CLINICAL VIGNETTE

Treatment of Iatrogenic Essential Fatty Acid Deficiency with a Lipid-Rich Matrix in a Child with Intestinal Failure-Associated Liver Disease: Case Report

Christina Yuen, MD, Danielle Mein, RD and Joanna Yeh, MD

Department of Pediatrics, David Geffen School of Medicine at UCLA

Abstract

Parenteral nutrition (PN) is a life-saving intervention but may lead to many complications including intestinal failure-associated liver disease (IFALD). Decreasing the amount of intravenous lipid emulsions (ILE) a patient receives is one way to address IFALD. However, this may lead to essential fatty acid deficiency (EFAD). For patients with both conditions, the ideal solution is to increase enteral fatty acid absorption in order to decrease the amount of ILE necessary. Unfortunately, some patients are not able to tolerate a sufficient quantity of fatty acids enterally. We present a case study of a pediatric PN-dependent patient whose IFALD and EFAD improved after a successful decrease in ILE due to the use of the lipid matrix Encala™ (Envara Health, Malvern, PA), demonstrating the importance of considering its use to increase the enteral absorption of essential fatty acids.

Introduction

Parenteral nutrition (PN) is a life-saving intervention, but it comes with complications including intestinal failure-associated liver disease (IFALD). IFALD can manifest as steatosis, cholestasis, hepatitis, or a combination of these diseases.[1] IFALD does not have a clear pathophysiology. It is thought that soybean oil (SO), a component in most intravenous lipid emulsions (ILEs), may be a factor. Though the minimization of SO may improve IFALD, it can also lead to essential fatty acid deficiency (EFAD).[2] Linoleic acid (LA) and alpha-linolenic acid (ALA) are essential fatty acids (FA) that cannot be synthesized by the human body and must be obtained externally. Patients with EFAD can experience poor wound healing, growth restriction, and increased susceptibility to infection, so it is crucial to provide ILEs to patients who do not receive these fats enterally.[3]

Encala™ (previously LYM-X-SORB™, Envara Health, Malvern, PA) is a phospholipid- and triglyceride-rich matrix[4] that has been shown to improve fat absorption. It is made from metabolites of dietary fats, including lysophosphatidylcholine, monoglycerides, and FA.[5] We present a case of a PN-dependent patient who developed IFALD, who was at high risk for developing EFAD. This lipid matrix was successfully used enterally, enabling decreasing ILE dose with improvement in his IFALD without progression to EFAD.

Case

The patient is a 22-month male with a history of prematurity (born at 32 weeks and 6 days), Bohring-Opitz Syndrome, bronchopulmonary dysplasia with ventilator dependence, and gastrointestinal dysmotility requiring gastrostomy tube and PN dependence.

The patient was hospitalized for the first 21 months of life and was discharged on PN and a mixed-oil ILE (SMOFlipid®, Fresenius Kabi, Lake Zurich, IL) due to inability to tolerate gastric or jejunal feeds despite trials of multiple enteral formulas. On initial presentation to pediatric gastroenterology, he was started on 0.5 g/kg of mixed-oil ILE once weekly, averaging 0.08 g/kg/day. He was placed on this low dose regimen due to parental concerns about mixed-oil ILE given a prior elevated ALT and triglyceride levels.

At 30 months he had an elevated T:T ratio of 0.132 (normal 0.004-0.051), a decreased LA concentration of 834 nmol/mL (normal 1210-4300 nmol/mL), a decreased ALA concentration of 14 nmol/mL (normal 20-200 nmol/mL), and an elevated mead acid level of 54 nmol/mL (normal 1-35 nmol/mL), all suggestive of trending toward EFAD. At this time, there was also concern for IFALD as evidenced by an elevated alanine transaminase (ALT) of 255 U/L (normal < 40 U/L), elevated aspartate transaminase (AST) of 169 U/L (normal < 41 U/L), and elevated gamma-glutamyl transferase (GGT) of 643 U/L (normal 7-68 U/L) (Table 1). The mixed-oil ILE was increased to twice weekly and topical safflower oil was also initiated. The T:T ratio decreased to 0.111 over two months, however, remained elevated and the mixed-oil ILE dose was increased over 15 months to a maximum of 1.3 g/kg three times weekly at 45 months age, averaging 0.53 g/kg/day. His enteral feeds (Compleat® Pediatric Organic Blends Chicken-Garden, Vevey, Switzerland; 40% fat content) fluctuated from 0% to 66% of goal, with an average intake of 20%. The enteral feeds often needed to be held due to recurrent infections that led to feeding intolerance.

The patient initially had improvement in AST and ALT to 66 U/L and 109 U/L. As the mixed-oil ILE dose was increased, the patient's AST again increased to a peak of 162 U/L, with ALT of 245 U/L, and GGT elevated to a peak of 403 U/L. While his direct and total bilirubin remained within normal limits, these values likely reflected worsening IFALD. Recurrent infections may have contributed to these increases. They persisted after recovery from these infections. Abdominal ultrasound showed normal liver echogenicity and size, suggesting that liver steatosis was less likely due to suboptimal mixed-oil ILE dosing.

Given the persistently elevated T:T ratio, AST, ALT, and GGT, the enteral lipid matrix was started at 52 months age. Two servings (18 g per serving) per day was given enterally, totalling 200 kcals/day and 21 kcals/kg/day. Three months after starting the lipid matrix, the T:T ratio normalized to 0.03. It remained normal while the mixed-oil ILE dose was decreased over five months to 0.9 g/kg twice weekly with only a marginal increase in enteral feeds. After the decrease in the mixed-oil ILE dose, the AST decreased to 96 U/L, ALT decreased to 109 U/L, and GGT decreased to 283 U/L, reflecting improvement in the patient's IFALD.

With the patient's genetic condition, overall growth is not a good indicator of his nutrition status. There are no evidence-based goals or validated growth charts for this syndrome. His nutrition goals include ensuring appropriate adipose tissue stores on physical exam, promoting some weight gain, and ensuring an adequate intake of proteins and fats. Throughout this time, the patient did not have clinical signs of EFAD.

Discussion

EFAD is defined per the Holman Index as a T:T ratio > 0.2,[6,7] though the normal range is reported as 0.004-0.051. This ratio may reflect dietary fat, and analysis of the specific types of serum FA that are outside of normal range may be a more accurate representation of the patient's FA status. An elevated T:T ratio, decreased levels of LA and ALA, and increased levels of mead acid, which results from the absence of LA and ALA, are more reflective of a patient's essential FA status.[8] These abnormalities were all present in this patient. Though the patient's T:T ratio was never greater than 0.2, it was elevated out of range in the context of not being at goal fat intake. This in conjunction with trying to decrease ILE dose to treat IFALD and being unable to tolerate increased enteral feeds, placed the patient at high risk of developing EFAD. EFAD can result in elevated liver enzymes, which were present in this patient, and thus could represent worsening IFALD or developing EFAD.[7] To prevent EFAD, one should receive 2-4% of total calories from LA and 0.25-0.5% from ALA.[7,8] This patient's total intake from both parenteral and enteral lipid sources (excluding the essential FA content supplied from the lipid matrix) of LA and ALA never exceeded 0.01% and 0.001% respectively.

Patients who cannot tolerate sufficient enteral nutrition, require intravenous essential FA. Common ILE formulations include a pure SO formulation, a pure fish oil (FO) formulation, and a mixed-oil ILE that consists of 30% SO, 30% medium-chain triglyceride oil, 25% olive oil, and 15% FO. When used long-term, SO-containing ILEs can increase the risk of or exacerbate existing IFALD. SO is rich in phytosterols, which can inhibit an enzyme that synthesizes bile acids,[6,7] and its serum levels directly correlate with IFALD severity.[9] Additionally, SO has a high concentration of pro-inflammatory and hepatoxic precursors[9] and is low in antioxidants resulting in increased oxidative stress. FO is rich in antioxidants and LA and ALA metabolites, like arachidonic acid and docosahexaenoic acid.[6] Providing FO as the sole lipid source can be sufficient to prevent EFAD in infants who developed cholestasis while on PN.[10] Pure FO supplementation has been approved by the Food and Drug Administration to manage IFALD. It was not indicated in our patient as his direct bilirubin level never exceed 2 mg/dL. Our patient received mixed-oil ILE with decreased phytosterols and pro-inflammatory precursors and an increased number of antioxidants compared to pure SO ILE.

Besides changing ILE formulation, other approaches to managing IFALD include increasing enteral feeding to promote enterohepatic circulation of bile acids.[11] This patient was unable to tolerate any prolonged significant increase of enteral feeds due to gastrointestinal dysmotility. Decreased PN infusion time can also be beneficial as continuous glucose infusion can result in oxidative stress and liver damage.[11] This patient's PN was compressed from 17 to 12 hours daily, however the AST, ALT, and GGT remained elevated leading to use of lipid matrix.

The lipid matrix is an oral powder, structured lipid nutritional supplement synthesized from lysophosphatidylcholine, mono-glycerides, and FA.[5] It was originally introduced in 2021 for treating growth failure due to enteral fat malabsorption in children with cystic fibrosis and pancreatic insufficiency. Each 18gm serving provides 100 kcals and 6 g total fat, consisting of 1 g saturated FA, 3.5 g polyunsaturated FA, and 1.5 g mono-unsaturated FA, with 3g of LA and 0.5 g of ALA. A randomized controlled trial reported patients who received the lipid matrix had significantly higher levels of LA compared to placebo.[4] The ratio of the product's components results in a macromolecule with micelle-like activity that does not require lipase or bile acids allowing it to be readily absorbed enterally. A second mechanism of action has been proposed: it suggests lyso-phosphatidylcholine from the lipid matrix is recycled by gut epithelial cells and interacts with FA from food co-ingested with the lipid matrix, allowing for their improved enteral absorption.[12]

After this patient was started on the lipid matrix, the T:T ratio normalized, the LA and ALA concentrations increased, and the mead acid concentration decreased, reflecting improvement in essential FA status. This persisted while the mixed-oil ILE dose was decreased, which led to improvement in the AST and ALT, reflecting improvement in his IFALD. Though the patient's direct bilirubin was never greater than 2 mg/dL, his elevated liver transaminases and GGT improved with lipid minimi-zation, suggesting this liver disease was likely IFALD. With

this improvement, the patient did not require switching to a FO ILE. His overall was able to treat EFAD was treated with an enteral product without worsening his IFALD.

The lipid matrix Encala™ allows for the treatment of EFAD in PN-dependent patients who can only tolerate a small amount of enteral nutrition without increasing ILE dependence, therefore also acting as a management of IFALD. This case demonstrates the importance of considering the use of this lipid matrix in patients who have both EFAD and IFALD. Further research is needed to determine optimal dose and frequency. As more patients can be sustained on PN, it is important to be able to address both conditions which can be seen in PN-dependent patients.

	Prior to initial mixed-oil ILE increase (time = 0)	Prior to starting the lipid matrix (time = +20 months)	After starting the lipid matrix (time = +27 months)	After decreasing mixed-oil ILE while on the lipid matrix (time = +30 months)	**Normal values**
Fat intake from enteral feeds (excluding the lipid matrix) (g/kg/day)	1.59	1.65	1.57	2.09	**~2.5**
Fat intake from mixed-oil ILE (g/kg/day)	0.08	0.53	0.38	0.24	**~2.3**
% of kcals from LA in mixed-oil ILE	0.001	0.01	0.007	0.004	**2-4**
% of kcals from ALA in mixed-oil ILE	0.0001	0.001	0.0007	0.0004	**0.25-0.5**
% of kcal goal from fat intake	20%	20%	23%	28%	**~30**
Aspartate Transaminase (U/L)	169	162	125	96	**< 41**
Alanine Transaminase (U/L)	255	245	142	109	**< 40**
GGT (U/L)	643	403	283	Not available	**7-68**
T:T Ratio	0.132	0.087	0.034	0.015	**0.004-0.051**
LA (nmol/mL)	834	2421	3031	2671	**1210-4300**
ALA (nmol/mL)	14	79	125	66	**20-200**
Mead Acid (nmol/mL)	54	67	40	16	**1-35**

Table 1. Comparison of our patient's fat intake from enteral feeds and mixed-oil ILE[a], percent of kcals from LA[b] and ALA[c], percent of kcal goal from fat intake, liver enzyme levels, GGT[d] level, T:T[e] ratio, and fatty acid concentrations at specified patient events.

[a]ILE = intravenous lipid emulsion
[b]LA = linoleic acid
[c]ALA = alpha-linolenic acid
[d]GGT = gamma-glutamyl transferase
[e]T:T = triene to tetraene

REFERENCES

1. **Quigley EM, Marsh MN, Shaffer JL, Markin RS**. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology*. 1993 Jan;104(1):286-301. doi: 10.1016/0016-5085(93)90864-9. PMID: 8419252.
2. **Cober MP, Gura KM, Mirtallo JM, Ayers P, Boullata J, Anderson CR, Plogsted S; ASPEN Parenteral Nutrition Safety Committee**. ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations. *Nutr Clin Pract*. 2021 Dec;36(6):1106-1125. doi: 10.1002/ncp.10778. Epub 2021 Oct 27. PMID: 34705289.
3. **Mogensen K**. Essential fatty acid deficiency. *Practical Gastro*. 2017 Jun;40(6). Available at: https://practicalgastro.com/2017/06/01/essential-fatty-acid-deficiency/.
4. **Stallings VA, Schall JI, Maqbool A, Mascarenhas MR, Alshaikh BN, Dougherty KA, Hommel K, Ryan J, Elci**

OU, Shaw WA. Effect of Oral Lipid Matrix Supplement on Fat Absorption in Cystic Fibrosis: A Randomized Placebo-Controlled Trial. *J Pediatr Gastroenterol Nutr*. 2016 Dec;63(6):676-680. doi: 10.1097/MPG.0000000000001213. PMID: 27050056; PMCID: PMC5045744.

5. **Stallings VA, Tindall AM, Mascarenhas MR, Maqbool A, Schall JI**. Improved residual fat malabsorption and growth in children with cystic fibrosis treated with a novel oral structured lipid supplement: A randomized controlled trial. *PLoS One*. 2020 May 8;15(5):e0232685. doi: 10.1371/journal.pone.0232685. Erratum in: *PLoS One*. 2020 Sep 17;15(9):e0239642. PMID: 32384122; PMCID: PMC7209323.
6. **Anez-Bustillos L, Dao DT, Baker MA, Fell GL, Puder M, Gura KM**. Intravenous Fat Emulsion Formulations for the Adult and Pediatric Patient: Understanding the Differences. *Nutr Clin Pract*. 2016 Oct;31(5):596-609. doi: 10.1177/0884533616662996. Epub 2016 Aug 16. PMID: 27533942; PMCID: PMC5438313.
7. **Raman M, Almutairdi A, Mulesa L, Alberda C, Beattie C, Gramlich L**. Parenteral Nutrition and Lipids. *Nutrients*. 2017 Apr 14;9(4):388. doi: 10.3390/nu9040388. PMID: 28420095; PMCID: PMC5409727.
8. **Gramlich L, Ireton-Jones C, Miles JM, Morrison M, Pontes-Arruda A**. Essential Fatty Acid Requirements and Intravenous Lipid Emulsions. *JPEN J Parenter Enteral Nutr*. 2019 Aug;43(6):697-707. doi: 10.1002/jpen.1537. Epub 2019 Mar 25. PMID: 30908685.
9. **Nandivada P, Carlson SJ, Chang MI, Cowan E, Gura KM, Puder M**. Treatment of parenteral nutrition-associated liver disease: the role of lipid emulsions. *Adv Nutr*. 2013 Nov 6;4(6):711-7. doi: 10.3945/an.113.004770. PMID: 24228202; PMCID: PMC3823519.
10. **de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M**. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr*. 2010 Feb;50(2):212-8. doi: 10.1097/MPG.0b013e3181bbf51e. PMID: 20038849; PMCID: PMC3365554.
11. **Nowak K**. Parenteral Nutrition-Associated Liver Disease. *Clin Liver Dis (Hoboken)*. 2020 Mar 26;15(2):59-62. doi: 10.1002/cld.888. PMID: 32226616; PMCID: PMC7098663.
12. **Tindall A, Mascarenhas M, Maqbool A, Stallings VA**. Lysophosphatidylcholine-Rich Nutrition Therapy Increased Gut Absorption of Coingested Dietary Fat: a Randomized Controlled Trial. *Curr Dev Nutr*. 2023 Jul 31;7(9):101985. doi: 10.1016/j.cdnut.2023.101985. PMID: 37671264; PMCID: PMC10475471.