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Omega-3 Polyunsaturated Fatty Acids Improved Cholestasis in Biliary Atresia after the Kasai Operation

*Ji Yeon Han[1], Aram Kwon[1] and Sun Hwan Bae[1,2]**

[1]Department of Pediatrics, Konkuk University Medical Center, South Korea

[2]Konkuk University School of Medicine, South Korea

Abstract

Biliary atresia is a progressive fibro-inflammatory disease of the extrahepatic biliary tree that presents with biliary obstruction. An 8-week-old female infant was admitted our hospital due to jaundice and acholic stool. She has been jaundiced since two days after birth; her stool was acholic since she was 6 weeks of age. She was diagnosed biliary atresia; the Kasai operation was performed. However, after operation, her clinical symptoms and biochemical parameters got worse despite being on usual supportive therapy, including ursodeoxycholic acid. An oral omega-3 polyunsaturated fatty acids agent was started on day-77 after the operation. After this treatment, her clinical symptoms and biochemical parameters, including bilirubin and aminotransferase, improved. We report that omega-3 polyunsaturated fatty acids might work as a potent choleretic agent in infants with biliary atresia after Kasai operation.

Keywords: Omega-3 fatty acids; Biliary atresia; Cholestasis

Introduction

Lipid emulsions with omega-3 Polyunsaturated Fatty Acids (PUFAs) appear to improve cholestasis and, reduce hepatic triglyceride synthesis and inflammation in Intestinal Failure-Associated Liver Disease (IFALD) [1]. However, the exact mechanism by which omega-3 PUFAs improve bile flow is unclear; it is thought to be multifactorial [2]. In previous case reports, omega-3 PUFAs showed the ability to work as a potent choleretic agent [3,4]. Biliary atresia is the leading cause for liver transplantation in children, and the Kasai operation is not a definite treatment but a temporary treatment that allows time for liver transplantation [5]. It is necessary to delay liver transplantation as much as possible after the Kasai operation because liver transplantation is known to affect the patient's age [6]. Here, we present a case of biliary atresia, getting worse of cholestasis even after the Kasai operation, where omega-3 PUFAs improved cholestasis from a clinical and biochemical perspective.

Case Presentation

An 8-week-old female infant was admitted our hospital due to jaundice and acholic stool. She was born at the gestational age of 39 weeks, with a birth weight of 3900 gm. She has been jaundiced since two days after birth; her stool was acholic since she was 6 weeks of age. Upon physical examination, the sclera and skin color were icteric and the liver was palpable. Laboratory tests revealed the following results: Total Bilirubin (TB) 10.18 mg/dL; Direct Bilirubin (DB) 4.87 mg/dL; Aspartate Aminotransferase (AST) 271 IU/L; Alanine Aminotransferase (ALT) 202 IU/L; Alkaline Phosphatase (ALP) 613 IU/L; Gamma Glutamyl Transferase (GGT) 465 IU/L; Alpha Fetoprotein (AFP) 71.776 ng/ml; and bile acid >150 μmol/L. Some tests for viral markers (HBV, HCV, rubella, toxoplasma) and syphilis were negative; however, tests for cytomegalovirus and herpes virus IgM were positive. Ultrasound revealed that the gallbladder was ovoid shape and mild diffuse intrahepatic duct dilatation was observed. On Hospital Day 2 (HD#2), Magnetic Resonance Cholangiopancreatography (MRCP) revealed a collapsed gallbladder and non-visualized intrahepatic duct. On HD#3, a hepatobiliary scan showed no intestinal activity until the 24-h delayed image.

She was diagnosed with biliary atresia; the Kasai operation was performed on HD#6. An excisional biopsy showed the proliferation of many bile ducts with no bile plugs. Cytomegalovirus was found to be negative in the lesion. Steroid administration started on Post-Operative Day 9 (POD#9) and was tapered gradually. After the operation, acholic stool became normal and biochemical parameters,

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Correspondence:
Sun Hwan Bae, Department of Pediatrics, Konkuk University Medical Center, 120-1, Neungdong-ro, Gwangjin-gu, Seoul 05030, South Korea, Tel: +82-2-2030-7554; Fax: +82-2-2030-7748;
E-mail: baedori@hanafos.com

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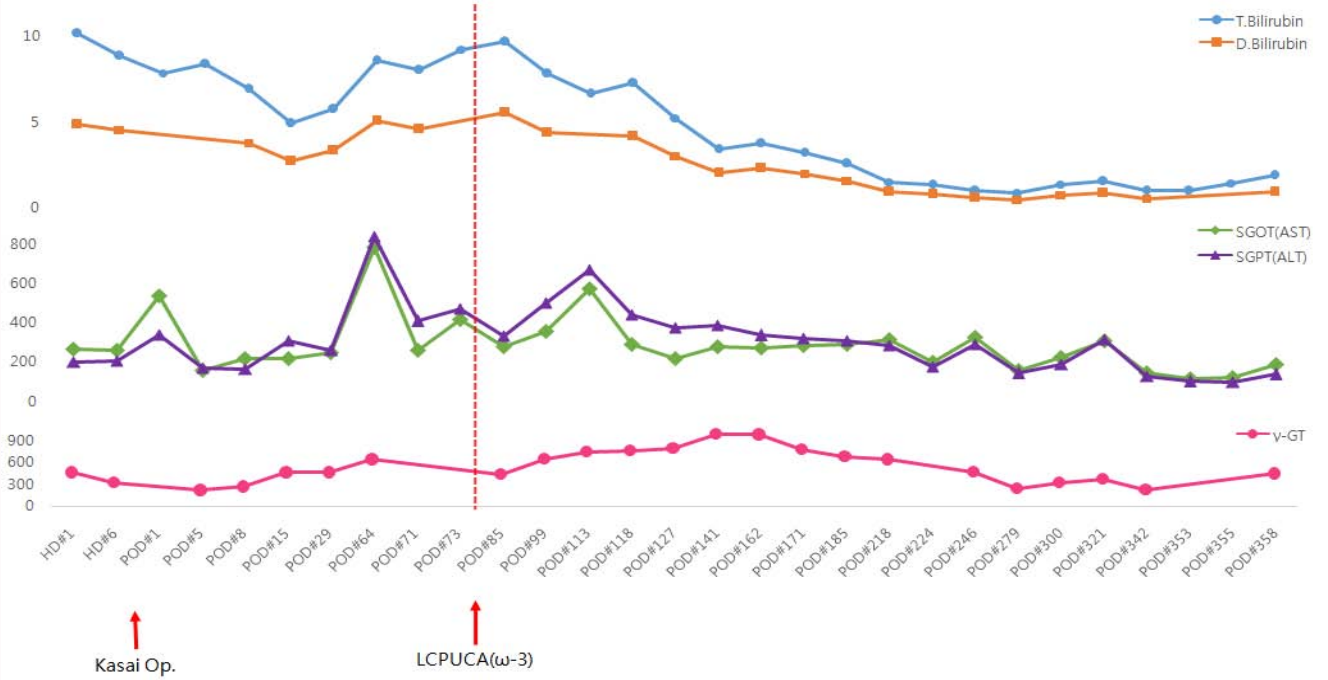

Figure 1: The laboratory findings according to the patient's clinical course. The patient with biliary atresia, after the Kasai operation, showed biochemical improvements after treatment with omega (ω)-3 polyunsaturated fatty acids.
T. Bilirubin: Total Bilirubin; D. Bilirubin: Direct Bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GT: Gamma Glutamyl Transferase; HD: Hospital Day; POD: Postoperative Day; PUFAs: Polyunsaturated Fatty Acids
X-axis, days throughout the course of treatment; Y-axis, mg/dl and IU/L

including bilirubin and aminotransferase, improved. The results from POD#15 were as follows: TB 4.97 mg/dL; DB 2.76 mg/dL; AST 219 IU/L; ALT 313 IU/L; ALP 257 IU/L; and GGT 467 IU/L. She was discharged and prescribed Ursodeoxycholic Acid (UDCA) and multivitamins. However, after 2 months, her stool became acholic again and her biochemical parameters worsened, despite being on the usual supportive therapy, involving UDCA. Laboratory tests revealed the following results: TB 8.60 mg/dL; DB 5.10 mg/dL; AST 786 IU/L; and ALT 845 IU/L. An oral omega-3 PUFAs agent, Omacor (omega-3 acid ethyl ester 90; Kuhnil Pharmacy Co., Cheonan, Korea; 840 mg, comprising EPA-ethyl ester (460 mg) and DHA-ethyl ester (380 mg) per 1-g capsule) was administered, starting on POD#77 at 500 mg, four times per day. After this treatment, the stool color returned to normal, the jaundice disappeared, and the biochemical parameters improved. The final laboratory tests, after 5 months of the omega-3 PUFAs treatment, revealed the following results: TB 1.40 mg/dL; DB 0.85 mg/dL; AST 199 IU/L; and ALT 178 IU/L (Figure 1). Since then, she has been treated with omega-3 PUFAs and UDCA.

Discussion

Biliary atresia is a progressive fibro-inflammatory disease of the extrahepatic biliary tree that presents with biliary obstruction. Kasai operation, to correct the biliary obstructions, should be completed within 8 weeks of birth to improve the long-term prognosis [5]. However, Kasai operation for biliary atresia is not a definite cure; it serves as temporary treatment that allows time for future liver transplantation. As liver transplantation in children with biliary atresia is more successful after 2 years of age, it is necessary to delay the liver transplantation to increase the rate of success [6].

Steroid and UDCA treatments following the Kasai operation have been used traditionally; however, this method is limited for improving the prognosis [7-9].

Recently, there have been attempts to use Intravenous Immunoglobulin (IVIG) therapy, instead of steroid treatment, but the results have not been successful [10]. IVIG is theoretically a therapeutic agent with several advantages (e.g., suppressing the ongoing injury of the intrahepatic bile ducts, delaying the progression of biliary cirrhosis, and maximizing bile excretion by reducing anastomosis inflammation after operation [10] or reducing immune-mediated bile duct injury by modulating the immune system [11]). Lately, the concept of early diagnosis of biliary atresia and early initiation of IVIG therapy, with less tissue damage, has emerged [11]. However, this warrants further studies. The level of TB within the first three months after the Kasai operation is valuable to predict the outcome of the first two years of life [12]. Infants with biliary atresia who achieved a TB of <2.0 mg/dL, within 3 months of the Kasai operation, showed a significantly reduced risk of complications of progressive liver disease, liver transplantation, or death by 2 years of age. This notion could be changed with omega-3 PUFAs, which might have a more potent choleretic effect than UDCA.

Omega-3 PUFAs have multiple functions, including anti-inflammatory effects. In addition, omega-3 PUFAs have shown to resolve cholestasis in several diseases, including IFALD, but the mechanism is unknown [1,2,13]. However, they improved bile flow in an animal model [14]. In a previous case reports, omega-3 PUFAs showed the possibility of acting as a potent choleretic agent in children with interlobular bile duct paucity and inspissated bile syndrome [3,4]. There are some mechanisms that could be considered. In one study, it was postulated that omega-3 PUFAs may induce the D-site binding protein and X-receptor alpha, which upregulates cholesterol 7-α hydroxylase, the enzyme in bile acid production and cholesterol

excretion [15]. In another study, it was suggested that the hepatic induction of bile acid synthesis in mice with fish oil through sterol 27-hydroxylase (Cyp27a1) may upregulate the expression of bile acid transporters in the liver and intestines [16].

There are reports that state the use of omega-3 PUFAs did not prevent the progression of fibrosis in IFALD [2]; some experts underrated the benefits of omega-3 PUFAs by claiming this. However, we think that even though omega-3 PUFAs cannot prevent the progression of fibrosis in biliary atresia, they can improve bile flow, delaying hepatocyte injury [1,2]. Delayed hepatocyte injury can delay liver transplantation to a more appropriate age, and in turn, it can increase the possibility of a successful liver transplant.

In this case, we improved cholestasis, clinically and biochemically, in an infant with biliary atresia after Kasai operation, through the administration of omega-3 PUFAs. We do not expect omega-3 PUFAs to cure biliary atresia. However, we postulate that omega-3 PUFAs, acting as supportive therapeutic agents, can effectively delay the need for liver transplantation. This treatment should be better regarded, given that the results of liver transplantation in patients over 2 years old are superior to those below this age [6].

Author Contributions

Conceptualization: BAE SH, HAN JY; Data curation: KWON AR; Formal analysis: HAN JY; Investigation: HAN JY, BAE SH; Methodology: HAN JY, BAE SH, KWON AR; Writing - original draft: HAN JY, BAE SH; Writing- review and editing: HAN JY, BAE SH.

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