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An Intravenous Fish Oil Based Lipid Emulsion successfully treats intractable pruritus and cholestasis in a patient with MVID

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INTRODUCTION

Patients with microvillous inclusion disease (MVID) are at risk for development of cholestatic liver disease. We report a case of a parenteral nutrition (PN)-dependent patient with MVID and intractable pruritus managed with a fish oil-based lipid emulsion (FOLE).

PRESENTATION OF THE CASE

A PN-dependent 3-year-old male with MVID presented with a history of worsening jaundice and severe pruritus. He was managed at an outside institution with low dose soybean oil-based lipid emulsion (SOLE) Intralipid® (Fresenius-Kabi, Uppsala, Sweden) at 0.2 g/kg/day as a strategy to prevent PN-associated liver disease (PNALD). At 11 months of age he complained of significant pruritus without dermatologic findings. Ursodiol and diphenhydramine were administered with partial resolution. Bile acids (BA) levels at the time were elevated and returned to normal after cholestyramine therapy was started at age 2 (Table 1). A liver biopsy demonstrated cholestasis with isolated bile duct loss but no

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inflammation or fibrosis. Bile salt export pump staining was consistent with canalicular changes typically seen in MVID (Figure 1) (2).

At 3 years of age the pruritus became severe leading to significant disruptions in his quality of life. Additional failed medications included rifampicin, hydroxyzine, and naltrexone. Over the following weeks he developed worsening jaundice and rising bilirubin levels. The patient was transferred to our institution where treatment with the FOLE Omegaven® (Fresenius Kabi, Bad Homburg, Germany) at 1 g/kg/day was initiated for presumed PNALD. There was no family history of liver disease. He appeared ill with scleral icterus, jaundiced skin with multiple excoriations, and fragile gray-colored hair. There were no signs of portal hypertension. Laboratory studies demonstrated direct hyperbilirubinemia with transaminitis and elevated BA (Table 1). An abdominal ultrasound revealed a normal liver size and no bile duct dilatation. A core needle liver biopsy was suggestive of PNALD (Figure 1).

The cholestasis and pruritus improved steadily beginning 2 weeks after FOLE initiation and completely resolved. The patient's quality of life continued to improve. Jaundice resolved and BA and direct bilirubin levels normalized. The patient continued to do well after one year on FOLE without pruritus.

DISCUSSION

Many *MYO5B* gene mutations associated with MVID affect biliary function and present similarly to some types of progressive familial intrahepatic cholestasis with intermittent jaundice, pruritus, elevated serum BA and normal gamma-glutamyl transferase levels, as seen in this patient (1,2). Interestingly, he had pruritus for most of his life, even in the presence of normal liver enzymes and bilirubin.

The manifestation of liver disease in patients with the *MYO5B* mutation may be influenced by genetic, epigenetic, and/or environmental factors (3). Patients with MVID are thus predisposed to suffer from the hepatotoxic effects of SOLE. The inflammatory (or lack thereof) properties of omega-3 fatty acids (O3FA) in fish oil (FO) justify its efficacy in some inflammatory conditions. O3FA are precursors to leukotrienes and prostaglandins which are less pro-inflammatory than those derived from omega-6 fatty acids. The local shift in predominating polyunsaturated fatty acids alters the amount of leukotrienes and recruitment of inflammatory leukocytes to the skin. FO-supplemented animals have a higher "leukotriene inhibition potential" which affects the amounts of epidermal anti-inflammatory molecules (4).

FOLE therapy not only proved beneficial in the resolution of cholestasis, but also reduced the levels of BA and eradicated the pruritus. Similar to the efficacy of FOLE in treating PNALD, it seems likely that the resolution of symptoms for this case is multifactorial and we hypothesize that it was due to (1) resolution of cholestasis; (2) shift in epidermal inflammatory properties induced by O3FA present in FO; and (3) reduction in circulating pruritogenic BA. Properties of FOLE make it an option for treating intractable pruritus in patients with PNALD and MVID.

List of Abbreviations

MVID	microvillous inclusion disease
PN	parenteral nutrition
FOLE	fish oil-based lipid emulsion
SOLE	soybean oil-based lipid emulsion
PNALD	parenteral nutrition-associated liver disease
BA	bile acids
O3FA	omega-3 fatty acids
FO	fish oil

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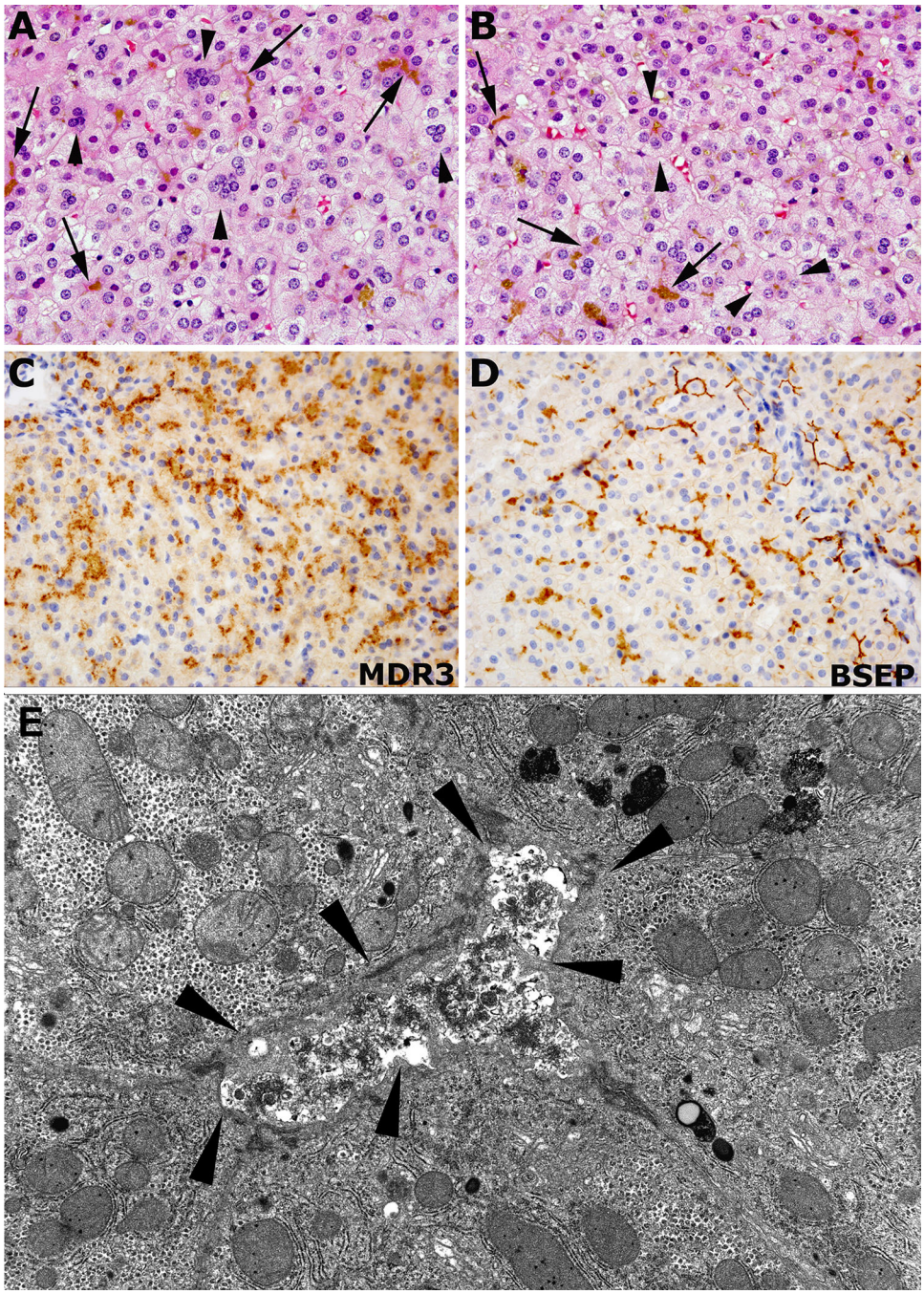

Figure 1.

Representative images of core needle liver biopsies stained with hematoxylin and eosin, and immunohistochemistry performed at our institution. Diffuse hepatocellular damage with loss of the radial orientation of hepatocellular trabecules, multinucleated giant cells (arrowheads in **A**) and pseudoacinar transformation of hepatocytes (between arrowheads in **B**), and cytoplasmic and canalicular cholestasis (arrows in **A** and **B**). MDR3 (**C**) and BSEP (**D**) immunohistochemistry showing thickened and granular reactivity along the canaliculi (in brown color). Representative image of the ultrastructure of the core needle liver biopsy

performed at outside institution showing a distended canaliculus (between arrowheads), with luminal osmophilic granular bile and microvillous effacement (**E**). Abbreviations: BSEP – bile salt export pump.

Table 1.

Liver function tests and fatty acid values before and after initiation of fish oil-based lipid emulsion monotherapy.

	30m Pre-FOLE	18m Pre-FOLE	1d Pre- FOLE	1w Post-FOLE	1m Post-FOLE	3m Post-FOLE	5m Post-FOLE	7m Post-FOLE	1y Post-FOLE
Total bilirubin (mg/dl)	1.7	0.3	10.5	9.4	4.9	1	0.8	0.6	0.4
Direct bilirubin (mg/dl)	1.1	0.1	7.8	6.1	3	0.2	0.2	0.1	<0.2
Serum bile acids (μmol/L)	108	13	211			15			
AST (U/L)	65	40	197	70	101	119	41	41	54
ALT (U/L)	104	47	355	117	154	143	51	56	46
GGT (U/L)	10	7	8	14	31	20	14	15	14
Alkaline phosphatase (U/L)	716	552	521	525	217	219	254	227	130
Alpha-linolenic acid (nmol/ml)	11	95	71	94	47	20	23	21	27
Linoleic acid (nmol/ml)	571	1458	2548	2847	1690	744	659	618	569
Eicosapentaenoic acid (nmol/ml)	108	23	33	1155	1144	508	755	730	1294
Docosahexaenoic acid (nmol/ml)	68	100	349	2027	1432	541	748	695	1224
Arachidonic acid (nmol/ml)	641	494	970	1032	520	242	209	229	255
Total ω-3 fatty acids (nmol/ml)	0.1	0.22	0.45	3.28	2.62	1.07	1.53	1.45	2.54
Total ω-6 fatty acids (nmol/ml)	1.4	2.1	3.7	4	2.2	1	0.9	0.9	0.8
ω-6:ω-3 ratio	14	9.55	8.22	1.22	0.84	0.93	0.59	0.62	0.31
Triene:Tetraene ratio	0.097	0.113	0.029	0.011	0.008	0.004	0.005	0.009	0.008

Abbreviations: AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; FOLE – fish oil-based lipid emulsion.