Table 1. Diagnostic criteria for CIPO proposed by the Research Group of the Ministry of Health, Labour and Welfare

Definition of CIPO

Chronic bowel obstruction not explained by structural abnormalities

Criteria for CIPO

Must include all of the following four points:

1. Onset of one or more symptoms of bowel obstruction[1] at least 6 months prior to the diagnosis
2. One or both of the following for the previous 12 weeks
   a. Abdominal bloating
   b. Abdominal pain
3. Dilatation and/or air-fluid level of the intestine on abdominal X-ray, echo and/or CT imaging
4. No evidence of structural disease (by upper and lower gastrointestinal endoscopy, computed tomography, barium enema, and small-bowel follow-through) that could explain the dilatation and/or air-fluid level of the intestine

Important notice

1. Congenital and/or onset at under 15 years of age must be excluded. Only adult onset is included
2. Surgical history, except surgery for CIPO, within the 6 months prior to the diagnosis must be excluded to rule out Ogilvie syndrome
3. CIPO is defined at two levels: primary CIPO or secondary CIPO. Primary CIPO consists of three types: the myogenic type, neurogenic type and idiopathic type. Secondary CIPO consists of two types: the SSc type and the unclassified type
4. Family accumulation may exist
5. Neuropathy, such as problems with urination, may exist
6. Some psychosocial disorder may be present

[1] Symptoms of bowel obstruction include: abdominal pain, nausea, vomiting, abdominal bloating, abdominal fullness, lack of gas and/or passing gas.

by acute functional transit failure. It is speculated that this syndrome is caused by collapse of the regulation of autonomic nerves distributed in the colorectum. The Ogilvie syndrome is secondary to various diseases and has been mainly reported to occur after abdominal surgery [6].

The chronic type of IPO is the so-called 'CIPO'. Although there are no specific laboratory findings, malabsorption due to bacterial overgrowth, anemia, hypocalcemia, hypolipidemia, folic acid deficiency, iron deficiency and hypoalbuminemia are often observed in CIPO patients due to malnutrition [2–4]. CIPO may affect the entire gut from the esophagus to the rectum in the broad sense, but predominantly, the small intestine is affected. CIPO can be categorized as primary or secondary [7]. Primary CIPO includes the myogenic, neurogenic, mesenchymopathic (arising from the dysfunction of the interstitial cells of Cajal) and the mixed or unclassifiable type (inflammation). Secondary CIPO includes a subtype that is secondary to underlying diseases such as systemic sclerosis (SSc) or mitochondrial encephalomyopathy as well as a subtype that is related to antipsychotic or antidepressant drug use. The subtype of CIPO that is not associated with any apparent underlying disease has been called 'chronic idiopathic intestinal pseudo-obstruction' (CIIP).

At present, the diagnostic criteria for CIPO are not well established. The Research Group for the Survey of the Actual Conditions of Epidemiology, Diagnosis, and Treatment of CIIP in Japan (chief investigator, Atsushi Nakajima), Research Project for Overcoming Intractable Disease, Health Labour Sciences Research Grant in the fiscal year 2009, proposed Japanese diagnostic criteria for CIPO in order to facilitate the diagnosis of this rare disease by the general physician. The criteria are composed of four mandatory requirements and an important note for the diagnosis, as shown in table 1. Recently, Iida et al. [8] investigated the reported data of a total of 121 Japanese CIPO cases between 1983 and 2009 and calculated the sensitivity of the proposed diagnostic criteria, under the assumption that the case reports used contained sufficient information about each patient; therefore, all cases were considered to be correctly diagnosed as having CIPO. However, very little is still known about the pathophysiology of CIPO and the status of CIPO patients in Japan; therefore, we conducted an epidemiologic survey to assess the present status of this rare disease in the Japanese population following the investigation of previous case reports. We investigated the recognition rate of the disease in certified gastroenterology institutions as well as its epidemiology, including the clinical symptoms and

Table 2. Patient questionnaire sent to 378 institutions belonging to the JSGE

I. Patient information									
Sex:	Male	Female							
Age, years:	≤14	15–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
II. Clinical presentations at first hospital visit									
Abdominal pain for the previous 12 weeks:				Yes			No		
Vomiting for the previous 12 weeks:				Yes			No		
Abdominal bloating for the previous 12 weeks:				Yes			No		
Dilatation of the bowels on radiological imagings:				Yes			No		
Disease duration:				More than 6 months			Within 6 months		
Type of CIPO:				Primary			Secondary		
If secondary CIPO:				Secondary to SSc			Secondary to others		
III. Treatment									
Selected method of treatment:	Diet		Medication		Surgery		Others		No treatment
Medication drugs: (multiple answers allowed)	Mosapride[1]		Erythromycin		Pantothenic acid		Metoclopramide		Sulpiride
	Domperidone		Daikenchuto[2]		Somatostatin analogue		Kanamycin		Metronidazole
	Polymixin B		Probiotics		Itopride		Calcium polycarbophil		
	Magnesium oxide		Other laxatives		Loperamide		Albumin tannate		
	Dimethicone		PPI		H2RA		Mucosal protective drugs		

JSGE = Japanese Society of Gastroenterology; PPI = proton pump inhibitors.
[1] Mosapride is the 5-HT4 receptor agonist. [2] Daikenchuto is a herbal medicine.

radiological imaging findings; then, we evaluated the validity and usefulness of the diagnostic criteria for CIPO newly proposed by this research group.

Materials and Methods

A questionnaire was sent to 378 institutions belonging to the Japanese Society of Gastroenterology between December 2009 and February 2010. At first, we enquired whether or not each of the participating institutions was aware of CIPO as a disease entity or had encountered patients with CIPO. While enquiring about the institutions' recognition of this disease, CIPO was defined as a disease characterized by recurrent clinical episodes of intestinal obstruction in the absence of mechanical obstruction, as confirmed by clinical examinations, including radiological imaging and gastrointestinal endoscopy. The institutions that had knowledge about the disease entity were asked to fill out the questionnaire, based on the premise that the gastrointestinal specialists in the institutions had certainly performed the aforementioned examinations to exclude mechanical obstruction and made a correct diagnosis of CIPO. The details of the questionnaire are shown in table 2. Here, the term 'dilatation of the bowels on radiological imagings' indicates not only dilatation of the small intestine, but also of the colon. We decided to use the simplistic term 'the bowels' because of the following reasons: (1) our intention in establishing these diagnostic criteria is to facilitate the diagnosis of CIPO by the general physician without any need for complicated or specialized discussions, such as 'which is the dilated bowel, the small intestine or the colon?'; (2) the colon should not be excluded, because special cases such as the colorectal localized type (chronic colonic pseudo-obstruction (CCPO)) sometimes exist.

Table 3. Disease type of a total of 160 CIPO cases

Classification of CIPO	Cases
Primary CIPO	117 (73.1)
Secondary CIPO	41 (25.6)
SSc	23 (56.1)
Non-SSc	18 (43.9)
DM	4 (9.8)
MCTD	3 (7.3)
SjS	1 (2.4)
Amyloidosis	2 (4.9)
Others	8 (19.5)
Unknown	2 (1.3)

Figures in parentheses are percentages. DM = Dermatomyositis; MCTD = mixed-connective tissue disease; SjS = Sjögren syndrome.

Table 4. Clinical presentations at first hospital visit (**a**) and disease duration prior to the diagnosis (**b**) (n = 160)

a Clinical presentation

	Cases		
	Yes	No	Unknown
Clinical symptoms			
Abdominal pain	107 (66.9)	53 (33.1)	0 (0)
Vomiting	81 (50.6)	79 (49.4)	0 (0)
Abdominal bloating	156 (97.5)	4 (2.5)	0 (0)
Abdominal pain and/or bloating	157 (98.1)	3 (1.9)	0 (0)
Radiological imaging findings			
Dilatation and/or air-fluid level of the bowel	154 (96.2)	3 (1.9)	3 (1.9)

b Disease duration

	Cases
Disease duration	
>6 months	141 (88.1)
<6 months	16 (10.0)
Unknown	3 (1.9)

Figures in parentheses are percentages. Of the total CIPO cases, 138 (86.3%) fulfilled all the diagnostic criteria, including abdominal pain and/or bloating, dilatation and/or air-fluid level of the bowel, as well as disease duration >6 months.

The closing date for the receipt of the questionnaire responses was 19 February 2010. We aggregated the data on the type of CIPO (primary or secondary), age at the time of the first hospital visit, clinical symptoms, radiological imaging findings, duration of disease and method of treatment in each patient and conducted a statistical analysis.

Results

Recognition of CIPO and Experience with CIPO at Each Institution

Overall, 216 (57.2%) of the 378 institutions responded to our questionnaire, and of these, 200 (92.6%) were aware of CIPO as a distinct disease entity and 103 (51.5% of those aware of CIPO as a distinct disease entity) had encountered cases of CIPO. None of the institutions that were unaware of CIPO have encountered CIPO cases. The number of cases was 0 in 97 (48.5%), 1 in 52 (26.0%), 2 in 17 (8.5%), 3 in 7 (3.5%), 4 in 1 (0.5%), 5 in 2 (1.0%), 6 in 3 (1.5%), 7 in 2 (1.0%), 8 in 1 (0.5%), 10 in 2 (1.0%), and 27 in 1 (0.5%) of the institutions. A total of 213 patients were accumulated from 103 institutions until 19 February 2010. Of the 213 patients, 53 for whom detailed information (e.g., sex, clinical symptoms) was not available from the questionnaire were excluded. Eventually, the data of a total of 160 patients were included in our study.

Type of CIPO

Data analysis of the 160 cases revealed that 77 (48.1%) were males and 83 (51.9%) were females. The type of CIPO was primary in 117 cases (73.1%), secondary in 41 cases (25.6%) and unknown in 2 cases (1.3%), as shown in table 3. The underlying cause in the cases with secondary CIPO was SSc in 23 cases (56.1%) and non-SSc in 18 cases (43.9%). Collagen diseases were prominent among the non-SSc cases and included dermatomyositis in 4 cases (9.8%), mixed connective tissue disease in 3 cases (7.3%) and Sjögren syndrome in 1 case (2.4%). The other causes of non-SSc CIPO were amyloidosis in 2 cases (4.9%) and 'others' in 8 cases (19.5%).

Age at the Time of First Hospital Visit

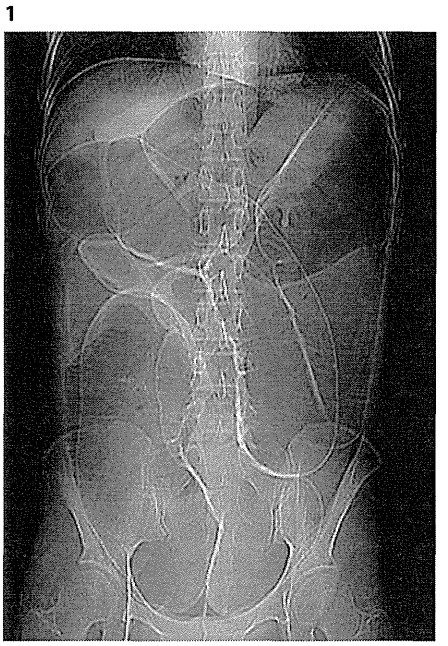
The majority of the patients of both sexes were in their 60s at the time of their first hospital visit (25.7% males, 24.1% females).

Clinical Symptoms

Our evaluation of the clinical symptoms in 160 cases showed that abdominal bloating was the most common symptom, recorded in 156 cases (97.5%), and that abdominal pain and vomiting were relatively common symptoms, recorded in 107 (66.9 %) and 81 cases (50.6%), respectively (table 4). Overall, 157 cases (98.1%) had at least one of these two symptoms, which fulfilled the diagnostic criterion 2.

Radiological Imaging Findings

In this survey, we defined positive imaging findings as the presence of dilatation and/or air-fluid levels of the bowels. Figure 1 shows a typical abdominal radiograph of a CIPO patient with marked distention of the small



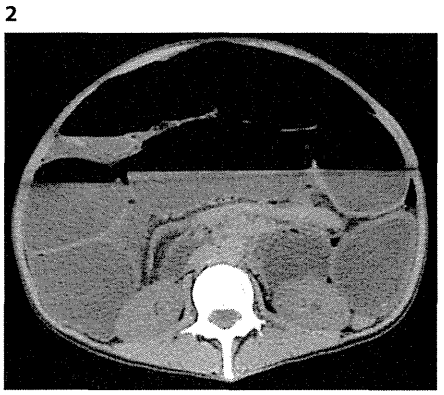


Fig. 1. Abdominal radiograph: marked distention of the intestine filled with a large amount of intestinal gas.
Fig. 2. Abdominal CT: markedly dilated intestinal loops and multiple air-fluid levels are observed. A large amount of small-intestinal gas occupies the greater part of the abdomen.

intestine and a large amount of intestinal gas. Figure 2 shows a typical CT image of a CIPO case. Among the 160 patients, 154 (96.2%) had positive imaging findings and 3 (1.9%) showed no positive findings; the status with regard to this finding was unknown in 3 cases (1.9%) (table 4a). Thus, 154 of the 160 cases (96.2%) showed dilatation of the bowel loops and/or air-fluid levels of the intestine on plain radiographs or CT images of the abdomen, which is included as a positive diagnostic criterion.

Duration of Disease

The number of patients with the criterion of disease duration >6 months was 141 (88.1%), and 16 (10.0%) had a disease duration <6 months; disease duration was unknown in 3 cases (1.9%) (table 4b).

Selected Method of Treatment

Our summarization of the responses to the questionnaire, where multiple answers were allowed, in relation to the selected method of treatment for each patient in the total of 160 cases (table 5) showed that medical conservative (drug) therapy was the most commonly selected treatment: it was selected in 135 cases (84.4%), diet in 107 cases (67.1%) and surgical treatment in 36 cases (22.5%). A total of 46 cases (28.8%) were treated by other methods, including home parenteral nutrition (intravenous hyperalimentation) in 33 cases (20.6%) and endoscopic intestinal decompression, ileus tube placement and enema in a few cases. One case (0.6%) received no treatment. The most commonly used drugs were mosapride citrate (5-HT4 receptor agonist), probiotics, Daikenchuto (herbal medicine), magnesium oxide, and others. Antacids such as proton pump inhibitors and H2 receptor antagonists were sometimes used in the cases treated conservatively (table 6).

As a result, 138 patients fulfilled all the diagnostic criteria, and the sensitivity of the proposed criteria for the diagnosis of CIPO in Japanese patients was 86.3%.

Table 5. Selected method of treatment (n = 160)

Treatment	Cases
Medication	135 (84.4)
Diet	107 (67.1)
Surgery	36 (22.5)
Others	46 (28.8)
Home parenteral nutrition	33 (20.6)
Endoscopic decompression	4 (2.5)
Ileus tube placement	2 (1.3)
Enema	1 (0.6)
No treatment	1 (0.6)

Figures in parentheses are percentages.

Table 6. Drugs used for treatment (n = 160)

Drugs	Cases
Mosapride citrate[1]	101 (63.1)
Daikenchuto[2]	83 (51.9)
Magnesium oxide	69 (43.1)
Probiotics	62 (38.8)
Proton pump inhibitor	45 (28.1)
Erythromycin	41 (25.6)
Pantothenic acid	36 (22.5)
Metoclopramide	34 (21.3)
Mucosal protective drugs	23 (14.4)
Domperidone	20 (12.5)
H2 receptor antagonist	19 (11.9)
Metronidazole	18 (11.3)
Itopride	16 (10.0)
Dimethicone	12 (7.5)
Calcium polycarbophil	11 (6.9)
Kanamycin	10 (6.3)
Somatostatin analogue	7 (4.4)
Loperamide	5 (3.1)
Sulpiride	5 (3.1)
Polymixin B	3 (1.9)
Albumin tannate	3 (1.9)
Other laxatives	45 (28.1)

Figures in parentheses are percentages.
[1] Mosapride is the 5-HT4 receptor agonist.
[2] Daikenchuto is a herbal medicine.

Discussion

CIPO is a serious digestive disease characterized by the disturbance of intestinal propulsive motility, which results in clinical features mimicking mechanical obstruction, in the absence of any mechanical occlusion [1–5]. Long-term outcomes are generally poor, with disabling and potentially life-threatening complications developing at a high frequency over time [9]. The diagnosis of CIPO is difficult and often delayed owing to the lack of biological markers and the symptomatic overlap with several other forms of digestive syndromes associated with similar gut motor dysfunction but different natural histories. The delay of correct diagnosis leads to repeated, useless and potentially dangerous surgical procedures.

Whole-gut transit scintigraphy and antroduodenal manometry are often performed in Western countries to evaluate gastrointestinal motility disorders [2]. In 1999, Di Lorenzo [10] proposed an algorithm for the evaluation of patients presenting with signs and symptoms suggestive of pseudo-obstruction. According to this algorithm, diagnosis of CIPO requires exclusion of mechanical obstruction by an abdominal X-ray series and/or contrast X-rays in patients with chronic signs and symptoms of bowel obstruction, as well as exclusion of potentially underlying causes of pseudo-obstruction. Manometory, scintigraphy and exploratory surgery with full-thickness biopsy are not absolutely necessary but may help confirm the diagnosis. On the other hand, Lacy [11] has proposed yet another diagnostic algorithm. For the diagnosis of CIPO, patients should have had symptoms for at least 6 months, and a stepwise approach is used to make the diagnosis of CIPO, generally including laboratory studies, radiological studies to exclude mechanical obstruction, tests to measure the gastrointestinal transit time and, if necessary, specialized tests of gastrointestinal motility, such as esophageal and antroduodenal manometry. In summary, previous algorithms emphasize that the diagnosis of CIPO requires at least chronic symptoms of bowel obstruction and exclusion of mechanical obstruction and, if necessary, manometry and scintigraphy to confirm the diagnosis.

Full-thickness biopsy of the small bowel should be performed in all patients with severe dysmotility of unknown etiology who are scheduled to undergo surgery for any reason, because of the potential to elucidate the pathophysiology of CIPO. Adoption of this procedure has revealed that neurogenic CIPO can be classified into two major forms, including degenerative neuropathy with hypoganglionosis, characterized by evidence of damage and/or marked reduction in the ganglion cells in the intestinal wall, and inflammatory neuropathy characterized by myenteric infiltration by inflammatory cells, and that myogenic CIPO is characterized by fibrosis or vacuolization of the inner circular muscle and/or the longitudinal muscle of the intestine [12–14]. Although full-thickness biopsy may not be absolutely necessary, it is an important procedure that helps to confirm the diagnosis of CIPO.

As mentioned above, gastrointestinal motility function tests, including whole-gut transit scintigraphy and manometry, and exploratory surgery with full-thickness biopsy of the small bowel are important; however, they are invasive in terms of patient tolerability. This is the reason why we were prompted to develop diagnostic criteria that would not necessitate the use of these special examinations.

Although a few diagnostic algorithms have been reported, no clear diagnostic criteria for CIPO have been established. Iida et al. [8] revealed that it took an average of >7 years from the initial symptoms before a correct

diagnosis of CIPO could be established, and therefore, emphasized the importance of a greater degree of awareness of this disease among physicians and the necessity of diagnostic criteria in order to shorten the period from the initial symptoms to correct diagnosis. Hongo et al. [6], who were co-researchers of the Survey Group, drafted interim diagnostic criteria referring to several textbooks and case reports. In addition, they discussed the usefulness of the interim diagnostic criteria with other collaborators specialized in gastrointestinal motility disorders, soliciting their opinions by e-mail, and laid down the proposed diagnostic criteria as shown in table 1. In our study, we investigated the clinical features of 160 patients and examined the validity of the proposed diagnostic criteria by calculating the diagnostic sensitivity. All the registered patients were diagnosed as CIPO based on the findings on plain abdominal X-ray, CT imaging, gastrointestinal endoscopy and, where necessary, barium enema and small-bowel follow-through. None of the patients underwent manometry, scintigraphy or exploratory surgery with full-thickness biopsy. Of the 160 patients, 138 fulfilled all the diagnostic criteria, and the sensitivity of the proposed criteria for the diagnosis of CIPO in Japanese patients was 86.3%. If the criteria included only 'No evidence of structural disease' (criterion 4) and 'Showing at least one of abdominal pain and abdominal bloating in the previous 12 weeks' (criterion 2), they would have shown higher sensitivity, but lower specificity, because patients with chronic constipation might be included as false-positives. However, most of these false-positives could be excluded based on criterion 1, i.e. 'Onset of one or more symptoms of bowel obstruction at least 6 months prior to the diagnosis', and on criterion 3, i.e. 'Dilatation and/or air-fluid levels of the bowels on plain abdominal X-ray, echo and/or CT images'.

The recognition rate of CIPO is not more than 92%, even in specialized gastroenterology institutes in Japan, which is not optimal. There seems to be an even poorer recognition rate among physicians and surgeons who are not specialized in gastroenterology. The recognition rate of CIPO in foreign countries does not seem to be too satisfactory either, given that no large-scale epidemiological studies have been reported and no clear diagnostic criteria for CIPO have been established. A greater awareness of the clinical features of CIPO among physicians would help limit unnecessary surgical procedures to the minimum.

Both the proposed diagnostic criteria and the previously described diagnostic algorithms have their own advantages and limitations. Previously described diagnostic algorithms are superior in terms of allowing systematic differential diagnosis; however, they are difficult to use for general physicians and need specialized invasive examinations. On the other hand, our proposed diagnostic criteria are superior to the previously described algorithms in terms of the ease of use for the diagnosis of CIPO by the general physician without specific examinations, and also the ease of use in clinical practice; however, they are inferior to the previously described algorithms in that they do not provide a stepwise diagnostic approach or systematic differential diagnosis. New diagnostic algorithms are needed that can complement the shortcomings of the proposed diagnostic criteria and can be used in combination with them.

The main limitation of this study is the lack of a previous gold standard with which to compare the results, and the lack of assessment of fulfillment of the criteria among other gastrointestinal motility disorders. The most important aim of establishing diagnostic criteria is to shorten the interval from the initial symptoms to correct diagnosis and referral to a specialist and to minimize the performance rate of unnecessary surgical procedures. Improved recognition of CIPO and practical use of the diagnostic criteria are urgently desired. In addition, further investigation is required to determine whether or not the proposed diagnostic criteria might also show a high sensitivity for patients in other countries. The proposed diagnostic criteria should be appropriately modified by consultation with additional researchers to make them more practical and internationally applicable.

Acknowledgement

This work was supported in part by Health and Labour Sciences Research Grants for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan to A.N.

Disclosure Statement

There are no conflicts of interest.

References

1 Dudley HA, Sinclair IS, McLaren IF, McNair TJ, Newsam JE: Intestinal pseudo-obstruction. J R Coll Surg Edinb 1958;3:206–217.
2 Manten HD: Pseudo-obstruction; in Haubrich WS, Schaffner F, Berk JE (eds): Bockus Gastroenterology, ed 5. Philadelphia, Saunders, 1995, pp 1249–1267.

3 Sutton DH, Harrell SP, Wo JM: Diagnosis and management of adult patients with chronic intestinal pseudoobstruction. Nutr Clin Pract 2006;21:16–22.
4 Anras S: The colon in the pseudo-obstructive syndrome. Clin Gastroenterol 1986;15:745–762.
5 Connor FL, Di Lorenzo C: Chronic intestinal pseudo-obstruction: assessment and management. Gastroenterology 2006;130:S29–S36.
6 Nakajima Group Research Report, Fiscal Year 2009 (chief investigator: Atsushi Nakajima). Research Group for the Survey of the Actual Conditions of the Epidemiology, Diagnosis and Treatment of CIIP in Japan. Research Project for Overcoming Intractable Diseases, Health Labour Sciences Research Grant. Yokohama, Sanou Printing Ltd, 2010, pp 1–42.
7 Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, Di Lorenzo C, Flores AF, Hillemeier AC, McCallum RW, Vanderhoof JA: Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr 1997;24:102–112.
8 Iida H, Inamori M, Sekino Y, Sakamoto Y, Yamato S, Nakajima A: A review of the reported cases of chronic intestinal pseudo-obstruction in Japan and an investigation of proposed new diagnostic criteria. Clin J Gastroenterol 2011;4:141–146.
9 Stanghellini V, Cogliandro RF, De Giorgio R, Barbara G, Cremon C, Antonucci A, Fronzoni L, Cogliandro L, Naponelli V, Serra M, Corinaldesi R: Natural history of intestinal failure induced by chronic idiopathic intestinal pseudo-obstruction. Transplant Proc 2010;42:15–18.
10 Di Lorenzo C: Pseudo-obstruction: current approaches. Gastroenterology 1999;116:980–987.
11 Lacy BE: Chronic intestinal pseudo-obstruction. The Association of Gastrointestinal Motility Disorders, Inc. (AGMD). http://www.agmd-gimotility.org/lacycip.pdf.
12 Amiot A, Cazals-Hatem D, Joly F, Lavergne-Slove A, Peuchmaur M, Bouhnik Y, Bedossa P, Messing B: The role of immunohistochemistry in idiopathic chronic intestinal pseudoobstruction (CIPO): a case-control study. Am J Surg Pathol 2009;33:749–758.
13 De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V: Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. Gut 2004;53:1549–1552.
14 Moore SW, Schneider JW, Kaschula RO: Unusual variations of gastrointestinal smooth muscle abnormalities associated with chronic intestinal pseudo-obstruction. Pediatr Surg Int 2002;18:13–20.

Case Report

DOI: 10.5582/irdr.2012.v1.1.35

Chronic intestinal pseudo-obstruction due to lymphocytic intestinal leiomyositis: Case report and literature review

Keiichi Uchida[1,*], Kohei Otake[1], Mikihiro Inoue[1], Yuhki Koike[1], Kohei Matsushita[1], Toshimitsu Araki[1], Yoshiki Okita[1], Koji Tanaka[1], Katsunori Uchida[2], Noriko Yodoya[3], Shotaro Iwamoto[3], Katsuhiro Arai[4], Masato Kusunoki[1]

[1] *Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[2] *Department of Pathology, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[3] *Department of Pediatrics, Mie University Graduate School of Medicine, Tsu, Mie, Japan;*
[4] *Division of Gastroenterology, Department of Medical Specialties, National Center for Child Health and Development, Tokyo, Japan.*

Summary **Lymphocytic intestinal leiomyositis is a rare entity, which causes chronic intestinal pseudo-obstruction (CIPO) in children. We present the first case of a boy who had pure red cell anemia 1 year before onset. Prolonged ileus developed after gastroenteritis and the patient was diagnosed using a biopsy of the intestinal wall. Findings from the present case indicate that there are three important factors for accurate diagnosis: history of enteritis, positive serum smooth muscle antibody, and lymphocyte infiltration with muscle destruction in the muscularis propria in the intestinal wall. Earlier diagnosis and induction of immunosuppressive therapy may be essential for a better outcome.**

Keywords: Chronic intestinal pseudo-obstruction (CIPO), pseudo-obstruction, leiomyositis, intestine

1. Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare intestinal dysmotility disorder characterized by repetitive or continuous bowel obstruction without mechanical causes (*1-3*). CIPO may be classified either as primary or secondary. Secondary CIPO is classified as a disease of gastrointestinal smooth muscle, nervous system, endocrine system, metabolism, and others (*2*). Smooth muscle fibers of the intestinal wall are affected by connective tissue disorders, muscular dystrophies, infiltrative disease, and mitochondrial myopathy.

Lymphocytic intestinal leiomyositis (LIL) in which lymphocytic infiltration causes muscle degeneration and fibrosis has been rarely reported in the literature (*3-8*). We present a rare case of a boy with CIPO due to T-lymphocytic intestinal leiomyositis (T-LIL). He suffered from pure red cell anemia (PRCA) and T-cell lymphocytosis 1 year before onset of T-LIL. Prolonged ileus developed after a gastroenteritis attack and accurate diagnosis was performed using a histopathological immunostaining study of full-thickness biopsies. We also review T-LIL cases in the literature and discuss the pathogenesis of T-LIL.

**Address correspondence to:*
Dr. Keiichi Uchida, Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan.
E-mail: ucchie@clin.medic.mie-u.ac.jp

2. Case report

A 2.5-year-old boy was diagnosed with PRCA and T-cell lymphocytosis. A complete response was obtained with steroid therapy. Steroids were ceased 1 year after the initial therapy. He was then admitted to a hospital with diarrhea and abdominal distension with symptoms of acute gastroenteritis. Laboratory data demonstrated leukocytosis (white blood cell count, 42,000/mm^3) and mild elevation of C reactive protein (CRP). Crohn's colitis was suspected and 5-ASA 60 mg/kg/d and prednisone 1 mg/kg/d were started. However, any attempt of oral feeding resulted in severe abdominal distention and vomiting due to paralytic ileus. Complete response was not obtained for 5 months; the patient was given prednisone 2

mg/kg/d with administration of azathioprine 1 mg/kg/d and tacrolimus (target trough: 10 ng/mL) and total parenteral nutrition. Since abdominal symptoms deteriorated after prednisone tapering, prednisone was never discontinued. The patient was transferred to our hospital for further examination. A plain abdominal X ray film demonstrated a huge dilatation of the small intestine with air fluid levels. Small bowel follow through indicated no apparent stricture. No mechanical cause of obstruction and normal mucosal findings were observed by esophagogastroduodenoscopy, colonoscopy, and double balloon enteroscopy. Mucosal biopsy showed mild non-specific inflammation in ileal and colonic mucosa. Laboratory data demonstrated no abnormal findings in blood counts, biochemical studies, CRP, and positive smooth muscle antibody.

We decided to perform laparotomy and a full-thickness biopsy to confirm the suspicion of intestinal disorder related to autoimmune disease because the patient suffered from CIPO with a response to prednisone and immunomodulators, and he had positive smooth muscle antibody A. Laparotomy revealed a huge dilated small intestine without the absence of mechanical obstruction. Enterostomy was created for intestinal decompression and irrigation. Full-thickness biopsies were performed in multiple locations of the small intestine and colon.

Histological findings (Figure 1) in the colon and all small intestine specimens demonstrated massive mononuclear infiltration and muscle fiber degeneration in the muscularis propria and lamina muscularis mucosae in the intestinal wall. Mononuclear cells moderately infiltrated the mucosal and submucosal layers. Ganglion cells in the submucosal and myenteric plexuses were normal. Immunostaining of a small intestine specimen predominantly showed T lymphocytic inflammation consisting of T lymphocytes (CD3, CD4, and CD8), monocytes and macrophages (CD68), and activated white cells (CD45RO). B lymphocytes (CD20, CD30) and NK cells (CD56) were absent. The specimen was also characterized by inflammatory targets that were not smooth muscles of vessels, but they were the muscularis propria and lamina muscularis mucosae in the intestinal wall. Based on the histopathological and immunological findings, the final diagnosis was confirmed as T-LIL.

Postoperatively, the patient began to orally ingest food with regular decompression and irrigation through enterostomy. However, he had intermittent episodes of obstruction associated with intestinal bacterial overgrowth. One year later, the pseudo-obstruction was gradually resistant to treatments and he died from sepsis due to bacterial translocation 1.5 years later.

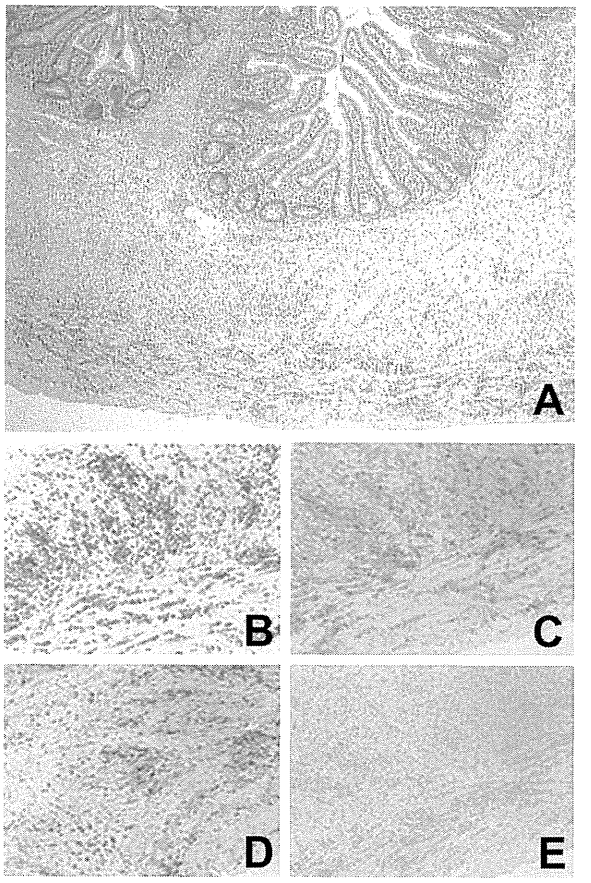


Figure 1. Immunostaining of the biopsy samples. (**A**), Full-thickness biopsy of the small intestine. Histological findings show inflammation in the muscularis propria of the small intestine. Intestinal mucosa and submucosa were mostly normal. Ganglion cells in the submucosal and myenteric plexuses were normal. Immunostaining of a biopsy sample showed predominantly T lymphocytic inflammation consisting of T lymphocytes (**B**, CD3; **C**, CD4; **D**, CD8). B lymphocytes (**E**, CD20) are absent. (Original magnification 100×)

3. Discussion

CIPO is a rare, severe, disabling disorder characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of a dilated bowel with air-fluid levels, in the absence of a fixed, lumen-occlusive lesion (*2*). CIPO may be classified as either congenital or acquired (*1,2*). Acquired CIPO is classified according to presumed underlying pathogenesis to facilitate an organized approach to evaluation (*9*). Autoimmune reactions to smooth muscle fibers or nerve plexuses have also been reported as very rare causes of acquired CIPO (*7,10*). CIPO due to true T-LIL, such as in the present case, has only been reported in six cases of specific histopathological findings by full-thickness biopsy (*4-8*).

The clinical and histopathological characteristics of this entity are summarized in Tables 1 and 2. It is noteworthy that almost all patients have a preexisting episode of gastroenteritis, and intestinal ileus and abdominal distension occur. Anti-yersinia pseudotuberculosis antibodies were detected in one case (*4*). Molecular mimicry with infectious agents resulting in the initiation of the autoimmune

Table 1. Clinical characteristics in lymphocytic intestinal leiomyositis

Items	Age/Sex	Preexisting disease	Abnormal laboratory findings	Treatment	Progress
Case 1 (*4*)	6 mth./M	*ns*	Anti-*Yersinia pseudotuberculosis*	Steroid	4 yr. follow, death
Case 2 (*5*)	1 yr./M	*ns*	SMA	Steroid	*ns*
Case 3 (*5*)	2.5 yr./F	*ns*	SMA	Steroid	*ns*
Case 4 (*6*)	2 yr./M	AIH, gastroenteritis	SMA, ANCA, ANA	Steroid, AZA, Ciclosporin, enterostomy	3 yr. follow, TPN, relapsing obstruction
Case 5 (*7*)	5 yr./F	Enteritis	SMA	Steroid, AZA, FK 506	1.5 yr. follow, relapsing obstruction after steroid tapering
Case 6 (*8*)	16 yr./F	Enteritis	*ns*	Steroids, AZA, budesonide	2 yr. follow, normal oral diet
our case (2011)	3.5 yr./M	PRCA, TCLC, enteritis	SMA	Steroid, AZA, budesonide, FK 506, enterostomy	1.5 yr. follow, death

mth., month; yr., year; M, male; F, female; AIH, autoimmune hepatitis; *ns*, not specified; PRCA, pure red cell aplasia; TCLC, T cell lymphocytosis and cytopenia; SMA, smooth muscle antibody; ANCA, anti-neutrophil cytoplasmic antibody; ANA, antinuclear antibody; AZA, azathioprine; FK506, tacrolimus; TPN, total parenteral nutrition.

Table 2. Pathological characteristics in lymphocytic intestinal leiomyositis

Items	Affected digestive Organ	Histopathological findings of small intestine			
		MSM	LPM	MP	NP
Case 1 (*4*)	Small intestine	Atrophic	*ns*	Mono infil, degeneration, fibrosis	
Case 2 (*5*)	Small/large intestine	*ns*	*ns*	Severe T-lym infil, degeneration, fibrosis	Intact
Case 3 (*5*)	Small/large intestine	*ns*	*ns*	Severe T-lym infil, degeneration, fibrosis	Intact
Case 4 (*6*)	Ileum, large intestine	Mild inflammation	Moderate T-lym infil	Severe T-lym infil, degeneration	Intact
Case 5 (*7*)	Small/large intestine	Moderate T-lym infil	Moderate T-lym infil	Severe T-lym infil, degeneration	Intact
Case 6 (*8*)	Small intestine	Intact	Intact	T-lym infil, fibrosis, degeneration	Intact
our case (2011)	Small/large intestine	Mild T-lym infil	Moderate T-lym infil, degeneration	Severe T-lym infil, degeneration, fibrosis	Intact

MSM, mucosa and submucosa; LPM, lamina propria mucosae; MP, muscularis propria; NP, nerve plexus; *ns*, not specified; Mono infil, monocyte infiltration; T-Lym infil, T-lymphocytic infiltration.

inflammatory process has been previously suggested for other gastrointestinal autoimmune disorders (*6,11,12*). Myositis is associated with circulating autoantibodies directed against smooth muscle cells with or without nonspecific antibodies to nuclear antigens and neutrophil cytoplasmic antigens.

Diagnosis of LIL was performed by full-thickness biopsy of the small and large intestines. Mucosal and submucosal biopsy through endoscopy never results in a definite diagnosis. Severe T-lymphocyte inflammation is found in the muscularis propria, and there is no significant inflammation in the mucosal and submucosal layers. Although the pathogenesis and mechanism of LIL remain unclear, autoreactive cross-reactivity between pathogens and T-lymphocytes with smooth muscle fibers of the intestinal wall may cause a reaction. However, it is unknown why smooth muscle fibers of vessels are completely intact, while the muscularis propria of the intestinal wall is affected.

In this series, two patients had autoimmune disease as a preexisting disease: autoimmune hepatitis (AIH, case 4) and PRCA (our case). Several diseases such as type I diabetes, Addison's disease, and autoimmune thyroiditis are closely associated with AIH in children. In case 4, autoreactive T-lymphocytes promoted the development of LIL under immunosuppressive therapy for AIH (*6*).

PRCA has been associated with a variety of clinical disorders, and various autoimmune mechanisms have been described to account for red cell suppression because of its frequent association with thymoma and successful responses to thymectomy and immunosuppressive agents (*13*). Generally, the pathogenesis of PRCA is considered to be due to the expansion of B-lymphocytes producing immunoglobulins (IGs), which suppresses erythropoiesis, and IGs are thought to be antibodies against erythropoietin or erythroblasts (*14*). However, another report demonstrated that suppressor/cytotoxic T-lymphocytes can inhibit erythropoiesis (*15*). Recent evidence using gene rearrangement studies has indicated that PRCA with T-lymphocytosis is a clonal chronic T cell lymphoproliferative disorder in which the T cells suppress erythropoiesis (*16*). This disorder has a unique feature of T cell lymphocytosis. The present case had PRCA with T cell lymphocytosis as preexisting disorders of LIL. Additionally, an autoimmune inflammatory reaction, mainly on the muscularis propria in the intestinal wall, was shown by T lymphocytic inflammation using immunostaining. The present case is considered to be the first case of T-LIL with preexisting PRCA. Katabami *et al.*

(*17*) reported an adult female case with polymyositis associated with thymoma who subsequently developed PRCA. They considered that cytotoxic T cells may play an important role in the pathogenesis of polymyositis and PRCA.

Immunosuppressive therapies including steroids and immunomodulators are recommended and they were performed in previous reports. The patient's clinical course is eventful and their quality of life is deteriorated by recurrent relapsing, paralytic ileus, insufficient oral intake, intestinal infections, complications of fluid therapy, and prolonged hospitalizations. Abdominal distension and vomiting recurred after prednisone withdrawal in our case, which is similar to other cases. Oton *et al.* recommended AZA and budesonide while tapering off conventional steroids, if the clinical response continues, to avoid steroid complications (*8*).

Uncontrolled inflammation induces degenerative, atrophic, and fibrotic changes in smooth muscle fibers in the intestinal wall. In case 1, histopathological findings demonstrated a diminished nerve plexus together with mononuclear infiltration, muscle degeneration, and fibrosis proliferation in the muscularis propria. Impairment of the myenteric plexuses is explained as the final histopathological findings (*4*). These seven previous cases and our reports may have consisted of different phenotypes of LIL between the early and end stages. Ruuska *et al.* (*7*) described that disease progress may be prevented resulting in end-stage intestinal motility failure, if immunosuppressive treatments are used aggressively early in the course of illness.

Prognosis of CIPO is generally poor. Generally, liver disease and sepsis due to bacterial overgrowth and complications of TPN are the most common causes of death in CIPO (*18*). Bacterial overgrowth often causes malabsorption and may be associated with increased mucosal permeability and bacterial translocation across the bowel (*19-21*). In the present case, uncontrolled CIPO due to LIL easily caused bacterial overgrowth under immunosuppressive conditions.

Clinicians should be aware of lymphatic intestinal leiomyositis for the differential diagnosis of CIPO. Three important factors for accurate diagnosis are a history of enteritis, positive serum smooth muscle antibody, and T-cell infiltration in the muscularis propria in intestinal full-thickness biopsies. Earlier diagnosis and induction of immunosuppressive therapy may be essential for a better outcome.

References

1. Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: Assessment and management. Gastroenterology. 2006; 130 (2 Suppl 1):S29-36.
2. Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, Di Lorenzo C, Flores AF, Hillemeier AC, McCallum RW, Vanderhoof JA. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: Report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997; 24:102-112.
3. Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. Gut. 1997; 41:675-681.
4. Nezelof C, Vivien E, Bigel P, Nihoul-Fekete C, Arnaud-Battandier F, Bresson JL, Arhan P, Ricour C. Idiopathic myositis of the small intestine. An unusual cause of chronic intestinal pseudo-obstruction in children. Arch Fr Pediatr. 1985; 42:823-828. (in French)
5. Smith VV, Milla PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. Histopathology. 1997; 31:112-122.
6. Ruuska TH, Karikoski R, Smith VV, Milla PJ. Acquired myopathic intestinal pseudo-obstruction may be due to autoimmune enteric leiomyositis. Gastroenterology. 2002; 122:1133-1139.
7. Haas S, Bindl L, Fischer HP. Autoimmune enteric leiomyositis: A rare cause of chronic intestinal pseudo-obstruction with specific morphological features. Hum Pathol. 2005; 36:576-580.
8. Oton E, Moreira V, Redondo C, Lopez-San-Roman A, Foruny JR, Plaza G, de Vicente E, Quijano Y. Chronic intestinal pseudo-obstruction due to lymphocytic leiomyositis: Is there a place for immunomodulatory therapy? Gut. 2005; 54:1343-1344.
9. De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. Gut. 2004; 53:1549-1552.
10. Smith VV, Gregson N, Foggensteiner L, Neale G, Milla PJ. Acquired intestinal aganglionosis and circulating autoantibodies without neoplasia or other neural involvement. Gastroenterology. 1997; 112:1366-1371.
11. Kagnoff MF, Paterson YJ, Kumar PJ, Kasarda DD, Carbone FR, Unsworth DJ, Austin RK. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. Gut. 1987; 28:995-1001.
12. Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: Virtuous intentions, malign consequences. Liver. 2001; 21:225-232.
13. Tötterman TH, Nisell J, Killander A, Gahrton G, Lönnqvist B. Successful treatment of pure red-cell aplasia with cyclosporin. Lancet. 1984; 22:693.
14. Marmont A, Peschle C, Sanguineti M, Condorelli M. Pure red cell aplasia (PRCA): Response of three patients of cyclophosphamide and/or antilymphocyte globulin (ALG) and demonstration of two types of serum IgG inhibitors to erythropoiesis. Blood. 1975; 45:247-261.
15. Litwin SD, Zanjani ED. Lymphocytes suppressing both immunoglobulin production and erythroid differentiation in hypogammaglobulinaemia. Nature. 1977; 3:57-58.
16. Nidorf D, Saleem A. Immunosuppressive mechanisms in pure red cell aplasia – A review. Ann Clin Lab Sci. 1990; 20:214-219.
17. Katabami S, Sugiyama T, Kodama T, Kamijo K, Azuma N, Tamaki T, Katanuma A, Fujisawa Y, Kinoshita H, Imai K, Yachi A. Polymyositis associated with thymoma and the subsequent development of pure red cell aplasia. Intern Med. 1995; 34:569-573.
18. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo

C. Long-term outcome of congenital intestinal pseudoobstruction. Dig Dis Sci. 2002; 47:2298-2305.
19. Vantrappen G, Janssens J, Hellemans J, Ghoos Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest. 1977; 59:1158-1166.
20. Pignata C, Budillon G, Monaco G, Nani E, Cuomo R, Parrilli G, Ciccimarra F. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. Gut. 1990; 31:879-882.
21. Lichtman SN, Keku J, Schwab JH, Sartor RB. Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. Gastroenterology. 1991; 100:513-519.

(Received December 14, 2011; Accepted January 25, 2012)

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2012) **54**, 899–904 doi: 10.1111/j.1442-200X.2012.03739.x

Original Article

Plasma citrulline may be a good marker of intestinal functions in intestinal dysfunction

Kan Suzuki, Yutaka Kanamori, Masahiko Sugiyama, Makoto Komura, Kan Terawaki, Tetsuro Kodaka, Masataka Takahashi, Eriko Fukami and Tadashi Iwanaka

Department of Pediatric Surgery, The University of Tokyo Hospital, Tokyo, Japan

Abstract ***Background***: Plasma citrulline has been reported to be a good indicator of intestinal functional volume in patients with intestinal dysfunction. We reconfirmed the facts and also investigated the dynamic changes of plasma citrulline in acute-phase patients with intestinal dysfunction.

Methods: We measured plasma citrulline in six patients with intestinal dysfunction who were in the acute and chronic phase for more than 6 months.

Results: Four patients out of six could be withdrawn from total parenteral nutrition, and their plasma citrulline level dynamically changed according to their intestinal states and finally increased up to 15 nmol/mL. Two patients, who could not be withdrawn from parenteral nutrition, showed very low levels of plasma citrulline throughout the treatment course (under 15 nmol/mL).

Conclusion: The cut-off level of plasma citrulline indicating permanent intestinal dysfunction may be 15 nmol/mL in our data. In the acute phase, plasma citrulline changed dynamically according to the intestinal state and may be a good indicator of fluctuating intestinal functions. Thus, although only a few patients were enrolled in this study, plasma citrulline may be a good indicator of stable-state as well as acute-unstable-state intestinal functions.

Key words citrulline, intestinal dysfunction, intestinal function.

In patients with intestinal dysfunction, it is very important to assess whether or not they can be withdrawn from parenteral nutrition, but there has been no easy examination on which to base that judgment. From the early 2000s, the plasma citrulline level has been shown to be a good indicator for the functional intestinal volume in various diseases, such as intestinal failure,[1] short bowels,[2–4] inflammatory bowel disease,[5] villous atrophy diseases,[6] acute mucosal enteropathy due to antineoplastic treatment[7] and bowel transplantation.[8]

We investigated the dynamic changes of plasma citrulline in acute or chronic phases of intestinal dysfunction for more than 6 months. There are still only a few reports available to show the dynamic changes of the citrulline level in adults[9] and pediatric patients[10,11] in the acute phase, and our result suggested that plasma citrulline level is a good indicator of functional intestinal volume in both the acute and stable phases of intestinal dysfunction in pediatric patients.

Methods

We investigated the dynamic changes of plasma citrulline in six pediatric surgical patients (three girls and three boys) who were treated by surgical procedure and/or by parenteral nutrition to improve their general conditions for more than 6 months at Tokyo University Hospital. A retrospective chart review was performed on all six patients, and age, sex, diagnosis, bodyweight, body height, and calorie intake via the parenteral nutrition were recorded.

The Kaup index (body mass index [BMI]) was calculated using the following formula: bodyweight (g)/body height^2 (cm) $\times$ 10. The characteristics of the enrolled patients are listed in Table 1.

Four patients had congenital intestinal diseases, such as intestinal atresia (case 1), meconium peritonitis (case 2), gastroschisis with intestinal perforation and colonic atresia (case 3), and volvulus with malrotation (case 4). Case 5 suffered from refractory enteritis with immunodeficiency. The last patient had undergone resection of almost all of the small bowel at another institution and was brought to our hospital at 2 years of age.

The remnant small bowel length of five of the patients was between 8 and 150 cm, as measured by the surgeon in the operating room and/or on radiograph films. In one patient, the bowel length was not measured.

The blood samples were taken fasting and kept in heparinized tubes; the plasma citrulline level was measured by high-performance liquid chromatography. Routine serum biochemical indexes, such as choline esterase (ChE) and albumin, were all determined automatically by a biochemical analyzer. The normal range of ChE in our institution is 179–354 IU/L and that of albumin is 3.9–4.9 g/dL.

Correspondence: Yutaka Kanamori, MD, PhD, Department of Pediatric Surgery, The University of Tokyo Hospital, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan. Email: kanamori-y@ncchd.go.jp

Received 18 March 2011; revised 12 July 2012; accepted 22 August 2012.

Table 1 Profile of patients whose plasma citrulline was measured for more than 6 months

Case	Age at entry (months)	Sex	Diagnosis	Bowel length (cm)	Age weaned off parenteral nutrition (months)	Duration of follow up (months)
1	0	F	Congenital jejunal atresia (multiple)	Jejunum: 10 Ileum: 25	5	29
2	0	M	Meconium peritonitis, intestinal atresia	130	1	14
3	0	F	Gastroschisis with intestinal perforation and atresia	85	3	13
4	38	F	Adhesive ileus, malrotation	150	39	26
5	46	M	Refractory enteritis, immunodeficiency	Unknown	(–)	31
6	29	M	Volvulus with malrotation, short bowel syndrome	8	(–)	113

Results

Dynamic changes of plasma citrulline level and the clinical course in four pediatric patients who could be withdrawn from total parenteral nutrition

Case 1 (Fig. 1a)

The female patient was born at 35 weeks and 6 days of gestation with 2420 g bodyweight. She was suspected to suffer from intestinal atresia by fetal ultrasound examination, and it was confirmed by a roentgenogram after birth. She underwent curative surgery at 1 day of age. The superior mesenteric artery was thrombotic, and the residual jejunum was only 10 cm long. The distal intestine was necrotized by ischemia, and only 25 cm of the ileum was alive (Table 1). Intestinal anastomosis was accomplished with peritoneal drainage. The postoperative course was uneventful, and she started enteral feedings with the mother's milk at 18 days after surgery. The plasma citrulline level at 1 month was 6.2 nmol/mL. Intravenous hyperalimentation (70 kcal/kg/day) was started just after surgery but gradually tapered, along with the increase of enteral feeding. Intravenous administration of electrolytes and water was stopped at 5 months of age, and she was discharged at 6 months of age. Serum albumin (3.9 g/dL), ChE and citrulline were within normal limits at the time. The plasma citrulline level increased during the admission period to 15.5 nmol/mL, and it stayed around 15 nmol/mL after discharge. She had normal physical growth, shown as bodyweight gain in Figure 1a.

Case 2 (Fig. 1b)

The male patient was born at 34 weeks of gestation with 2425 g bodyweight. His fetal diagnosis was meconium peritonitis. He underwent drainage at 1 day of life, and curative surgery at 16 days of age. The operative diagnosis was intestinal atresia with fetal intussusception and meconium peritonitis due to rupture of the intestine at the oral side of the intussusception. The residual small intestine was 130 cm (Table 1). Enteral feeding was started at 26 days of age, and he was weaned from parenteral nutrition at 2 months of age. The plasma citrulline level was 10.4 nmol/mL at neonatal age, but parenteral nutrition could be tapered to one-third at 1 month. It stayed around 15–25 nmol/mL after independence from parenteral nutrition, and the patient gained weight and had normal serum albumin (3.9–4.3 g/dL), ChE and Kaup index (BMI).

Case 3 (Fig. 1c)

The female patient was born at 34 weeks and 6 days of gestation with 2222 g bodyweight. She was suspected of having gastroschisis at 16 gestational weeks. The protuberant intestine was ruptured at 31 gestational weeks. She was brought to the operating room immediately after birth and underwent silo placement using the Applied Alexis wound protector (AAWP; Applied Medical Resources Corp, Rancho Santa Margarita, CA, USA) under general anesthesia. The diagnosis at the procedure was gastroschisis with multiple ileum perforations, cecal necrosis and colonic atresia. At 6 days of life, she underwent surgery to close the gastroschisis and construct an ileostomy. But intestinal movement was not well, and she suffered from malnutrition by intestinal dysfunction. Then we performed additional resection of the dilated intestine. The residual intestine was 85 cm at the operation. Thereafter, the residual intestine dilated again, and she received a tube ileostomy for decompression. Her bodyweight gain was good after the serial operations, and she was discharged. The plasma citrulline level was 5.0 nmol/mL, albumin was 2.7 g/dL and ChE was 164 IU/L at 15 days of life and gradually increased to 51.9 nmol/mL, 3.8 g/dL and 327 IU/L, respectively. After the resection of dilated intestine, the citrulline level decreased to 17.8 nmol/mL, but has now re-increased up to 45.3 nmol/mL. In this case, parenteral nutrition was gradually reduced and stopped at 6 months. Her Kaup index (BMI: 15.4) is now in the normal range and bodyweight gain is satisfactory.

Case 4 (Fig. 1d)

The female patient was transferred to our institution for treatment of repetitive ileus and prolonged intestinal dysfunction. She was 3 years old and sustained by total parenteral nutrition. She underwent her first surgery in a local hospital at 1 year and 4 months of age because of duodenal and colonic perforation. Her bodyweight was only 8 kg, and her plasma citrulline level was 13.7 nmol/mL at admission. She had segmental dilatation of the intestine and could not tolerate enteral feeding. We decided to resect the dilated intestine and release the adhesive ileum. The laparotomy was done at 3 years and 3 months of age. The dilated intestine was resected, and the strong adhesions in some intestine were released. The length of the residual intestine was estimated to be 150 cm. Postoperative enteral feeding was restricted because of one episode of bacterial translocation, and parenteral

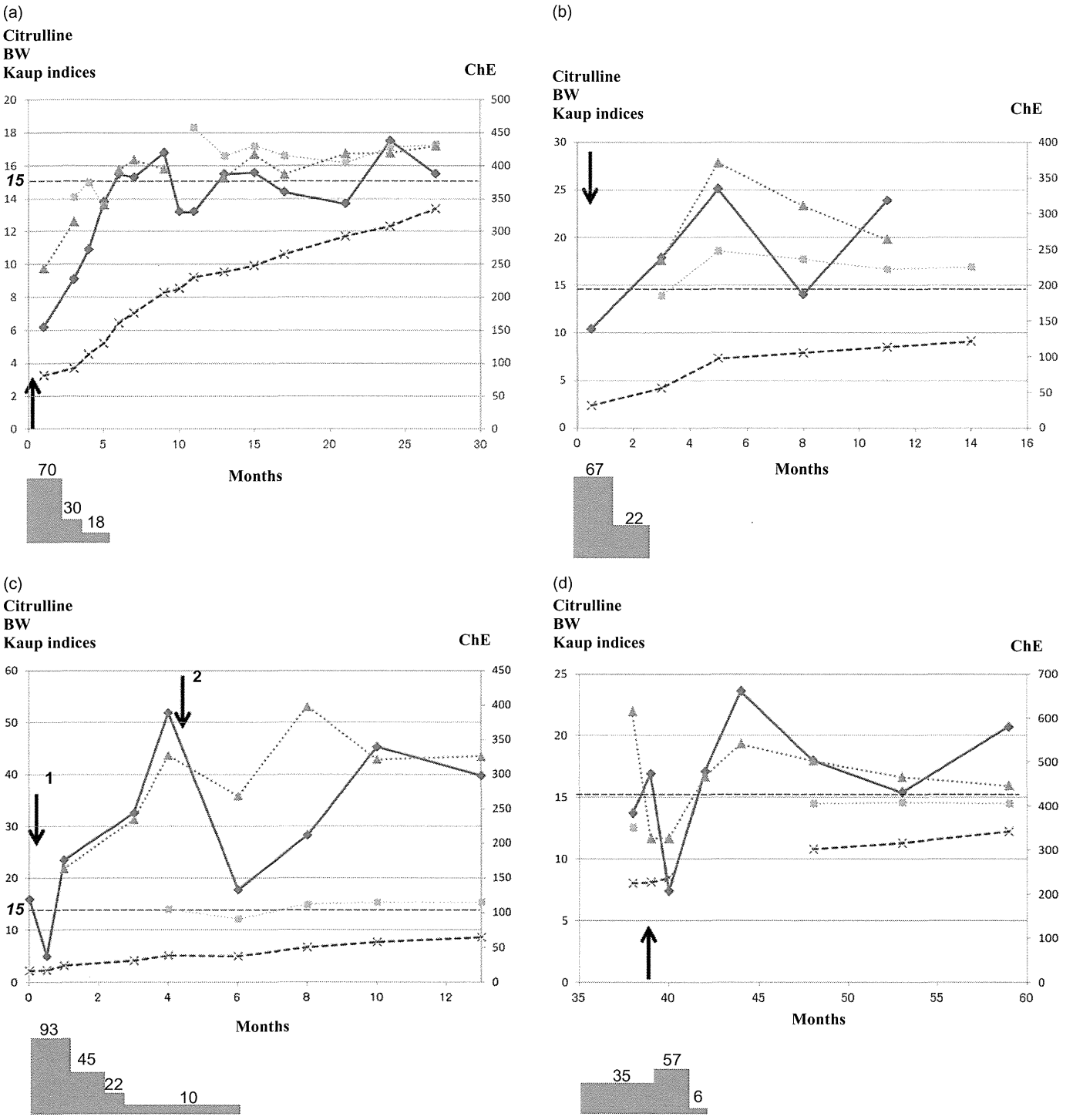


Fig. 1 (a–d) Plasma citrulline levels (Cit), serum cholinesterase (ChE) and calories taken by parenteral nutrition in cases (a) 1, (b) 2, (c) 3 and (d) 4. The dotted horizontal line in each graph represents a Cit of 15 nmol/mL. Black arrows indicate the time of operation. Square boxes under the graph express the parenteral nutrition, and figures written above the boxes indicate the calories administered by parenteral nutrition (kcal/kg/day). (-◆-) Cit (nmol/mL); (···■···) Kaup (body mass index); (-×-) bodyweight (kg); (···▲···) ChE (IU/L).

nutrition (57 kcal/kg/day) was temporarily needed. The plasma citrulline level decreased to 7.4 nmol/mL. Serum albumin (from 4.3 g/dL to 3.1 g/dL) and ChE (from 615 IU/L to 327 IU/L) levels also decreased, and she lost weight. She gradually recovered and became able to tolerate enteral feeding, and at 50 post-operative days she was discharged from our institution. She now lives at home with oral feeding and good weight gain (Kaup index [BMI] was up to 14.5 from 12.5), and ChE level was recovered. The plasma citrulline level was monitored at the outpatient clinic and remained higher than15 nmol/mL.

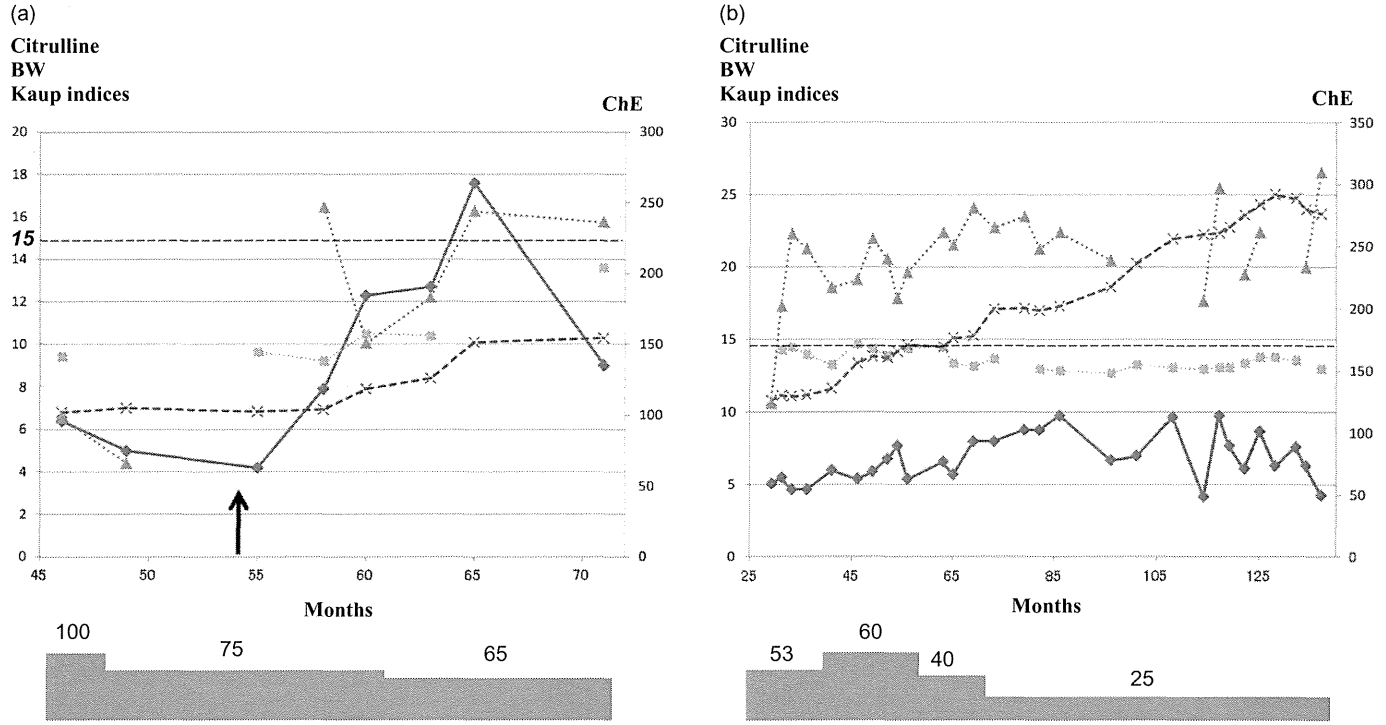


Fig. 2 (a,b) Plasma citrulline levels, serum cholinesterase (ChE) and calories administered by parenteral nutrition in cases (a) 5 and (b) 6, who could not be weaned from i.v. hyperalimentation even with an intensive intestinal rehabilitation program. The dotted horizontal line in each graph represents a plasma citrulline level of 15 nmol/mL. Black arrows indicate the time of operation. Square boxes under the graph express the parenteral nutrition, and figures written above the boxes indicate the calories administered by parenteral nutrition (kcal/kg/day). (—◆—) Cit (nmol/mL); (···✱···) Kaup (body mass index); (—×—) bodyweight (kg); (···▲···) ChE (IU/L).

Dynamic changes of plasma citrulline level and clinical course in two patients who could not be withdrawn from parenteral nutrition

Case 5 (Fig. 2a)

The 3-year-old boy was transferred to our institution with severe malnutrition and repetitive enteritis. He had jejunostomy and ileostomy to decompress the intestinal fluid and needed total parenteral nutrition (100 kcal/kg/day) at admission. After admission, intensive care was started, and several examinations revealed that he had some kind of immunodeficiency (we could not identify the type of immunodeficiency and concluded that it was an unknown type). We performed an operation to close the jejunostomy and ileostomy and constructed tube gastrostomy and tube cecostomy to maintain the continuity of the gastrointestinal tract and make the effective decompression possible via those ostomies as well. His enteritis became less severe and the nutritional state improved, but he could not tolerate enteral feeding. Plasma citrulline, albumin, and ChE levels were very low at admission (6.4 nmol/mL, 2.0 g/dL and 98 IU/L, respectively) (Fig. 2a). The Kaup index (BMI) was low (9.2–13.6; Fig. 2a) and bodyweight had been under the normal range even with the support of parenteral nutrition. Intravenous hyperalimentation could not be stopped through the course (65–75 kcal/kg/day).

Case 6 (Fig. 2b)

The 2-year-old boy was transferred to our institution with severe short bowel syndrome. He suffered from midgut volvulus as a neonate due to malrotation of the intestine, and his residual intestine was only 8 cm long. After admission, we started oral feeding but repetitive enteritis and central venous catheter infections occurred, and it was difficult to increase the oral feeding. He is now 11 years old, and the length of his intestine on a radiograph is 32 cm. He could not be withdrawn from the i.v. supplementation of calories and water. Parenteral supplementation was gradually decreased (from 60 kcal/kg/day to 25 kcal/kg/day), but could not be stopped. The plasma citrulline level increased gradually from a level under the detection threshold to 9.8 nmol/mL at 9 years of age, but it was always under 10 nmol/mL. Minimal bodyweight gain was attained but bodyweight had been under the normal range even with the support of parenteral nutrition. He is now scheduled to receive intestinal transplantation but is waiting for a donor.

Discussion

Citrulline is a specific amino acid that is not a component of proteins, and it is mainly synthesized in small intestinal epithelial cells.[12] In the body, citrulline produced by intestinal epithelium is metabolized into arginine in the kidneys. Since the early 2000s

the plasma citrulline level has received a great deal of attention because several reports pointed out that it reflects well the functional intestinal volume in several intestinal disorders, such as short bowel,[2–4] inflammatory bowel disease,[5] intestinal villi atrophy disease,[6] acute mucosal enteropathy due to antineoplastic treatment[7] and intestinal transplantation.[8] Citrulline is contained in watermelon, but oral intake of watermelon does not affect the plasma citrulline level.[3] Plasma citrulline is now being widely tested in clinical areas to assess whether it is a good indicator of the functional intestinal volume.

We reconfirmed the usefulness in our patients. A total of 20 patients who had been treated by parenteral nutrition at one time and now were sustained by enteral feeding had their plasma citrulline level checked (data not shown). Rhoads *et al.*[10] suggested that the citrulline cut-off value for permanent intestinal failure was 20 nmol/mL, but a recent report from the USA demonstrated that it was only 15 nmol/mL.[4] In our data, four patients out of 20 in stable states showed plasma citrulline levels between 15 and 20 nmol/mL (data not shown). In an acute phase, i.v. hyperalimentation could be stopped in four patients, when the plasma citrulline level had reached a final concentration of 15 nmol/mL (Fig. 1). Conversely, two other patients whose plasma citrulline values were less than 15 nmol/mL were difficult to withdraw from the i.v. supplementation (Fig. 2). Our result thus indicates that 15 nmol/mL is the cut-off level for permanent intestinal failure. Crenn *et al.*[3] commented that there may be racial differences in plasma citrulline level and noted that healthy Chinese subjects showed lower values of citrulline than did Caucasians. Nevertheless, our data implied that there is no difference in plasma citrulline levels between Japanese subjects and Caucasians.

Another important point is the relation between citrulline level and intestinal states in our six patients. Intestinal function is mainly defined by the following three factors: (i) total volume of functioning intestinal epithelial cells; (ii) intestinal peristalsis that effectively transports the orally taken nutrients and prevents bacterial overgrowth; and (iii) water and electrolytes absorption mainly seen in the colon. Among these factors, citrulline mainly reflects factor (i). But factor (ii) is also very important for intestinal functions and factors (i) and (ii) are inseparably related. We believe that our total treatment, including cyclic i.v. hyperalimentation (IVH) and probiotics use, was effective in improving factor (i) in cases 1–4. In addition, probiotics were routinely used in severely ill patients to promote intestinal peristalsis and prevent bacterial overgrowth, which improved factor (ii) in cases 1–4. In case 5, however, intestinal function was mainly disturbed by refractory enterocolitis that was caused by systemic immunodeficiency. Such severe enterocolitis could reduce the total volume of functioning intestinal epithelial cells. Thus, we consider that factor (ii) was a critical factor of intestinal failure in case 5 and factor (i) was also affected by severe inflammatory reaction caused by factor (ii) deterioration. In case 6, intestinal length did not increase enough (less than 50 cm) and intestinal dilatation was not seen in spite of our intensive treatment. Therefore factor (i) was the main factor why the patient could not be withdrawn from IVH.

There have been very few reports published showing the dynamic changes of plasma citrulline levels in the acute phase, and in those reports, plasma citrulline was followed for very restricted periods.[9,11] We followed plasma citrulline levels for more than 6 months in six pediatric patients with intestinal failure. Our data demonstrated that the plasma citrulline level changed dynamically according to the intestinal state, and showed that it may be a good indicator of intestinal adaptation after intestinal resection. The plasma citrulline level may also be an indicator of the effectiveness of treatment of intestinal dysfunction and may be used to judge whether or not a patient can be withdrawn from parenteral nutrition. The level of ChE, another nutritional index, was comparatively parallel with the plasma citrulline level; however, the ChE level was within normal range in cases 5 and 6 with parenteral nutrition (Fig. 2), so this indicates that the serum ChE level is not a reasonable indicator to judge whether patients with intestinal dysfunction may be withdrawn from parenteral nutrition. The data presented here are still preliminary, and we need more data on citrulline levels in pediatric surgical children with intestinal failure.

We have shown the diagnostic importance of plasma citrulline measurements, but recently citrulline supplementation has been suggested as an attractive treatment strategy in intestinal failure considering that citrulline is converted to arginine in the kidneys, and arginine plays an important role in compromised hosts.[13] Citrulline supplementation is not yet in clinical use, and more basic research is needed in the future to assess whether citrulline administration will be effective in supporting patients with intestinal failure.[14]

References

1 Crenn P, Coudray-Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of enterocyte mass and intestinal failure in humans. *Gastroenterology* 2000; **119**: 1496–505.

2 Jianfeng G, Weiming Z, Ning L *et al.* Serum citrulline is a simple quantitative marker for small intestinal enterocytes mass and absorption function in short bowel patients. *J. Surg. Res.* 2005; **127**: 177–82.

3 Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clin. Nutr.* 2008; **27**: 328–39.

4 Fitzgibbons S, Ching YA, Valim C *et al.* Relationship between serum citrulline levels and progression to parenteral nutrition independence in children with short bowel syndrome. *J. Pediatr. Surg.* 2009; **44**: 928–32.

5 Papadia C, Sherwood RA, Kalantzis C *et al.* Plasma citrulline concentration: a reliable marker of small bowel absorptive capacity independent of intestinal inflammation. *Am. J. Gastroenterol.* 2007; **102**: 1474–82.

6 Crenn P, Vahedi K, Lavergne-Slove A, Cunober L, Matuchansky C, Messing B. Plasma citrulline: a marker of enterocyte mass in villous atrophy-associated small bowel disease. *Gastroenterology* 2003; **124**: 1210–19.

7 Van Vliet M, Tissing WJM, Rings EHHM *et al.* Citrulline as a marker for chemotherapy induced barrier injury in pediatric patients. *Pediatr. Blood Cancer* 2009; **53**: 1188–94.

8 Ruiz P, Tryphonopoulos P, Island E *et al.* Citrulline evaluation in bowel transplantation. *Transplant. Proc.* 2010; **42**: 54–6.

9 Piton G, Manzon C, Monnet E *et al.* Plasma citrulline kinetics and prognostic value in critically ill patients. *Intensive Care Med.* 2010; **36**: 702–6.
10 Rhoads JM, Plunkett E, Galanko J *et al.* Serum citrulline levels correlate with enteral tolerance and bowel length in infants with short bowel syndrome. *J. Pediatr.* 2005; **146**: 542–47.
11 Wales PW, de Silva N, Langer JC, Fecteau A. Intermediate outcomes after serial transverse enteroplasty in children with short bowel syndrome. *J. Pediatr. Surg.* 2007; **42**: 1804–10.
12 Curis E, Moinard C, Osowska S, Zerrouk N, Benazeth S, Cynober L. Almost all about citrulline in mammals. *Amino Acids* 2005; **29**: 177–205.
13 Moinard C, Cynober L. Citrulline: a new player in the control of nitrogen homeostasis. *J. Nutr.* 2007; **137**: 1621S–25S.
14 Bahri S, Curis E, El Wafi FZ *et al.* Mechanism and kinetics of citrulline uptake in a model of human intestinal epithelial cells. *Clin. Nutr.* 2008; **27**: 872–80.

Pediatr Surg Int (2012) 28:21–25
DOI 10.1007/s00383-011-3009-y

ORIGINAL ARTICLE

Strategies for catheter-related blood stream infection based on medical course in children receiving parenteral nutrition

Wataru Sumida · Yoshio Watanabe · Hidemi Takasu

Published online: 19 October 2011

Abstract
Purpose The central venous catheter (CVC) is a useful device for patients requiring parenteral nutrition (PN). However, the risk for catheter-related blood stream infection (CRBSI) is always present. We analyzed the medical course pattern and considered the strategies against febrile events in patients with CVC.
Methods Nine patients receiving PN in our institute from January 2009 to December 2010 were reviewed. Statistical analysis was performed with the Mann–Whitney U test. A p value of <0.05 was considered statistically significant.
Results Eighty-four febrile events were observed. Fifty-six specimens had a positive blood culture, and 52 (93%) specimens were found to be positive in 48 h. The fever dissolved within 48 h in 76 (90%) events after our scheduled treatment. Between the positive and negative blood culture groups, no statistical difference was observed in the count of white blood cell ($p = 0.15$), the proportion of neutrophils ($p = 0.11$) and C-reactive protein ($p = 0.64$). None of the CVCs were removed because of failure to control infection.
Conclusion We recommend the treatment for CRBSI be initiated when patients with CVC develop a high-grade fever, even before exact identification of the cause of infection. The treatment can be corrected after the re-evaluation at 48 h.

W. Sumida (✉) · Y. Watanabe · H. Takasu
Department of Pediatric Surgery,
Aichi Children's Health and Medical Center,
474-8710, 1-2 Osakada, Morioka-cho, Obu, Aichi, Japan
e-mail: wsumida288gto@yahoo.co.jp

Keywords Catheter-related blood stream infection · Parenteral nutrition · Children · Treatment · Central venous catheter

Background

Parenteral nutrition (PN) is essential for patients with intestinal failure. Intestinal failure is a condition in which the alimentary tract is not able to absorb enough nutrition [1]. For patients who require PN, a central venous catheter (CVC) must be used. As long as the CVC is embedded, there is a risk of catheter-related blood stream infection (CRBSI).

The best therapeutic choice for CRBSI is the immediate removal of the infected catheter [2]. However, the vein that was used for catheter insertion will be occluded once the catheter has been removed. This results in the loss of the available venous access sites.

The loss of the venous access site for CVC insertion can be fatal for patients who depend on PN. Therefore, we have attempted to preserve the CVC during the treatment of CRBSI.

The aim of this study was to search for treatments against CRBSI without removal of the infected CVC by reviewing and analyzing the medical course of CRBSI in patients dependent on PN.

Methods

Nine patients who received PN with CVC over 3 months in our institute from January 2009 to December 2010 were reviewed. The etiologies of intestinal failure of the nine patients enrolled in this study were hypoganglionosis in

five patients, short bowel syndrome in three, and chronic idiopathic intestinal pseudo-obstruction in one. None of the nine patients had other implanted devices such as prosthetic heart valves or vessels. When the patient with CVC developed high-grade fever up to 38°C, we treated them with the same strategy. The strategy involved initiation of treatment for suspected CRBSI immediately if an apparent condition such as pneumonia, influenza or urinary tract infection was not proven. The specimens for blood culture and laboratory tests were collected from the CVC. The CVC was locked and filled with antibiotics (5 mg/ml of amikacin solution) or 70% ethanol. We principally chose antibiotics for filling for the first treatment on admission. But we used ethanol for the events on one patient who insisted on filling with ethanol. A continuous dripped infusion from the peripheral vein and antibiotics were administered for 5 days. The antibiotics were chosen based on the past results of blood culture. When the past results were not referable, cefotiam was used empirically. If the fever dissolved after administration of antibiotics for 5 days, the PN was resumed from the CVC and we ensured no recurrence of developing fever. Unfortunately, when the scheduled treatment failed, the treatment should be corrected, which involved removing the CVC.

The medical data of the patients with suspected CRBSI were collected including the following; (1) the results of blood culture obtained on admission, (2) the period for detection of positive blood culture, (3) the period in which the high-grade fever was observed, (4) the data of laboratory examination and (5) whether the CVC was removed.

The data of each laboratory examination were divided into two groups depending on the result of the blood culture (positive group and negative group). The laboratory examination data were compared between the positive group and negative group. Statistical analysis was performed with the Mann–Whitney U test and a p value <0.05 was considered statistically significant.

Results

During the study period, we experienced 84 events of suspected CRBSI. We locked and filled the CVC with 70% ethanol for the 10 events in one patient who insisted on filling with ethanol. For the 74 other events, we principally chose antibiotics for filling for the first treatment on admission.

In total, 84 blood cultures were performed, as a result, 56 specimens were positive and the other 28 specimens were negative. In the 56 positive specimens, *Escherichia coli* was detected in 19, methicillin-resistant coagulase-negative *Staphylococci* (MRCNS) in 15, *Klebsiella pneumoniae* in 11, methicillin-resistant *Staphylococcus aureus* (MRSA) in 4, *Klebsiella oxytoca* in 3, *Pseudomonas aeruginosa* in 2, *Candida parapsilosis* in 1 and others in 10 (Table 1). In six specimens, multiple species of bacteria were detected.

When the 56 positive blood cultures are viewed from a point of time for positivity, 52 (93%) specimens were found to be positive after a 48-h incubation (Fig. 1). The remaining four specimens that were not found to be positive until after 48 h were considered false positives, resulting from contamination.

When all 84 febrile events were viewed from the point of the febrile period, the fever dissolved within 48 h in 76 (90%) events (Fig. 2). Of the eight events in which the fever persisted over 48 h, three events seemed to be CRBSI from the clinical course. In these three events, *C. parapsilosis*, *K. pneumoniae* and *P. aeruginosa* were detected from blood cultures. We were able to control the infection without removing the CVC in all three events after we had performed CVC locking with 70% ethanol instead of antibiotics. In the remaining five events, the other obvious origin was found from results of the other examination or subsequent clinical course; enterocolitis in two events, primary infection of Epstein–Barr virus in 1, otitis media in 1, and side-effect of vaccination in 1.

In 52 events whose blood culture revealed positive results within 48 h, the fever dissolved within 48 h in 48 events. Of the four events in which the fever persisted over 48 h, one

Table 1 Species of micro-organisms detected from the blood culture

Gram negative bacilli	
Escherichia coli	19
Klebsiella pneumoniae	11
Klebsiella oxytoca	3
Pseudomonas aeruginosa	2
Acinetobacter sp.	1
Pseudomonas putida	1
Enterobacter asburiae	1
Gram positive cocci	
MRCNS	15
MRSA	4
Staphylococcus aureus	1
Streptococcus pneumoniae	1
Micrococcus luteus	1
Enterococcus faecalis	1
Staphylococcus caprae	1
Gram positive bacilli	
Corynebacterium sp.	1
Bacillus subtilis	1
Fungi	
Candida parapsilosis	1
Negative	28