irregular rim, and numerous small deposits in the gallbladder. Since there was no reason to diagnose any other cause, PNALD was diagnosed. Changing the quantity and quality of fat emulsion, reducing the total caloric content or modifications to the hourly intravenous infusion schedule did not improve the situation. During the diagnostic workup, a positive family history of liver disease was noted and primary biliary hepatitis (PBC) was diagnosed based on liver biopsy results. The patient was referred to a liver transplant center but was not placed on the recipient list and died of progressive organ failure.

Case 2. A 70-year-old patient who has been parenterally fed for 4 years because of short bowel syndrome with a jejunostomy who had a malignant neuroendocrine neoplasm with dissemination to the liver who was treated with somatostatin analogues. During treatment, high bilirubin levels (up to 12 mg%) with a more than twofold increase in liver enzymes were noted (ALT 62 U/l, AST 79 U/l). The percentage of involvement of the liver parenchyma by the cancer process did not indicate that this condition was the only cause of liver failure. The patient also had evidence of liver injury prior to the initiation of parenteral nutrition on a background of chronic treatment with thiamazole. It was concluded that the cause of the end-stage liver failure was an interaction of all three factors: the treatment with thiamazole, the spread of neuroendocrine neoplasms and the chronic parenteral nutrition.

Group 2

Group 2 included 131 patients who were still receiving parenteral nutrition at home on 31.12.2021. The most common reason for qualifying for HPN in group 2 was short bowel syndrome (86.8% – group 2A, 90.9% – group 2B).

The average duration of PN at the beginning of the analysis was 11.7 years (group 2A – 11.8, group 2B – 10.9 years). The longest duration of parenteral nutrition was 33 years.

In the Department of General Surgery and Clinical Nutrition, all people made their nutritional mixtures on their own at home from preparations delivered by hospital transport. Of these, 80% circulated the nutrient mixture 7 days a week. Analysis using the Mann-Whitney U test showed a statistically significant difference, indicating that a slightly higher number of nutrition days applied to subjects in group 2A (p = 0.032) (Table 2).

Table 2. Frequency of supply of parenteral admixtures

| Group   | Number of feeding days | Mean | Median | n   | SD    | Min | Max |
|---------|------------------------|------|--------|-----|-------|-----|-----|
| Group 2A |                        | 6.52 | 7.00   | 121 | 1.111 | 2   | 7   |
| Group 2B |                        | 5.91 | 7.00   | 11  | 1.514 | 3   | 7   |
| All     |                        | 6.47 | 7.00   | 132 | 1.155 | 2   | 7   |
| p Mann-Whitney U |             |      |        |     |       |     | 0.032 |

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The average amount of energy from non-protein sources per 7 days was 6922.97 kcal. The differences between the subgroups were not statistically significant. In group 2B, the maximum amount of non-protein energy consumed was 1094.8 kcal lower than in group 2A. Data with the distinction of carbohydrates and fats are presented in Table 3.

The type of fat emulsions the patients received was analyzed. Five preparations with different compositions per 100 ml were used: Intralipid 20%, Clinoleic 20%, Smoflipid 20%, Omegaven 10%, Lipofundin MCT 20%. Intralipid was the most commonly used treatment at baseline (74.2% of patients). Three patients in group 2A received Smoflipid and Omegaven alternately.

Eleven patients (8.3%) had elevated total bilirubin levels, including 5 patients with levels above 2 mg%. A summary of all biochemical parameters is presented in Table 4. The analysis showed that despite the higher bilirubin level in group 2A, no significant differences were found in AST, ALT, INR and albumin.

Bilirubin levels in groups 2A and 2B did not differ statistically significantly by age. In group 2A, bilirubin levels were higher in females (2.46 mg%) than in males (1.71 mg%). In group 2B, the concentrations were not significantly different between sexes. In group 2B, higher levels were found in patients who were on parenteral nutrition for more than 15 years. Group 2A showed an increasing trend in bilirubin concentration with duration of HPN treatment. Mean total bilirubin levels were also higher in those who did not take food by mouth. A correlation was observed between the amount of fat emulsion in the mixture and bilirubin levels. In addition, lower energy expenditure and less catheter-related sepsis were associated with lower bilirubin levels, but these correlations were found to be statistically insignificant.

Group 2B showed higher levels in individuals who had participated in the program for 6 to 10 years (Table 5). Group 2A showed a slightly increasing trend in relation to bilirubin concentration and the duration of HPN use (Table 6). For both analyses, $p > 0.005$.

In 5 of 11 patients in group 2A, the ultrasound image of the liver showed moderate enlargement and features of steatosis.

**Discussion**

Most publications indicate a high prevalence of PNALD. Cavicchi *et al.* followed a group of adult patients in France during 1986-1996 and reported the incidence of complicated liver disease associated with home parenteral nutrition in 26% at 2 years and 50% at 6 years. Liver disease was responsible for 22% of deaths.

| Group | Glucose/week (g) | Fat/week (g) | Non-protein energy per week (kcal) |
|-------|-----------------|--------------|-----------------------------------|
| Group 2A | Mean 1413.56 | 144.02 | 6950.39 |
| Median 1516.20 | 140.00 | 7324.80 |
| $n$ | 121 | 121 | 121 |
| SD | 415.46 | 76.25 | 1939.38 |
| Min | 0 | 0 | 0 |
| Max | 2391.20 | 800 | 11454.80 |
| Group 2B | Mean 1378.81 | 122.91 | 6621.42 |
| Median 1350.00 | 140.00 | 6480.00 |
| $n$ | 11 | 11 | 11 |
| SD | 489.29 | 23.60 | 2050.17 |
| Min | 510.00 | 80 | 3300.00 |
| Max | 2275.00 | 140 | 10360.00 |
| All | Mean 1410.66 | 142.26 | 6922.97 |
| Median 1516.20 | 140.00 | 7324.80 |
| $n$ | 132 | 132 | 132 |
| SD | 420.10 | 73.50 | 1942.82 |
| Min | 0 | 0 | 0 |
| Max | 2391.20 | 800 | 11454.80 |

$p$ Mann-Whitney U 0.558 0.122 0.367
in this group [9]. In our patient group, the incidence was much lower and was 8.3% with 0% mortality after 9 years. 2 cases of death (3.2%) were associated with liver disease but not related to PNALD. The most common cause of death was cardiovascular disease. In another study, Lakananurak and Tienchai examined 44 adults. The prevalence of PNALD was 59.1% (22.7% steatosis, 34.1% cholestasis, and 2.3% mixed type). In this study group, the presence of PNALD was found in more than half of the hospitalized patients [7]. The difference between our center and centers with a higher percentage of PNALD is the use of individually formulated nutrient mixtures for parenteral nutrition. An individually formulated mixture is used for each patient according to their metabolic capabilities and nutritional needs. In many centers, standard RTU (ready to use) prepa-

### Table 4. Results of biochemical studies in patients from group 2

| Group | Bilirubin | AST | ALT | INR | Albumin |
|-------|-----------|-----|-----|-----|---------|
| Group 2A | Mean 2.0545 | 33.91 | 46.18 | 1.3836 | 35.45 |
|       | Median 1.7000 | 31.00 | 38.00 | 1.0700 | 35.00 |
|       | n 11 | 11 | 11 | 11 | 11 |
|       | SD 0.75148 | 17.032 | 27.845 | 0.71605 | 4.698 |
|       | Min 1.50 | 18 | 21 | 0.96 | 27 |
|       | Max 4.00 | 79 | 124 | 3.02 | 41 |
| Group 2B | Mean 0.6028 | 32.56 | 48.09 | 1.1483 | 34.83 |
|       | Median 0.5000 | 29.00 | 40.00 | 1.0900 | 35.00 |
|       | n 121 | 121 | 121 | 121 | 121 |
|       | SD 0.30334 | 16.933 | 29.442 | 0.26938 | 4.539 |
|       | Min 0.10 | 11 | 13 | 0.90 | 23 |
|       | Max 1.30 | 83 | 171 | 2.87 | 45 |
| Total | Mean 0.7238 | 32.67 | 47.93 | 1.1680 | 34.89 |
|       | Median 0.5000 | 29.00 | 39.50 | 1.0900 | 35.00 |
|       | n 132 | 132 | 132 | 132 | 132 |
|       | SD 0.53816 | 16.880 | 29.215 | 0.33147 | 4.538 |
|       | Min 0.10 | 11 | 13 | 0.90 | 23 |
|       | Max 4.00 | 83 | 171 | 3.02 | 45 |

*p Mann-Whitney U*

### Table 5. Bilirubin concentration and time of home parenteral nutrition (HPN) in group 2B

| Time of HPN | Mean | Median | n | SD | Min | Max |
|------------|------|--------|---|----|-----|-----|
| 6-10 years | 2.1833 | 1.9000 | 6 | 0.94745 | 1.50 | 4.00 |
| More than 10 years | 1.9000 | 1.7000 | 5 | 0.48477 | 1.50 | 2.70 |
| All | 2.0545 | 1.7000 | 11 | 0.75148 | 1.50 | 4.00 |

*p Mann-Whitney U* 0.782

### Table 6. Bilirubin concentration and time of home parenteral nutrition (HPN) in group 2A

| Time of HPN | Mean | Median | n | SD | Min | Max |
|------------|------|--------|---|----|-----|-----|
| 2-5 years | 0.5000 | 0.4000 | 8 | 0.23905 | 0.30 | 1.00 |
| 6-10 years | 0.5490 | 0.4050 | 58 | 0.27086 | 0.10 | 1.20 |
| More than 10 years | 0.6745 | 0.6000 | 55 | 0.33123 | 0.20 | 1.30 |
| All | 0.6028 | 0.5000 | 121 | 0.30334 | 0.10 | 1.30 |

*p Kruskal-Wallis test* 0.093
Liver dysfunction in patients on home parenteral nutrition

The symptoms of PNALD are mainly abnormal production of liver enzymes, cholestasis, fatty liver, occurrence of gallbladder stones, progressive fibrosis and finally cirrhosis as a result of total parenteral nutrition. Diagnosis in patients is mainly based on the exclusion of other factors of chronic liver disease [4, 17]. The clinical manifestation of fatty liver disease, which occurs in 40-55% of patients, is an increase in liver enzyme levels on blood tests. Cholestasis is the result of obstruction of the bile ducts or inappropriate secretion. It is manifested by an increase in the levels of alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGTP) and bilirubin [14, 17]. The degree and severity of liver dysfunction can be classified based on organ features observed on radiological examination – ultrasonography (USG), liver imaging with computed tomography, magnetic resonance imaging (MRI) and liver biopsy, which is the gold standard [17].

The main principle of treatment is constant monitoring of liver enzyme levels and, if possible, changing the fat emulsion administered or reducing its concentration in the nutritional mixture. Fat emulsion intake cannot be completely eliminated – lipids are not only a source of energy, but also provide fatty acids necessary for maintaining cell membrane integrity, supporting immune function, and regulating gene expression. Studies show that fish fat emulsions reduce the likelihood of PNALD [17-20].

Lipid intake depends on the patient’s underlying disease, energy requirements, body weight and recent weight loss, and the body’s metabolic capacity. The dose of 2.5 g lipids/kg body weight/day should not be exceeded [17, 19].

Ideally, intestinal adaptation should be accelerated, enteral nutrition introduced, and parenteral nutrition avoided. However, not all patients are able to do this, and some will be dependent on parenteral nutrition for the rest of their lives. If possible, at least trophic nutrition should be introduced [6]. It is also possible to implement hormone therapy – for example, with glucagon-like peptide-2 (GLP-2), because according to many studies, it plays an important role in stimulating intestinal adaptation [21].

In conclusion, the prevention and treatment of PNALD requires an integrated approach to the patient and the collaboration of a medical team consisting of physicians, nurses, pharmacists, dietitians, laboratory personnel and psychologists. Nutritional management involves optimizing nutrition through the gastrointestinal tract, thereby stimulating enterohepatic circulation. Liver disease associated with parenteral nutrition is a complication that can be diagnosed in chronic patients. In the studied population, only 8.3% of peo-
ple had elevated levels of total bilirubin (≥ 1.5 mg/dl) in plasma. This may suggest that a properly balanced, individualized program of nutrition parenteral treatment reduces the risk of developing PNALD.

Disclosure

The authors declare no conflict of interest.

References

1. Mullady DK, O’Keefe SJ. Treatment of intestinal failure: home parenteral nutrition. Nat Clin Pract Gastroenterol Hepatol 2006; 3: 492-504.
2. Pironi L, Boeykens K, Bozzetti F, et al. ESPEN guideline on home parenteral nutrition. Clin Nut 2020; 39: 1645-1666.
3. Mizock BA. Immunonutrition and critical illness: an update. Nutrition 2010; 26: 701-707.
4. Mitra A, Ahn J. Liver disease in patients on total parenteral nutrition. Clin Liver Dis 2017; 21: 687-695.
5. Kumpf JGV. Complications of parenteral nutrition. C. Mueller (Ed.). The ASPEN adult nutrition support core curriculum (3rd ed.). American Society for Parenteral and Enteral Nutrition, The United States 2017; 345-360.
6. Lee WS, Chew KS, Ng RT, et al. Intestinal failure-associated liver disease (IFALD): insights into pathogenesis and advances in management. Hepatol Int 2020; 14: 305-316.
7. Lakananurak N, Tienchai K. Incidence and risk factors of parenteral nutrition-associated liver disease in hospitalized adults: A prospective cohort study. Clin Nutr ESPEN 2019; 34: 81-86
8. Cahova M, Bratova M, Wohl P. Parenteral nutrition-associated liver disease: the role of the gut microbiota. Nutrients 2017; 9: 987.
9. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000; 132: 525-532.
10. Javid PJ, Oron AP, Duggan CP, et al. The extent of intestinal failure-associated liver disease in patients referred for intestinal rehabilitation is associated with increased mortality: an analysis of the Pediatric Intestinal Failure Consortium database. Pediatr Int 2015; 57: 1399-1402.
11. Guzman M, Manthody C, Krebs J, et al. Impaired gut-systemic signaling drives total parenteral nutrition-associated injury. Nutrients 2020; 12: 1493.
12. Tran K, Butcher R. Lipid formulations for patients requiring parenteral nutrition: a review of clinical effectiveness, cost-effectiveness, and guidelines – an update. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Aug 2.
13. Wu SC, Chen TA, Tsai JJ, et al. Lipid-free parenteral nutrition is associated with an increased risk of hepatic dysfunction in surgically critically ill patients: a retrospective observational study. Healthcare (Basel) 2021; 9: 1096.
14. Wu SC, Chen TA, Cheng HT, et al. Lipid-free PN is associated with an increased risk of hyperbilirubinemia in surgical critically ill patients with admission hepatic disorder: a retrospective observational study. Ther Clin Risk Manag 2021; 17: 1001-1010.
15. Jain AK, Teckman JH. Newly identified mechanisms of total parenteral nutrition related liver injury. Adv Hepatol 2014; article ID 621380.
16. Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Hepatobiliary Pancreat Dis Int 2012; 11: 586-593.
17. Fedja A. Rochling intravenous lipid emulsions in the prevention and treatment of liver disease in intestinal failure. Nutrients 2021; 13: 895.
18. Nandivada P, Chang MI, Engl M, et al. The natural history of cirrhosis from parenteral nutrition-associated liver disease after resolution of cholestasis with parenteral fish oil therapy. Ann Surg 2015; 261: 172-179.
19. Stramara L, Hernandez L, Bloom BT, et al. Development of parenteral nutrition-associated liver disease and other adverse effects in neonates receiving SMOFlipid or intralipid. JPEN J Parenter Enteral Nutr 2020; 44: 1530-1534.
20. Lam K, Schiano T, Fiel IM, et al. Index use of smolipid in a tertiary intestinal rehabilitation and transplantation program. JPEN J Parenter Enteral Nutr 2017; 41 (1_suppl): 205-235.
21. Kocoshis SA, Merritt RJ, Hill S, et al. Safety and efficacy of teduglutide in pediatric patients with intestinal failure due to short bowel syndrome: a 24-week, phase III study. JPEN J Parenter Enteral Nutr 2019; 44: 621-631.