

Glutamine-Supplemented Parenteral Nutrition and Probiotics in Four Adult Autoimmune Enteropathy Patients

Ren-Ying Xu^{*†}, Yan-Ping Wan^{*†}, Yi-Quan Zhou^{*}, Li-Ping Lu^{*}, Zhi-Qi Chen^{*}, Ying-Jie Wu^{*}, and Wei Cai^{†‡}

^{*}Department of Clinical Nutrition, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, [†]Shanghai Key Laboratory of Pediatric Gastroenterology and Nutrition, and [‡]Clinical Nutrition Center, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

To evaluate the effects of glutamine-supplemented parenteral nutrition (PN) and probiotics in adult autoimmune enteropathy (AIE) patients. Four adult AIE patients were identified from April 2006 to January 2012. Clinical and nutritional data were obtained from the patients' medical records. Glutamine-supplemented PN started immediately when the AIE diagnosis was confirmed. The total PN duration was 351 days. According to the PN prescription, the average caloric intake ranged from 20 to 25 kcal/kg/day, and the protein intake ranged from 1.2 to 1.5 g/kg/day. Alanine-glutamine (20 g/day) was administered to AIE patients for 4 weeks followed by a 2-week break, and this treatment schedule was repeated when PN lasted for more than 6 weeks. Body weight gain and an increased serum albumin level were achieved after PN, and defecation frequency and quality also improved. Each patient received oral supplements, 250 mL of Ensure and two probiotics capsules (each capsule containing 0.5×10^8 colonies) three times a day when enteral nutrition started. Three AIE patients were successfully weaned off PN, and one patient died of pneumonia. Glutamine-supplemented PN and probiotics show promise in managing patients with AIE and related malnutrition. (**Gut Liver 2014;8:324-328**)

Key Words: Autoimmune enteropathy; Malnutrition; Parenteral nutrition; Probiotics; Glutamine

INTRODUCTION

While most cases of intestinal malabsorption syndrome are caused by massive intestine resection due to congenital and acquired diseases, a small portion of patients with structurally

intact intestines also display intestinal malabsorption syndrome. Autoimmune enteropathy (AIE), characterized by protracted diarrhea and weight loss, often occurs in infants and young children and can occasionally be observed in adults.¹

Fewer than 100 adult AIE patients have been reported worldwide. Mutations in FOXP3, a transcription factor that controls regulatory T-cell development and function, play an important role in its pathogenesis.² Induction of clinical remission has usually required immunosuppressive drugs such as steroids, azathioprine, cyclosporine, and tacrolimus.^{3,4} Some AIE patients who do not respond to immunosuppressive therapy can be treated by infliximab.⁵ Interestingly, though malnutrition is common in AIE patients, nutrition support has rarely been reported in these special patients. Only one paper described total parenteral nutrition (PN) in 10 pediatric AIE patients. The results showed five of them were weaned off PN, three died of sepsis after a mean period of 18 months; one underwent total colectomy and one patient is still dependent on TPN for 24 months.⁶ Our paper describes our experience with glutamine-supplemented PN in managing adult patients with AIE and its related malnutrition.

CASE REPORT

From April 2006 to January 2012, four adult patients were identified from Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine. All the patients met the criteria for the diagnosis of adult AIE: 1) adult-onset chronic diarrhea (>6 weeks' duration); 2) malabsorption; 3) specific small bowel histology: partial/complete villous blunting, deep crypt lymphocytosis, increased crypt apoptotic bodies, and minimal intraepithelial lymphocytosis; 4) exclusion of other causes of villous atrophy including Crohn's disease, refractory sprue, and intestinal lym-

Correspondence to: Yan-Ping Wan

Department of Clinical Nutrition, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, 1630, Dong Fang Road, Shanghai 200125, China

Tel: +86-021-68383318, Fax: +86-021-68383318, E-mail: wanyp204@yahoo.com.cn

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phoma; 5) AE and/or AG antibodies. Criteria 1 to 4 are required for a definite diagnosis of AIE. Presence of AE and/or AG antibodies is an important diagnostic support, but their absence does not exclude the diagnosis of AIE.⁷ Written informed consent was obtained, and the study was approved by the ethics committee of the same hospital.

1. Clinical data

Clinical data are obtained at the first admission to our hospital (Table 1). The primary symptom of AIE was watery and persistent diarrhea without evidence of infection. Case 2 had undergone enucleation of an ovarian cyst 3 years before the symptoms appeared.

The stool routine test was negative without red blood cells, white blood cells, fat drops, and eggs. All immune tests were negative: indirect immunofluorescence antinuclear antibody (IFANA), convection immune assay for detection of ENA antibody (CLE), immunoblot assay for detection of ENA polypeptide antibody spectrum (IBT), detection of anticardiolipin antibodies (ACL), and double-stranded DNA antibodies (anti-dsDNA). The results were negative for virus hepatitis, human immunodeficiency virus and tuberculosis. Serum immunoglobins showed a decreasing trend. Flow cytometric detection showed that the percentage of CD³⁺ and CD⁸⁺ increased while the percentage of CD⁴⁺ and natural killer cells decreased according to the normal range. The creative response protein level was significantly high

Table 1. Clinical Characteristics of Autoimmune Enteropathy Patients

Characteristic	Reference range	Case 1	Case 2	Case 3	Case 4
Sex	-	F	F	M	M
Age at diagnosis, yr	-	28	29	22	41
Duration of symptoms before diagnosis, yr	-	5	0.5	10	4
ESR, mm/hr	M: 0-15 F: 0-20	9	40	20	20
CRP, mg/L	0-8	14.5	150	65.5	13.0
Immunoglobins					
Ig A, g/L	0.7-4	2.46	0.25	0.24	2.92
Ig G, g/L	7-16	6.88	1.43	4.1	10.20
Ig M, g/L	0.4-2.3	2.23	0.18	0.16	0.74
Autoantibodies	-	-	-	-	ASMA+
Flow cytometric detection, %					
CD ³⁺	66±10	75.0	78.0	78.9	82.8
CD ⁴⁺	44±9	20.0	23.8	35.2	35.6
CD ⁸⁺	31±7	64.3	61.7	48.0	49.7
NK	15±6	5.8	6.1	9.5	7.2

M, male; F, female; ESR, erythrocyte sedimentation rate; CRP, creative response protein; ASMA, antismooth muscle antibody; NK, natural killer cells.

Table 2. Evaluation for Anemia in Autoimmune Enteropathy Patients at the Time of Hospital Admission

	Reference range	Case 1	Case 2	Case 3	Case 4
RBC, ×10 ¹² /L	M: 4.5-5.5×10 F: 4.0-4.5×10	3.88	2.53	2.22	1.43
Hb, g/L	M: 12-16 F: 11-15	116	82	75	63
HCT, L/L	0.335-0.508	0.342	0.240	0.223	0.177
MCV, fL	82.6-99.1	88.1	94.9	100.5	123.8
MCHC, g/L	320-362	339	342	336	356
Vitamin B ₁₂ , pg/mL	180-914	543	592	335	298
Folate, ng/mL	>5.21	NT	1.68	7.16	2.07

RBC, red blood cells; M, male; F, female; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; NT, not tested.

in all cases.

2. Nutritional assessment and intervention

Malnutrition is classified according to BMI and anemia is defined as serum hemoglobin.^{8,9} Severe malnutrition was found

Table 3. Nutritional Indexes in Autoimmune Enteropathy Patients

		Case 1	Case 2	Case 3	Case 4
PN days	-	125	191	15	16
In-hospital days	-	173	213	28	33
Height, cm	-	158.0	174.0	172.0	173.0
Body weight, kg	A	33.0	42.0	38.0	49.0
	B	38.0	43.0*	45.0	48.5
	C	40.0	-	52.0	49.0
BMI, kg/m ²	A	13.2	13.9	12.8	16.4
	B	15.2	14.2*	15.2	16.2
	C	16.0	-	17.6	16.4
RBC, ×10 ¹² /L	A	3.88	2.53	2.22	1.43
	B	3.98	5.01*	2.63	2.18
	C	4.04	-	2.88	3.06
Hb, g/L	A	116	82	75	63
	B	112	166*	85	87
	C	122	-	97	110
Total protein, g/L	A	47.2	36.7	41.7	55.5
	B	50.7	46.5*	41.8	59.1
	C	56.6	-	53.5	72.3
Albumin, g/L	A	30.0	22.3	26.5	32.1
	B	30.6	26.1*	28.3	32.6
	C	35.2	-	34.9	40.3
Prealbumin, mg/L	A	68	69.5	38	257
	B	238.4	151.1*	182.5	297.2
	C	303.8	-	241.2	358.3
Calcium, mmol/L	A	1.75	1.78	1.80	1.72
	B	2.05	1.7*	NT	1.70
	C	2.02	-	2.03	1.95
Phosphorus, mmol/L	A	1.05	0.26	1.01	0.83
	B	0.70	1.44*	NT	0.95
	C	1.06	-	1.17	1.25
Magnesium, mmol/L	A	0.39	0.64	0.57	0.62
	B	0.60	0.32*	NT	0.85
	C	0.59	-	0.89	0.87

Reference range: BMI, 18.5–23.9 kg/m²; RBC, 4.0–4.5×10¹²/L for female and 4.5–5.5×10¹²/L for male; Hb, 11–15 g/L for female and 12–16 g/L for male; total protein, 60–80 g/L; albumin, 35–55 g/L; prealbumin, 200–400 mg/L; calcium, 2.0–2.5 mmol/L; phosphorus, 1.0–1.6 mmol/L; magnesium, 0.67–1.04 mmol/L.

PN, parenteral nutrition; A, at the time of hospital admission; B, PN off; C, hospital discharge; BMI, body mass index; RBC, red blood cell; Hb, hemoglobin; NT, not tested.

*Data were obtained a week before the patient died.

in all of the cases. Moderate anemia was found in three of four patients (Table 2).

The serum foliate level decreased as well. Hypocalcemia, hypomagnesemia, and low phosphorus were common in all AIE patients (Table 3).

PN was given to these patients for rehydration and nutrition support. A low-calorie (15 to 20 kcal/kg/day) PN was initiated and total calorie increased slowly. It usually took 1 to 2 weeks to achieve the standard goal. A standard PN solution contained a balanced mixture of amino acids, lipids, and glucose in addition to electrolytes, trace elements, and vitamins. The average caloric intake was 20 to 25 kcal/kg/day and the protein amount was 1.2 to 1.5 g/kg/day for the PN prescription. Glutamine (Dipeptiven; Sino-Swed Pharmaceutical Ltd., Wuxi, China) was given to AIE patients (100 mL/day, every 100 mL containing 20 g) for 4 weeks followed by a 2-week break, a cycle which was repeated when PN lasted for more than 6 weeks (Fig. 1).

Then if the frequency of defecation decreased (to ≤3 times per day) and quality improved (soft and formed stools were achieved), enteral nutrition (EN) began. When EN increased, PN decreased accordingly. If the oral diet met 60% of the daily caloric goal, PN was stopped. Each patient was supplemented orally with 250-mL Ensure (250 kcal; Abbot Laboratories Ltd., Abbot Park, IL, USA) and two probiotics capsules (a mixture of viable, lyophilized *Bifidobacterium*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*, each capsule containing 0.5×10⁸ colonies) three times a day when EN started.

Total PN and in-hospital duration was 351 and 447 days, respectively. Nutritional indexes did improve significantly in three cases, but not in case 2 (Table 3). Three patients were weaned off PN, and one died of uncontrolled pneumonia.

PN-associated liver disease (PNALD) was found in case 2 when she had received PN for 7 weeks.^{10,11} The fat emulsion was stopped and drugs (polyene phosphatidylcholine injection and glutathione injection) were administered to protect liver function. Liver function returned to normal after 2 weeks. Immune medications were applied in two AIE patients who didn't response to glutamine-supplemented PN. Immune medications were applied in two AIE patients who didn't response to glutamine-supplemented PN. Case 1 received both steroids for 146 days and azothioprine for 73 days. Case 2 just received steroid for 116 days. The details were shown in Fig. 1.

DISCUSSION

Not surprisingly, severe malnutrition, anemia and deficiency of calcium, phosphate and magnesium were found in all AIE patients because of intestinal malabsorption. To resolve the nutritional problem, artificial nutrition support had to be initiated.

PN is very important for supplying life-essential micronutrients, vitamins and minerals before intestinal function recovers. If the diagnosis of AIE is confirmed, PN should begin immedi-

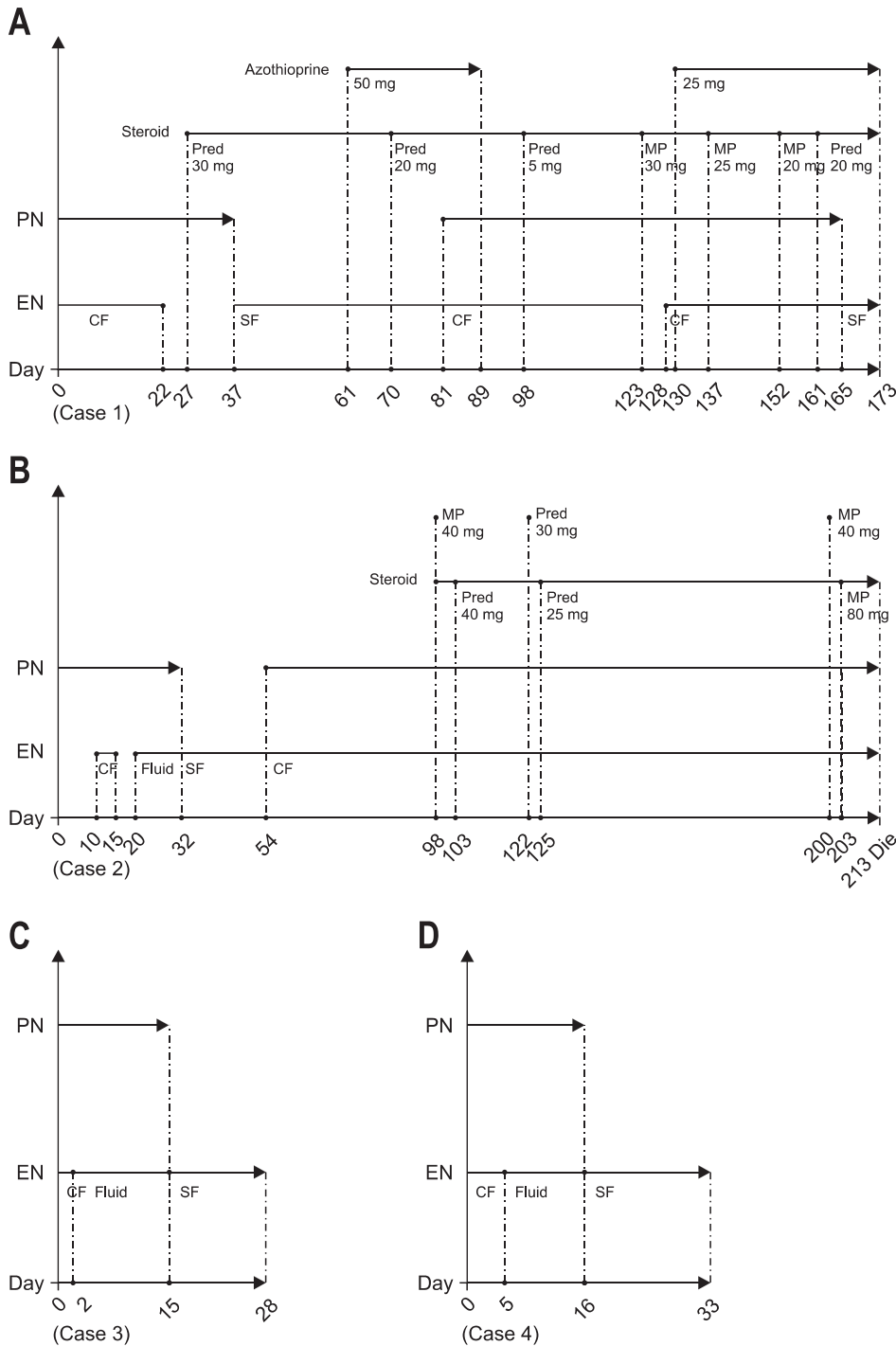


Fig. 1. Treatment procedure in four autoimmune enteropathy patients. (A) Case 1. (B) Case 2. (C) Case 3. (D) Case 4. The medication amounts shown in the figure represent the daily amounts. MP was administered intravenously, and prednisolone and azathioprine were administered orally. PN, parenteral nutrition; EN, enteral nutrition; Pred, prednisolone; MP, methylprednisolone; CF, clear fluid; SF, semifluid.

ately to avoid deterioration of nutritional status. Secondly, the duration of PN in patients with AIE (in our study, at least 15 days) was longer than that in patients with other conditions. It is important to consider PN-associated complications, especially PNALD, the prevalence of which is 20% to 75% in patients who require long-term PN.¹² One measure to prevent PNALD is to start PN in a small amount (15 to 20 kcal/kg/day) and to increase the supply slowly to the goal. A second measure is to modify the PN regimen by reduction of calories and the fat

emulsion dose.¹³ Another measure is to initiate EN.¹⁴ The earlier EN began, the less likely was PNALD to occur. In AIE patients, EN need not require fasting because the diarrhea does not respond to complete bowel rest.⁷

The recovery of intestinal function is the key to treating AIE. Glutamine, fuel for rapid proliferation of intestinal mucosa cells, is reported to be helpful in promoting intestinal rehabilitation. Guo *et al.*¹⁵ reported seven pediatric patients with short bowel syndrome (SBS) were treated with growth hormone and supple-

mental glutamine plus EN for 3 weeks. The intestinal absorptive capacity and plasma levels of proteins were significantly improved after treatment. Six patients were weaned off PN. Wu *et al.*¹⁶ reported that a 3-week treatment including growth hormone plus glutamine resulted in weight gain and a dramatic decrease in stool output in eight adult patients with SBS. Our study showed that glutamine-supplemented PN induced clinical remission without steroids in two patients. Steroid and azothioprine were required in patients who didn't respond to glutamine-supplemented PN.^{4,5,7}

The limitations of our study were the small number of patients and the lack of a control group. Another limitation was that probiotics, which are also considered effective in promoting intestinal rehabilitation, were used in the study; however, their possibly confounding effects were not evaluated.^{17,18}

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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