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Nutritional therapy and effect assessment of infants with primary intestinal lymphangiectasia

Case reports

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Abstract

Rationale: Intestinal lymphangiectasia (IL) is a rare enteropathy involving the expansion and rupture of intestinal lymphatic channels. Although several reports have studied cases of primary IL (PIL), this condition is very rare, and is even less commonly encountered in infants. This study aimed to investigate the nutritional therapy and effect assessment of chylous reflux disorder caused by PIL in infants.

Patient concerns: Infantile patients were enrolled in the Affiliated Beijing Shijitan Hospital of the Capital Medical University between January 2012 and March 2014. The minimum age of onset was 4 months and the maximum age of onset was 16 months, with an average age of 4.9 months.

Diagnoses: All children were inpatient who had been diagnosed with chylous reflux syndrome (chylothorax and/or chylic abdomen) caused by PIL.

Interventions: Retrospective analysis and individualized nutrition therapy of these cases were carried out. Finally, nutritional therapy and prognosis of PIL were assessed and summarized.

Outcomes: All the children survived, showed improvement in the serum total protein, albumin, and HGB levels after nutritional therapy. After comprehensive nutritional therapy, we were able to achieve diarrhea control for all the 9 patients, and after treatment, the children passed soft, yellow stools 1 to 2 times/d. After treatment, the height and weight of all patients increased to within the normal ranges of the World Health Organization standard chart. The mean serum albumin level reached 41.3 g/L. All nutrition-related indicators were found to have significant improvement compared with the baseline levels.

Lessons: The results revealed that nutritional therapy for the 9 children with PIL was effective, and it may be able to improve the clinical syndromes and symptoms of children with PIL and promote recovery.

Abbreviations: IL = intestinal lymphangiectasia, LCT = long-chain triacylglycerol, MCT = medium-chain triacylglycerol, NICU = neonatal intensive care unit, PIL = primary intestinal lymphangiectasia, TPN = total parenteral nutrition, WHO = World Health Organization.

Keywords: chylous reflux disorder, infant, intestinal lymphangiectasia, nutritional support

1. Introduction

Intestinal lymphangiectasia (IL) is a rare protein-losing enteropathy that involves the expansion and ruptures of intestinal lymphatic channels, and is induced by a variety of causes. This rare disease leads to considerable loss of material such as protein, fat, and immune cells in the lymph, and is associated with clinical features such as severe hypoproteinemia,[1,2] decrease in blood lymphocytes, edema, chylous ascites, and diarrhea.[3] IL is classified into 2 types: primary and secondary. Primary intestinal lymphangiectasia (PIL) is caused by congenital abnormalities of the chest and/or abdominal lymphatics, and involves hypoplasia, agenesis, and stenosis in the thoracic duct and mesenteric lymph nodes or cisterna chyli, which results in increased pressure, expansion, and rupture of the intestinal lymphatic vessels. Alternatively, due to a congenital disorder in the intestinal lymphatics, chyloperitoneum and/or chylothorax occur. PIL most commonly occurs in infants and adolescents. Secondary IL can be caused by various diseases that induce lymphatic obstruction. The first case of IL was reported by Waldmann in 1961.[4] Since then, although several studies have investigated cases of IL,[5–7] it remains to be a rare occurrence, and cases of infants with PIL are even rarer.[8,9]

Along with limiting the intake of high-fat foods, medium-chain triacylglycerol (MCT) oil is frequently used in place of ordinary cooking oil (consisting primarily of long-chain fatty acids) for the nutritional therapy of IL in China and worldwide.[10,11] For

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unweaned infants, nutritional therapy involves administration of a simple combination of MCT oil and skimmed milk. Due to the lack of corresponding nutritional therapy and personalized formula milk, and the lack of a standardized strategy for nutritional therapy and breast milk alternatives, the cure rate of infants with this condition is low. A single-center study of a 16-bed neonatal intensive care unit (NICU) reported 10 cumulative cases of PIL over a 10-year period, with a survival rate of 30%.[12] Another multicenter retrospective NICU study from 8 large medical schools showed that all the 31 cases of chylous reflux disorder with chylopleura and(or) pericardial effusion received total parenteral nutrition (TPN) and thoracentesis drainage, and two-thirds of the patients were fed formula containing medium-chain fatty acid, while 8 cases received octreotide. In the subsequent 6-month follow-up, 22 patients survived (67%) while 9 died (27%).[13] Diarrhea that cannot be effectively corrected is usually misdiagnosed as milk protein intolerance; therefore, hydrolyzed protein formula milk containing amino acid or amino acid peptides is used as the main form of nitrogen, and partially substituted with MCT. Although disease symptoms could be controlled to some extent, the patients continued to consume an abnormal diet for a long time, resulting in potential long-term adverse effects.

Here, by treating 9 infants with PIL who had been hospitalized in our hospital, we carried out exploratory observations regarding personalized nutritional therapy and standardized therapy for the disease. We summarize the process of the nutritional therapy and its efficacy, providing a basis for further normative therapy to treat infants with PIL.

2. Methods

2.1. Patients

From January 2012 to March 2014, inpatient children at the Affiliated Beijing Shijitan Hospital of the Capital Medical University who had been diagnosed with chylous reflux disorder induced by PIL were enrolled into this study. There were a total of 9 cases. The birth history, feeding history, age of onset, accompanying signs, and accessory examinations were collected at admission.

2.2. Nutritional therapy

We developed individualized nutritional therapy for the children based on relevant information such as their age in months, height, weight, nutriture, duration of diarrhea, whether fasting, and fasting time, presence of other complications, and organ dysfunction. Based on the growth and developmental needs of children and disease characteristics, the diet was designed to contain normal energy, moderately high protein (slightly higher than breast milk protein, supplemented with peptide preparations), restricted levels of long-chain fatty acids (long-chain triacylglycerol [LCT]; <2 g/100 g of powder), appropriate amounts of medium-chain fatty acids (MCT), and essential fatty acid supplement. Children with severe diarrhea or total parenteral nutrition over 1 week received low caloric diet at the beginning of the treatment, gradually increasing to normal levels of energy. These patients were also given formulations containing partial or complete short peptides, and allowed to a gradual transition to whole protein preparations after their symptoms improved. For the children who received a total parenteral nutrition for a longer duration, they were administered a small amount of hypotonic (0.5–0.6 kcal/mL) whole-carbohydrate preparation based on maltodextrin as the initial treatment. If the patients showed a good response, the dose of peptide preparations was gradually increased by 3 to 5 g/d. When the calories reached 80% of the basic requirement, the whole protein preparation was gradually increased by 1 to 2 g/d. After the calories reached the children's requirement, and the patients adapted with no gastrointestinal reactions such as bloating and vomiting, and the diarrhea improved significantly, the whole protein preparation was gradually increased and the short peptide preparation was simultaneously decreased, while the MCT dose was appropriately increased (from 0.5 mL).

Children over 6 months of age who had good control of their symptoms and were about to begin supplementary food were given linseed oil, safflower oil, sunflower oil, and soybean oil as the main sources of essential fatty acids. The starting amount of these oils was from 0.2 to 0.3 mL/d, and the total amount did not exceed 1.5 to 2 mL/d. At the same time, sequential nutritional therapy was adopted with age and/or disease stabilization. Children below 6 months were given specially prepared low LCT formula. Children between 4 and 6 months of age or older who had achieved effective control of their symptoms by gradually adjusting the nutrient ratio in formula and osmotic pressure, received supplementary food depending on their recovery status. After 12 months, based on a strictly controlled LCT diet and appropriately supplemented MCT, individually formulated low LCT formula milk was given to assist the treatment. The formula milk administered at different stages of treatment and different disease stages were all individualized prescriptions (LCT < 2 g/100 g). In elder children who were primarily on solid diets with formula milk as a supplement, the maximum amount of MCT that could be given was 10 to 15 mL/d, and the amount of ordinary cooking oil, which is the source of essential fatty acids, did not exceed 3 g/d.

2.3. Observation indicators

As all the 9 children were nonlocal patients, they were discharged from the hospital after their symptoms were under control, and subsequently treated mainly via remote guidance. Telephone follow-up checks were conducted every week. Data regarding relevant indicators such as the amount of milk fed, stool, edema, and gastrointestinal reactions were obtained and recorded. In addition, physical development (height, weight), timely review of routine blood test, blood chemistry (including liver and kidney function, electrolytes, levels of blood protein), abdominal B ultrasound, and echocardiography were regularly monitored. Based on these indicators, the nutritional therapy was periodically adjusted as required via remote guidance. The time interval of adjusting the protocol depended on tolerance and status of the children, and the protocol was usually adjusted 1 to 2 times/wk. Because the level of medical care differed for different patients and the parents of some of the children had insufficient knowledge of the disease, the parents tended to perceive improved symptoms as a sign of full recovery, as a result of which it was difficult to follow-up.

Start and endpoints of observation: the time the patients started receiving clinical nutritional therapy was considered the start point; the time at which no clinical interventions, including the use of laxative drugs, blood transfusions, intravenous infusion of human albumin (ALB), and parenteral nutrition, were used was considered as the end point. The end point included management of symptoms, including controlled diarrhea with normal stool (1–2 times/d, formed soft stool) and normal results of routine blood test and blood biochemistry 3 times consecutively.

Table 1

Basic status of the patients.

Case number	Gender	Weight at birth, kg	Birth and postbirth history	Feeding history	Age of onset
1	Male	4.5	Cesarean section at term	Artificial feeding	2 mo
2	Female	4	Natural birth at term	Artificial feeding	1.5 mo
3	Female	3.5	Cesarean section at term	Breast feeding	3 mo
4	Female	2.35	Natural birth at term	Breast feeding	1 y and 2 mo
5	Male	Unknown			1 mo
6	Female	3.5	Natural birth at term	Breast feeding	3 mo
7	Female	3.1	Cesarean section at term	Mixed feeding	3 mo
8	Female	Unknown			8 mo
9	Male	3.2	Natural birth at term	Breast feeding	5.5 mo

2.4. Statistical methods

Data were statistically analyzed using SPSS 22.0. The relevant indicators before and after nutritional therapy were analyzed using paired t test. Missing data were handled using list-wise deletion. Descriptive data were presented as means and stand deviation (mean ± standard deviation). Statistical significance was considered at $P < .05$.

3. Results

3.1. Patient characteristics

Table 1 presents the characteristics of the patients. Of the 9 patients, there were 3 male and 6 female patients. One of the patients had a low birth weight, and 2 were found to have seroperitoneum in antenatal care in utero. The birth weights ranged from 2.35 to 4.5 kg (average weight, 3.45 kg). All the children were delivered at normal term. Three of the infants were delivered via cesarean section, and the remaining 4 were delivered naturally. Data regarding delivery and weight at birth for 2 patients were unknown. Four of the infants were breastfed, 2 were fed formula, and 1 infant received a combination of breast milk and formula milk. The minimum age of onset was 4 months and the maximum age of onset was 16 months, with an average age of 4.9 months. The disease course was between 5 and 17 months, with an average disease course of 7.5 months. The main symptom was persistent diarrhea in 6 infants; edema, in 2; and in 1 infant, vomiting was the initial symptom accompanied with persistent diarrhea.

3.2. Symptoms and signs

All infants suffered from severe hypoproteinemia, 5 had abnormal liver function, 8 had anemia, and 7 had electrolyte imbalance. Abdominal B-mode ultrasound showed varying degrees of edema and effusion in all the cases; cardiac B-mode ultrasound showed pericardial effusion (small) in 3 infants, acleistocardia in 2, and atrial septal defect accompanied with acleistocardia in 1. Chest X-ray showed a sign of lung inflammation in 6 infants, and intestinal pneumatosis in 2. Test for the effusion puncture of chyle was positive in 3 cases; endoscopy in 4 cases revealed white granular-like changes in the descending duodenum; 7 cases showed clear signs of intestinal protein loss (Fig. 1); and lymphoscintigraphy of the 9 patients showed that all of them had dysplasia in the primary lymphatic duct, and malformation of the thoracic duct with outlet obstruction was the most important sign (Fig. 2).

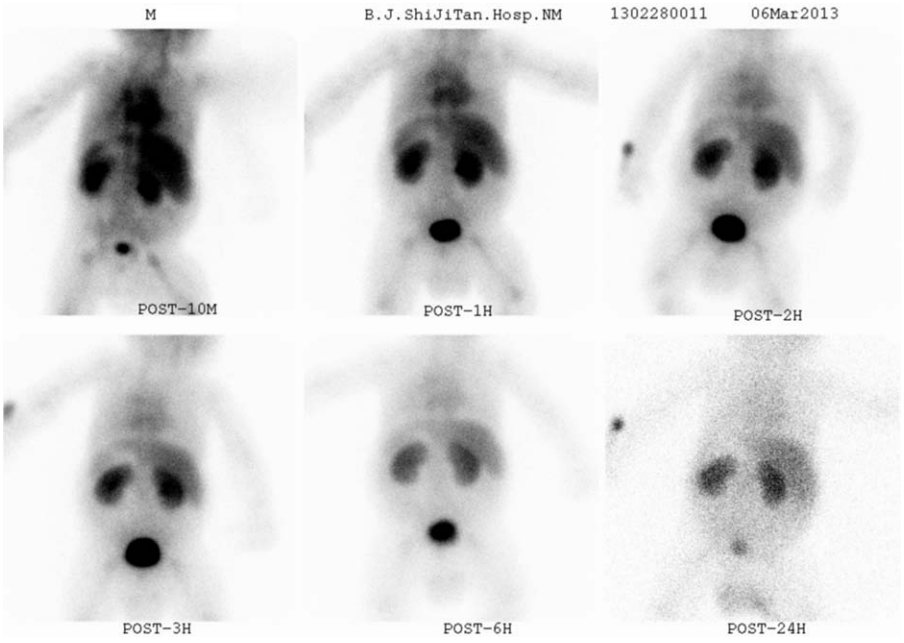

Figure 1. Protein-losing enteropathy scintigraphy (^{99}Tcm-HSA) showed that 7 cases showed clear signs of intestinal protein loss.

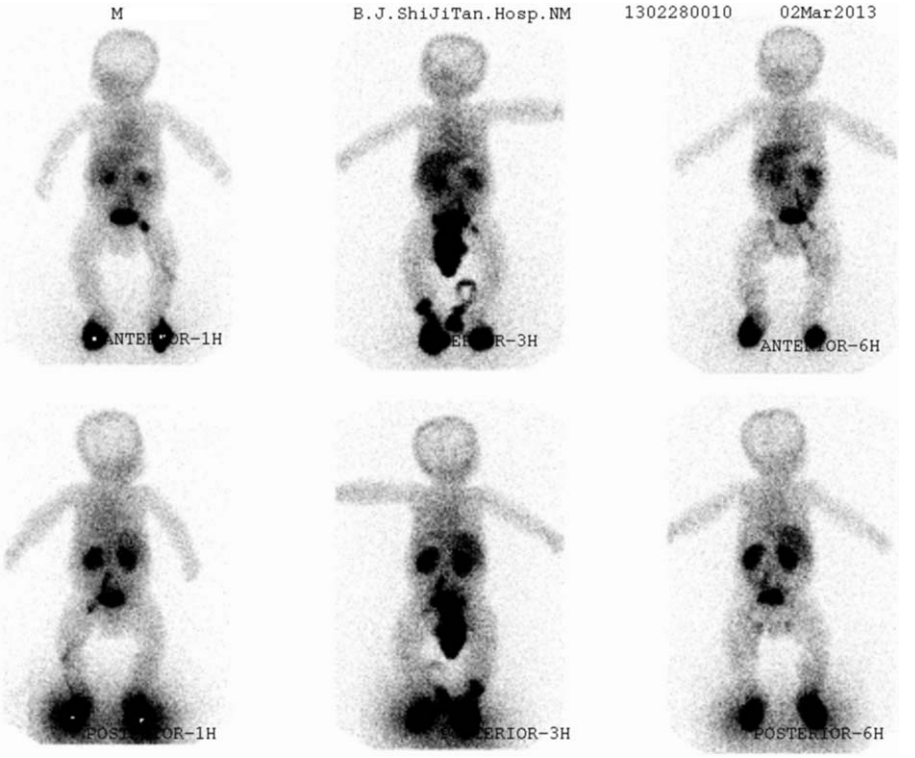

Figure 2. Radionuclide lymphoscintigraphy (^{99}Tcm-DX) of the 9 patients showed that all of them had dysplasia in the primary lymphatic duct, and malformation of the thoracic duct with outlet obstruction was the most important sign.

Total enteral nutrition (oral) was performed for the 9 infants. Of these, 1 patient (PIL onset at 1 month of age, treated after 14 months) received total enteral nutrition after performing thoracic duct exploration, lysis of adhesion, followed by dissection of the left supraclavicular lymph node. None of the other infants received clinical treatment.

After comprehensive nutrition therapy for 20 to 147 days (average, 60.7 days), diarrhea control was achieved for all the 9 patients, and defecation was 1 to 2 times/d with yellow soft or mushy excrement. Cardiac ultrasound was carried out at 1 year after nutritional therapy for 1 child who also had congenital heart disease (pulmonary stenosis, atrial septal defect combined with oval hole), and the results of the ultrasound revealed that the atrial septal defect (oval hole) had self-cured; after treatment in another hospital, the patient's pulmonary stenosis had improved and lymphatic edema of the upper left portion of the right leg was alleviated (and the patient went from being completely unable to wear shoes to being able to wear shoes normally). The other 2 children with acleistocardia were not monitored to determine whether or not the foramen ovale was open because their parents did not notice any symptoms in their children.

3.3. Blood laboratory testing

Before clinical nutritional therapy, all the children were subjected to repeated infusions of ALB and diuresis to restore or maintain normal electrolyte balance. Then, TPN and anti-infection treatment were performed. The general condition and blood ALB levels were significantly better than those at the early stage at onset, but the ALB levels were not stable and treatment involved repeated intermittent infusions of ALB. After the start of nutritional therapy, 1 case (case 7) recovered slowly due to impaired liver function (liver function impairment occurred before the treatment). The patients received infusion of human serum ALB twice during the process (5 g/times). Moreover, the remaining 8 cases did not receive relevant treatment such as parenteral nutrition or infusion of human serum ALB, plasma, and other blood products. The serum ALB of 7 children was >25.6 g/L at the start of treatment, and the ALB level of 2 children was about 20 g/L.

For 20 to 147 days after comprehensive nutritional therapy (average, 60.7 days), except for 1 case without collected accurate data after recovery as the child's parents did not cooperate with follow-up and refused blood test and physical monitoring (severe abnormality of liver function existed before nutritional therapy, alanine aminotransferase 336 U/L, aspartate aminotransferase 376 U/L, then nutritional therapy was performed). Simultaneously, the patients received 10 g of infused human ALB per day for 17 days, and the tested serum total protein (TP), ALB, and hemoglobin (HGB) levels were 38.4, 30.7, and 108 g/L, respectively. The child continued nutritional therapy for 61 days after discharge from the hospital, and intermittent nutritional therapy after the symptoms improved. Regardless, the TP levels increased to >35 g/L for all the remaining 8 children ($P < .001$). Because all the children were nonlocal, the methods for testing blood samples with the reference value were not the same. Nevertheless, the results indicated that nutrition-related indicators were significantly improved compared with that before treatment, and all the patients survived (Table 2).

3.4. Physical development

During the treatment, the height and weight of the 9 patients were between the 3rd and 97th percentiles of the World Health

Table 2

Comparison of relevant indicators before and after nutritional therapy.

Case number	Time of therapy, d	TP, g/L		ALB, g/L		GLB, g/L		WBC, 10^9/L		LY%		NE%		RBC		HGB	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
1	147	49.6	52	27.5	36	22.1	16	3.88	7.27	55.9	41	32.2	45.6	4.8	4.8	123	129
2	81	58.1	50.7	41	35.2	17.1	15.5	16.97	Not examined	63.5	Not examined	31.4	Not examined	3.62	Not examined	100	Not examined
3	20	33.2	59.4	25.6	46.2	8.2	13.2	4.37	4.89	11.7	40.5	71.8	26.2	3.08	5.34	85	158
4	43	53.2	Not examined	33.6	41	19.4	Not examined	5.5	5.1	31.5	19.3	54.8	67.7	5.18	5.16	107	120
5	33	48.1	52.2	37.8	38.5	10.3	13.7	12.53	Not examined	55.2	Not examined	29.6	Not examined	5.02	Not examined	99	103
6	30	41.7	58.4	30.7	39.3	11	19.1	2.89	2.68	28.7	53.3	44	15.7	4.39	3.61	124	90
7*	63	29.3	62.7	20.7	46.4	8.6	16.3	2.47	8.31	32.8	50.44	43.3	37.74	4.42	4.43	133	126
8	51	60.8	71.6	43	49.8	17.8	21.8	2.54	7.56	50.4	58.7	33.1	31	3.16	4.72	92	113
9	48	27.1	38.4	20	30.7	7.1	7.7	7.49	6.65	13.2	19.8	75.9	59.1	4.38	3.83	105	108
P		.035		.019		.165		.121		.239		.254		.436		.387	

ALB = albumin, GLB = globulin, HGB = hemoglobin, LY = lymphocyte, NE = neutrophils, TP = total protein, RBC = red blood cells, WBC = white blood cells.
* Taking 2 intravenous infusions of Human Albumin (5g/time) during the nutritional therapy process.

Organization (WHO) standards, and the growth curve showed an instantaneous increase. Of the 9 patients involved, the percentage of height development slightly decreased in 3 (although the trend of the height growth curve was normal) due to specific reasons (1 patient did not effectively recover from impaired liver function, 1 patient had congenital heart disease and abnormalities of lower limb lymphatic flow, and 1 patient was not fed formula milk according to the doctor's advice). In 1 case, the parents did not cooperate with follow-ups after the child's symptoms improved, and the remaining 5 cases showed improved development of height, and the weight development of the children significantly improved and could be controlled to within the normal range (Table 3). Nevertheless, based on the appropriate low-fat diet, normal growth and development, no occurrence of lymphatic fluid leakage, and working and living as normal children as the basic expectations, and from the view of function, complete recovery of disease was observed in all patients ($P < .001$).

4. Discussions

We reported a series of 9 infants diagnosed with PIL who were treated using nutritional therapy and ALB infusions. The patients were monitored remotely every week and data regarding relevant indicators were collected. All the children survived, showed improvement in their serum TP, ALB, and HGB levels after nutritional therapy. Comprehensive nutritional therapy helped achieve diarrhea control for all patients. Except in 1 case where the parents did not cooperate with the follow-up and the TP content could not be examined, the TP level was significantly higher than the baseline level ($P = .035$). All nutrition-related indicators had significantly improved from baseline. During treatment, the height and weight of the 9 patients showed an instantaneous increase and were between the 3rd and 97th percentiles of the WHO standard chart.

Lymphatic vessels are distributed in the intestinal lamina propria, submucosa, and serosa. If the intestinal lymphatic flow is blocked due to any reason, this will result in a loss of protein, fat, and lymphocytes in the intestinal lumen and membrane cavity, triggering a series of symptoms such as hypoalbuminemia, peripheral edema,[14] chylous diarrhea, chylous ascites, and protein loss enteropathy, all being signs of PIL. As PIL is rare, diarrhea that cannot be effectively corrected is often misdiagnosed as milk protein intolerance, and formula milk containing hydrolyzed protein is selected with amino acids or amino acid peptides as the main form of nitrogen. Protracted disease would affect intestinal function, resulting in damage to the digestive tract. The leakage of lymph reduces the immunity of children patients and easily causes infection. Second, in the early stage, the children patients also present with diarrhea, pyrexia, and great decrease in lymphocyte count. When they visited other hospitals, they were often diagnosed with infection and given anti-infective therapy.

Surgical intervention is still a common strategy for patients with IL in whom the location of malformation or chyle leakage can be determined, but surgery is unsuitable in patients who are young or have complicating conditions such as congenital heart disease, lymph reflux disorder at other sites, and malnutrition. Thus, conservative treatment should be performed. Nevertheless,

Table 3

Indicators of physical development of the children before and after nutritional therapy.

Case number	Time of follow-up	Height, cm (percentile)		Weight, kg (percentile)	
		Pretreatment	Post-treatment	Pretreatment	Post-treatment
1	13 mo	65 (15th)	82.0 (3rd)	9 (85th)*	14.0 (87th)
2	8 mo	70 (97th)	77.0 (70th)	7 (75th)	12.0 (97th)
3	12 mo	65 (15th)	88.0 (97th)	6.5 (15th)*	13.0 (85th)
4	5 mo	76 (<15th)	83.0 (15th)	9 (15th)*	11.0 (50th)
5	7 mo	80 (50th)	82.0 (15th)	11 (60th)	13.0 (85th)
6	6 mo	61 (15th)	85.0 (97th)	7 (50th)	13.0 (97th)
7	7 mo	62 (15th)	88.0 (97th)	5.5 (3rd)	11.7 (85th)
8	7 mo	70 (50th)	90.0 (50th)	7.5 (3rd)	11.0 (3rd)
9	Loss to follow-up after improvement	73 (86th)	Lost to follow-up	9 (70th)	Lost to follow-up

* Taking seroperitoneum and Lower Extremity Edema before nutritional therapy.

improper nutritional treatments such as no strict limitations on LCT intake and relatively high protein supply during certain stages of the disease often play contributory roles in the development of intestinal dysfunction.

Nutritional therapy in PIL not only provides ALB and immunoglobulin, prevents infection, and corrects the electrolyte imbalance; it is also the primary strategy for conservative treatment. For infants with normal diet or very young children, MCT diet treatment (low LCT diet with MCT supplement) is the preferred choice for treating PIL, regardless of surgical treatment. Indeed, in a natural diet, fat consists primarily of LCTs, which are transported through the lymphatics as chylomicrons postabsorption. After being absorbed by the lymphatics, MCTs enter the hepatic portal vein and reduce the formation and leakage of chylous fluid, leading to a decrease in dietary LCT. Therefore, a diet consisting of MCTs can reduce the pressure inside the lymphatic vessels to a certain extent, relieving the symptoms of PIL.[10,11] The LCT content was strictly limited to <2 g/100 g of formula milk powder. After disease stabilization and diarrhea improvement, the intake of vegetable oils rich in essential fatty acids such as safflower and sunflower oils should be gradually increased to meet the requirement of essential fatty acids for physical growth and development. Meanwhile, the added MCT was gradually increased until the diarrhea was effectively controlled. The treatment duration ranged from 5 to 13 months. At the end of treatment, significant diarrhea control was achieved, and the stool changed from dilute watery stool to soft formed stool with a frequency of 1 to 2 times/d.

Nutritional therapies depend on factors such as cause, severity, and impact of protracted illness on intestinal and metabolic functions and can vary across individuals. Studies have reported that the efficacy of nutritional support treatment is better for young patients with IL[3,15] than for adult patients; this may be associated with the developmental potentials of children. When the symptoms of PIL are controlled, and the transition from amino acid or amino acid peptide to whole protein formulations is improperly made, children could suffer from diarrhea induced by protein dyspepsia, further complicating their disease status. If necessary, complete peptide should be used as the nitrogen source, and the whole protein amount should be increased after diarrhea control is achieved. The standard amount of supplied whole protein was adjusted to ensure that the digestive tract can effectively tolerate it without any vicious burden or damage. According to the 2006 version of the WHO child growth standards,[8] after treatment, the height and weight of 8 of the 9 children in this study crossed the 50th percentile, and the tendency of the growth curve for all the 9 children was instantaneous. The plasma ALB and HGB levels had both significantly increased after treatment compared with the pretreatment levels ($P<.05$). After enteral nutrition and diet therapy, the children exhibited good growth and development and effectively recovered digestive function. Finally, after the treatment, the indicators of physical development returned to the normal values or reached the standards of clinical cure, the symptoms were effectively controlled, and the prognosis of IL was greatly improved.

This study has several limitations. First, PIL is a rare disease, and due to the small number of cases and the complicated diagnosis, the study was performed in a single center. The sample size of 9 cases was small. Second, all the cases were followed-up in other centers or remotely, leading to loss of part of the follow-up data. Moreover, 1 case could not be followed up. Finally, as this study is a case report, it cannot explain the specific efficacy and safety of the treatment approaches used.

In conclusion, we demonstrated that nutritional therapy could be effective for infants with PIL, and the treatment alleviated the clinical symptoms of the infants and promoted recovery. These results could serve as a guide for clinicians who encounter this case in infants. Further studies with a larger sample size are required to clarify the specific efficacy and safety of the different treatment approaches used here.

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