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Utility of liver biopsy in the evaluation of pediatric total parenteral nutrition cholestasis

Christie L. Buonpane^a, Guillermo J. Ares^{a,b}, Ethan G. Englert^c, Irene Helenowski^c, Valeria C. Cohran^a, and Catherine J. Hunter^{a,c,*}

^aAnn and Robert H. Lurie Children's Hospital of Chicago, 211 E Chicago Avenue, Box 63, Chicago, IL, 60611, USA

^bUniversity of Illinois at Chicago, Department of Surgery, 840 South Wood Street, Suite 376-CSN, Chicago, IL, 60612, USA

^cFeinberg School of Medicine, Northwestern University, 310 East Superior Street, Morton 4-685, Chicago, IL, 60611, USA

Abstract

Background: Cholestasis is a serious complication of total parenteral nutrition (TPN) in neonates. Liver biopsies may be requested to assess the severity of cholestasis and fibrosis. We hypothesized that liver biopsy would not lead to changes in management or improved patient outcomes.

Methods: A single institution retrospective review of infants with TPN cholestasis from January 2008 to January 2016.

Outcomes: length of stay, complications, change in management and mortality. Statistical analysis was performed using Fisher's exact test.

Results: Twenty-seven out of 95 patients with TPN cholestasis underwent liver biopsy. Liver biopsy was associated with increased utilization of ursodeoxycholic acid ($p = 0.001$). There were no differences in length of stay (LOS) or mortality. One patient had a complication following anesthesia for liver biopsy, there were no bleeding complications recorded.

Conclusions: Liver biopsy in patients with TPN cholestasis was associated with an increase in utilization of ursodeoxycholic acid. The effects of this are not fully understood; however, liver biopsy was not associated with improved patient outcomes such as LOS or mortality.

Keywords

TPN; Cholestasis; Liver biopsy; Pediatric

*Corresponding author. Ann and Robert H. Lurie Children's Hospital of Chicago. Division of Pediatric Surgery, 211 E Chicago Avenue, Box 63, Chicago, IL, 60611, USA. Chunter@luriechildrens.org (C.J. Hunter).

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Conflicts of interest

There are no conflicts of interest by any of the authors.

Introduction

Total parenteral nutrition (TPN) cholestasis, also referred to as parenteral nutrition-associated liver disease, is a common and serious complication of prolonged parenteral nutrition in neonates with an incidence of 40—60%.^{1–4} Cholestasis occurs when there is stagnation of bile formed by hepatocytes, causing impairment in the secretion of bile. Since the 1960s, parenteral nutrition has revolutionized the care of patients unable to receive adequate enteral feeding; however, cholestasis and hepatic injury were quickly recognized as significant complications.^{3,5–8} Over time, there have been several advancements in the highly sophisticated nutrient solution in order to optimize the combinations of macro and micronutrients while minimizing the harmful effects.^{2,3,9,10} Despite the technical improvements and preventative strategies employed, TPN cholestasis remains a significant life threatening complication of long-term parenteral nutrition use,^{1,2,5,10,11}

The pathogenesis of TPN cholestasis is likely multifactorial; however, still remains poorly understood.^{2,4,8,10–13} Continued parenteral therapy can cause cholestasis, fibrosis and even cirrhosis over the course of several months.² Liver biopsies may be requested to assess the severity of cholestasis and fibrosis; however, the utility of this has not been defined. To elucidate the utility of liver biopsy in the evaluation of TPN cholestasis, this study aims to assess the impact on treatment strategies and patient outcomes in neonates with the disease.

Material and methods

Study population:

All patients with a diagnosis of TPN cholestasis at a single institution tertiary care children's hospital from January 2008 to January 2016 were screened for eligibility. We utilized the institution's electronic medical record reporting workbench to query any pediatric patient with the following diagnosis titles: cholestasis, cholestasis in newborn, cholestasis intrahepatic, cholestasis of parenteral nutrition, intrahepatic cholestasis, neonatal cholestasis, fatal intrahepatic cholestasis, and TPN- induced cholestasis. We identified a total of 355 patients. Each medical record was examined to exclude patients with cholestasis not associated with parenteral nutrition use (viral hepatitis, congenital hepatic fibrosis, biliary atresia, previous liver transplant). Ninety-five patients were found to have TPN cholestasis during this time period. Institutional Review Board approval was obtained prior to the initiation of this retrospective chart review.

Data Collection:

Clinical parameters collected by chart review included: date of birth, gender, race/ethnicity, primary insurance provider, zip code, gestational age, birth weight, chronic medical diagnoses, laboratory values (albumin, total bilirubin, gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT]), indication for TPN, duration of TPN, duration of enteral feeds and type, infectious history, liver biopsy pathology results, post-procedural complications, use of ursodeoxycholic acid (UDCA), use of lipid minimizing strategies, history of abdominal surgery, length of stay (LOS), and date of death.

Statistical Analysis:

Patients were divided into two groups; 1) those with liver biopsy and 2) those without. Primary outcome was a change in management after biopsy. Secondary outcomes included length of stay (LOS), mortality, and complication after biopsy. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). Comparisons between groups were compared using Fisher's exact test for categorical data. Statistical tests were 2-sided, with a p value < 0.05 considered statistically significant.

Results

Included in the analysis were 95 patients with TPN cholestasis, of which 27 (28.4%) had a liver biopsy. Of the patients with TPN cholestasis, 39% were hypoalbuminemic, 60% had short bowel syndrome and 4 patients (4%) had an active infection at the time of diagnosis. The underlying diagnoses for patients with short bowel syndrome included necrotizing enterocolitis (63%), gastroschisis (16%), intestinal atresia (14%), intestinal perforation (3.5%), and malrotation (3.5%).

Patient characteristics

First, we investigated which patients were selected for liver biopsy. Table 1 compares demographics between patients who had liver biopsy and those who did not. There was a significant difference in race (Asian, African American, Hispanic, Caucasian or other) between patients who received liver biopsy and those who did not ($p = 0.047$) (Table 1). Upon further analysis, 52% of African American patients underwent liver biopsy while only 20% of non-African American patients were chosen for the procedure ($p = 0.002$). Additionally, a higher percentage of patients with government insurance underwent liver biopsy than patients with private insurance (43% and 21%, respectively; $p = 0.03$) (Table 1).

Table 2 compares patient characteristics between patients who had liver biopsy versus those who did not. Patients with short bowel syndrome received more liver biopsies than those without ($p = 0.04$). There was a significant difference between the cohorts with regards to peak ALT and AST levels ($p = 0.01$ and 0.02 , respectively). Seventy percent of patients who underwent liver biopsy had a peak total bilirubin level greater than ten times the normal range.

There was no difference between cohorts with respect to pre-existing medical conditions (cardiac, pulmonary, musculoskeletal, neuromuscular, neurologic, metabolic and genetic disease) (Fig. 1). All liver biopsies were performed by an interventional radiologist or a pediatric surgeon. Nineteen patients (70%) underwent liver biopsy by a pediatric surgeon at the time of a concurrent abdominal surgery. Forty-two percent of these concurrent surgeries were emergent, while 58% were elective. Seven patients (26%) received a needle biopsy by an interventional radiologist. Only one patient had an open wedge liver biopsy by a pediatric surgeon without a concurrent abdominal surgery or procedure.

Liver histopathology

Of the 27 patients who underwent liver biopsy, 6 patients demonstrated cholestasis; however, no fibrosis was found on pathology (stage 0). Fifty-six percent of patients showed mild/moderate fibrosis (7 patients with stage 1, and 8 patients with stage 2) and 22% showed severe fibrosis (5 patients with stage 3, and 1 patient with stage 4/cirrhosis). Patients with short bowel syndrome did not have more severe fibrosis (87% mild/moderate, and 67% severe, $p = 0.29$). A majority of patients from both disease groups received enteral feeds (93% mild/moderate, and 100% severe, $p = 0.99$). Five patients without fibrosis (83%) were on UDCA prior to biopsy. Sixty-three percent of patients with mild/moderate fibrosis were on UDCA prior to biopsy versus 37% with severe fibrosis ($p = 0.08$). Peak AST, ALT, and total bilirubin were not different between patients with mild/moderate versus severe fibrosis.

Patient outcomes

The only significant change in management following liver biopsy was an increase in the utilization of UDCA ($p = 0.001$). Thirteen patients were on the medication prior to biopsy and an additional 11 patients were started on UDCA after the biopsy (Fig. 2). No patients were taken off therapy as a result of the biopsy. Of the 11 patients started on UDCA after biopsy, 73% had mild fibrosis and 27% had severe fibrosis. All patients were on lipid minimizing strategies at the time of biopsy (20% fat emulsion, 1 g/kilogram/day), which remained unchanged after the procedure. Omegaven (fish oil based lipid rich in omega-3 fatty acids) was not used in any of the study patients.^{13,14} There was no difference in LOS between patients with liver biopsy or without (Table 3). However, further analysis found that patients with severe fibrosis were more likely to have a LOS greater than 25 weeks ($p = 0.02$). Four patients with liver biopsy had reported complications; however, only one (3.7%) was directly related to the liver biopsy. The complication was apnea after anesthesia, which did not require intubation. There were no bleeding complications reported. Seven patients with TPN cholestasis died (7.4%) and there was no difference in mortality in patients who underwent liver biopsy versus not (Table 3). Three of the patients who expired underwent liver biopsy, including 2 patients with stage 2 fibrosis and 1 patient with stage 4 cirrhosis. Seventy-one percent of patients that died had concurrent bacteremia ($p = 0.047$) and mortality was higher in patients that received TPN for more than 6 weeks ($p < 0.001$). No patients in the study received liver and/or small bowel transplants.

Discussion

The role of liver biopsy in the diagnosis and management of TPN cholestasis has not been well established. In the setting of abnormal liver tests of unknown etiology a thorough non-invasive investigation is strongly recommended to confirm diagnosis.¹⁵ Advances in serologic testing, enzyme analysis, DNA sequencing, and novel imaging techniques have made diagnosis of several pediatric liver diseases possible without histologic analysis. The diagnosis of TPN cholestasis is often made with clinical and laboratory data alone; however, liver biopsy can assess the degree of cholestasis and fibrosis. Knowledge of the severity of histopathology does not alter the treatment options, as therapy for this disease is limited and only minimally successful.¹⁶ Regardless of the severity of disease, clinicians strive to wean

TPN and advance enteral feeding as soon as possible. For patients that require prolonged TPN, medical optimization is performed to prevent further liver dysfunction.

Existing literature shows that significant risk factors for TPN cholestasis include low birth weight, prematurity, short bowel syndrome, prolonged TPN administration and recurrent sepsis¹⁷ which was mirrored in our results. African Americans were more likely to receive liver biopsy in our study. Although the reason for this is not immediately discernible, several predominant factors stand out in this patient population. We found that African American infants with TPN cholestasis had high rates of Medicaid insurance, prematurity, extremely low birth weight (<1000 g), short bowel syndrome, and higher peak total bilirubin levels. Studies on racial disparity in the United States show that African American infants have worse birth outcomes requiring higher rates of NICU admission.¹⁸ Therefore, the reason for our study finding maybe multifactorial and perhaps related to poor birth outcomes and comorbid medical illness rather than the actual decision to perform biopsy.

A majority of the patients who underwent liver biopsy also had a concurrent abdominal surgery. A percutaneous liver biopsy approach can be used; however, this technique is more complicated in children and obtaining adequate sample size can be difficult due to patient size. The sampling error can be as high as 20–30%.¹⁵ Additionally, general anesthesia is required for biopsy in children which has its own inherent risks. Therefore, if the patient is being taken to the operating room for an abdominal surgery, the surgeon is often asked to obtain an intraoperative liver biopsy. Complication rates of liver biopsy in the literature range from 0.2% to 6.5%^{19–23} which is consistent with our study findings. The main complication reported is bleeding²²; however, only one patient in our study suffered a complication and this was apnea after anesthesia administration.

Studies analyzing histopathology results from patients with TPN cholestasis report the presence of cholestasis within 2 weeks of therapy and the progression to cirrhosis within as little as 3 months. Reports show varying results regarding the severity of histopathologic changes in relation to the duration of TPN administration.⁸ Our data did not show a correlation between the duration of TPN and the severity of fibrosis. Additionally, there are a paucity of data studying the relationship between elevated hepatic biochemical enzymes and severity of hepatic injury and fibrosis.⁸ In our study, there was no difference in peak ALT, AST, total bilirubin or GGT between patients with mild/moderate versus severe liver fibrosis. We did not find any patient characteristics that were associated with more severe histopathology. Therefore, duration of TPN, laboratory values or other patient characteristics should not be used to determine if a patient should have a liver biopsy. Since liver pathology and clinical metrics do not correlate, focus should be directed toward urgent utilization of medical therapies and prophylactic strategies once there is development of cholestasis.

In clinical practice, many infants with TPN cholestasis are treated with ursodeoxycholic acid (UDCA); however, data regarding efficacy of the drug are incongruent. Few early case reports and small uncontrolled trials report UDCA to be beneficial, showing a significant decrease in liver enzymes^{24,25}. However, a randomized controlled trial comparing tauroursodeoxycholic acid versus placebo showed the drug to be ineffective in prevention or treatment of TPN cholestasis in neonates.²⁶ Due to a limited consensus on the efficacy of

UDCA, there are no standard guidelines for use in TPN cholestasis in infants. The drug is however well tolerated in infants and no significant adverse reactions have been observed, even at high dosages²⁴. The patients in our study who were on UDCA prior to biopsy did have better pathology results; however, this was not statistically significant. Our study did find a significant increase in the utilization of UDCA after liver biopsy; however, we do not have data available regarding why UDCA was started or if the biopsy was obtained in order to make this decision.

There are several limitations to this study. We are limited by the retrospective nature of the study with possible selection bias. Additionally, our institution is a tertiary care Children's Hospital in a major US city, which may not be representative of populations seen at other centers. There were a low number of patients with TPN cholestasis and an even smaller number of patients who underwent liver biopsy, which limits the power of our conclusions.

Due to the observational nature of the study, infant care was not standardized. It is possible that the amount of enteral nutrition received by the patient could impact his/her outcomes; however, due to incomplete patient records we do not have this data available. Additionally, we were not able to retrieve data regarding which care team requested the biopsies and the decision making process behind the biopsy request or initiation of UDCA. Further studies including these data should be performed in a prospective manner with standardized patient care guidelines to shed further light on this important question.

Conclusion

In summary, the only change in management noted after liver biopsy was an increase in the use of ursodeoxycholic acid. However, the efficacy of this medical intervention is not fully understood. Additionally, we did not find improved outcomes such as length of stay or improved mortality in infants with TPN cholestasis undergoing liver biopsy. Furthermore, liver biopsy is not without risk and resulted in a complication in one study patient. We propose that a prospective study including standardization of the indications and resultant care in response to pathological findings is needed to assess the impact of liver biopsy in the diagnosis and management of neonatal TPN cholestasis.

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Fig.1. Patient characteristics.

There was no difference between patients who received liver biopsy versus those who did not with respect to pre-existing medical conditions such as cardiac disease ($p = 0.99$), pulmonary disease ($p = 12$), musculoskeletal disease ($p = 26$), neuromuscular disease ($p = 99$), neurologic disease ($p = 0.16$), metabolic disease ($p = 62$), or genetic disease ($p = 0.14$).

Fig. 2.

Change in management after liver biopsy. The majority of patients in both groups received lipid minimizing strategies both before and after biopsy. Following liver biopsy there was a significant increase in the use of ursodeoxycholic acid $p=0.001$.

Table 1

Demographics.

Variable	No Liver Biopsy n = 68	Liver Biopsy n = 27	p value
Gender			0.82
Male	40 (58.82%)	17 (62.96%)	
Female	28 (41.18%)	10 (37.04%)	
Gestational Age			0.70
> 37 weeks	16 (23.53%)	5 (18.52%)	
33–37 weeks	17 (25.00%)	5 (18.52%)	
28–32 weeks	11 (16.18%)	7 (25.93%)	
< 28 weeks	24 (35.29%)	10 (37.04%)	
Birth Weight			0.87
Normal (>2500 g)	19 (30.16%)	6 (26.09%)	
Low (1500–2500 g)	12 (19.05%)	3 (13.04%)	
Very low (1000–1500 g)	9 (14.29%)	4 (17.39%)	
Extremely low (<1000g)	23 (36.51%)	10 (43.48%)	
Unknown	5	4	
Great Circle Distance ^a			0.26
0–5 miles	10 (14.71%)	4 (14.81%)	
5–10 miles	16 (23.53%)	11 (40.74%)	
10–20 miles	11 (16.18%)	4 (14.81%)	
20–40 miles	23 (33.82%)	4 (14.81%)	
40–60 miles	5 (7.35%)	1 (3.70%)	
60+ miles	3 (4.41%)	3 (11.11%)	
Race			0.047
Asian	8 (11.76%)	1 (3.70%)	
African American	12 (17.65%)	13 (48.15%)	
Hispanic	17 (25.00%)	4 (14.81%)	
Caucasian	28 (41.18%)	9 (33.33%)	
Other	3 (4.41%)	0	
Insurance Status			0.03

Variable	No Liver Biopsy n = 68	Liver Biopsy n = 27	p value
Private	49 (75.38%)	13 (52.00%)	
Government	16 (24.62%)	12 (48.00%)	
None	3	2	

^aThe distance in miles between the patient's residence and the hospital.

Table 2:

Patient characteristics.

Variable	No Liver Biopsy n = 68	Liver Biopsy n = 27	p value
Hypoalbuminemia	25 (40.98%)	8 (33.33%)	0.62
Unknown	7	3	
Bacteremia during admission	20 (29.41%)	13 (48.15%)	0.10
Short Bowel Syndrome			0.04
Yes	36 (52.94%)	21 (77.78%)	
No	32 (47.06%)	6 (22.22%)	
Enteral Feeds			0.99
Yes	63 (92.65%)	25 (92.59%)	
No	5 (7.35%)	2 (7.41%)	
Type of Enteral Feed			0.30
Breast Milk	17 (26.98%)	4 (16.00%)	
Formula	29 (46.03%)	14 (56.00%)	
Both	17 (26.98%)	6 (24.00%)	
Solid Food	0	1 (4.00%)	
Unknown	5	2	
Duration of TPN prior to Diagnosis			0.76
< 2 weeks	19 (27.94%)	6 (22.22%)	
2–6 weeks	24 (35.29%)	10 (37.04%)	
6–12 weeks	14 (20.59%)	8 (29.63%)	
> 12 weeks	11 (16.18%)	3 (11.11%)	
Peak Total Bilirubin ^a			0.47
Normal	2 (2.94%)	0	
Expected increase on TPN	4 (5.88%)	1 (3.70%)	
2–5x Normal Range	4 (5.88%)	0	
5–10x Normal Range	24 (35.29%)	7 (25.93%)	
> 10x Normal Range	34 (50.00%)	19 (70.37%)	
Peak ALT ^d			0.01

Variable	No Liver Biopsy n = 68	Liver Biopsy n = 27	p value
Normal	14 (20.90%)	2 (7.41%)	
Expected increase on TPN	34 (50.75%)	7 (25.93%)	
2–5x Normal Range	10 (14.93%)	9 (33.33%)	
5–10x Normal Range	7 (10.45%)	7 (25.93%)	
> 10x Normal Range	2 (2.99%)	2 (7.41%)	
Unknown	1	0	
Peak AST ^a			0.02
Normal	26 (38.81%)	3 (11.11%)	
Expected increase on TPN	15 (22.39%)	5 (18.52%)	
2–5x Normal Range	21 (31.34%)	14 (51.85%)	
5–10x Normal Range	4 (5.97%)	3 (11.11%)	
> 10x Normal Range	1 (1.49%)	2 (7.41%)	
Unknown	1	0	

^aLevels based on institutional laboratory standards specific for patient gender and age.

Table 3:

Outcomes.

Variable	No Liver Biopsy n = 68	Liver Biopsy n = 27	p value
Length of Stay			
<2 weeks	3 (4.41%)	1 (3.70%)	0.55
2–8 weeks	17(25.00%)	3 (11.11%)	
9–16 weeks	16 (23.53%)	6 (22.22%)	
17–25 weeks	16(23.53%)	6 (22.22%)	
26–40 weeks	10(14.71%)	7 (25.93%)	
> 40 weeks	6 (8.82%)	4(14.81%)	0.40
Mortality	4 (5.88%)	3 (11.11%)	