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SHORT REPORT

Cow's milk allergy in extremely short bowel syndrome: Report of two infants

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Summary There is little known regarding cow's milk (CM) allergy in regard to complications in infants with extremely short bowel syndrome (ESBS).

Patient 1: A girl baby with postoperative esophageal atresia underwent a massive resection of the small intestine due to midgut volvulus at 2 months of age. Since 4 months of age, she had received parenteral nutrition (PN) and an elemental diet (ED). At 11 months of age, she began consuming CM and thereafter bloody stool occurred. Eosinophilia and an elevation of the serum specific antigen for CM were found. Her condition improved after the initiation of a hypoallergenic formula.

Patient 2: A boy baby with a midgut volvulus was transferred to our hospital 16 days after birth. A massive resection of the small intestine was performed. Since the age of 1 month, he had received both PN and ED. At 4 months of age, he began to consume CM but his activity declined. He was diagnosed based on the clinical data and symptoms. His condition improved after the administration of a hypoallergenic formula.

Conclusion: Clinicians should be aware that an allergy to CM is a possible complication in infants with ESBS.

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Introduction

Cow's milk allergy (CMA) is a well-known food allergy occasionally found in children.^{1,2} This allergy affects approximately 2% of infants under 2 years of age.^{1,2} The

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clinical spectrum ranges from immediate-type reactions, presenting with urticaria and angioedema to intermediate and late-onset reactions, including atopic dermatitis, infantile colic, gastro-esophageal reflux, esophagitis, infantile proctocolitis, food-associated enterocolitis and constipation.^{1,2} The CMA is not only mediated by IgE induced by T-cells but also partially by the non-IgE reaction.^{3,4}

Extremely short bowel syndrome (ESBS), where the residual small intestine is less than 30 cm, is thought to be associated with a very poor prognosis, mainly due to malnutrition and parenteral nutrition (PN) associated liver dysfunction.⁵ Therefore, almost all patients with ESBS require long-term PN, as well as surgical interventions, including intestinal lengthening or intestinal transplantation.⁵ Patients with ESBS often receive hydrolyzed formulas, including a semi- or complete elemental diet (ED), after the time that the enteral feeding starts.^{5,6} In general, CMA is not thought to occur by using such formulas.⁷ However, CMA was observed in 2 patients with ESBS receiving both long-term PN and ED. Therefore, this report describes the clinical course of those Japanese patients with ESBS associated with secondary CMA.

Patients report

Patient 1

A female infant with esophageal atresia (EA) and a birth weight of 1300 g was delivered at another hospital. Two months after a radical operation for EA, a massive intestinal resection was performed due to a midgut volvulus. The residual small intestine was 10 cm in length, including the ileo-cecal valve (ICV). At 5 months of age, she was transferred to the hospital for further nutritional management. Since 4 months of age, she had received both PN and ED (Elental-P®, which is a complete amino acid formula for children, Ajinomoto Co. Inc., Osaka, Japan). She sometimes experienced enteritis and had persistent moderate liver dysfunction since 4 months of age.

At 11 months of age, feeding with cow's milk was initiated but it resulted in bloody stool and a poor general condition. A laboratory examination at that time revealed eosinophilia and an elevation of the serum specific antigen for cow's milk protein (Table 1). In addition, a contrast study showed the residual small intestine to be spastic. Therefore, she was diagnosed to have CMA. Her condition improved after she was given a hypoallergenic formula for CMA (new MA-1®, Morinaga Co. Inc., Osaka, Japan).

Two months later, cholestatic liver cirrhosis progressed. Although the intestinal lengthening procedure, a serial transverse enteroplasty (STEP),⁸ was done to improve liver function, this patient died due to multiple organ failure secondary to liver cirrhosis at 15 months of age.

Patient 2

A male baby in 2848 g of body weight showing a midgut volvulus was transferred to the hospital at 16 days of age. A massive small bowel resection was performed. The residual small intestine was 5 cm in length with the ICV. Since 1 month of age, he received both PN and ED. He also

Table 1 Clinical data in ESBS patients with CMA

	Patient 1	Patient 2
Basic diseases	EA (P/O), ESBS due to midgut volvulus	ESBS due to midgut volvulus
Residual length of small intestine (cm)	10	5
Ileo-cecal valve	(+)	(+)
Age at onset of CMA (mo)	11	4
Duration of ED use (m)	8	3
Data at onset of CMA		
White blood count (/mL)	6990	11,700
Eosinophil (/mL)	1943	1287
C-reactive protein (mg/dL)	0.74	0.07
Total IgE (IU/mL)	<20	<20
Specific IgE (UA/mL)		
Cow's milk protein	6.97	7.76
Soybean's protein	2.14	<0.35

Abbreviations: CMA: cow's milk allergy, EA: esophageal atresia, ED: elemental diet, and ESBS: extremely short bowel syndrome.

occasionally experienced enterocolitis and had persistent mild liver dysfunction since 3 months of age.

At 4 months of age, feeding with cow's milk was initiated and the infant's activity thereafter declined. He was diagnosed to have cow's milk allergy based on an investigation similar to that involving Patient 1 (Table 1). His condition normalized after a hypoallergenic formula for CMA was initiated. At 6 months of age, food intake with allergen avoidance of cow's milk was started in addition to the hypoallergenic formula.

Discussion

Although patients with ESBS are thought to have a risk of food allergy during the clinical course, there are few published reports regarding the occurrence of CMA in patients with ESBS.^{7,9} In SBS, the hydrolyzed formula or ED is recommended to accelerate the intestinal adaptation.⁶ In our patients, the ED was also selected and used for that purpose. In general, a food allergy is not thought to occur by using such a hydrolyzed formula, therefore, it can be used for the treatment for food allergy.^{6,7} However, CMA occurred in both patients in a few days after they began to consume cow's milk. Therefore, the mechanism of CMA occurrence in these patients should be discussed.

Vanderhoof and Young suggested both the possible risk of CMA related to a non-IgE reaction in the small intestine, as being similar to the current patients, and the mechanism of CMA in younger children with SBS.⁷ According to their report, the possible mechanism is related to the following conditions; the residual intestinal dilatation and

dysfunction results in the intraluminal bacterial overgrowth. This induces enteritis leading to the mucosal damage. The mucosal persistent inflammatory changes in the residual intestine result in the increase of permeability to macromolecules.⁷ Furthermore, Mazon et al. recently reported 8 SBS patients with CMA and showed that chronic diarrhea and malabsorption associated with SBS were related to cause the food allergy, including CMA.⁹ These conditions were observed in our patients, although the mucosal persistent inflammatory changes were not microscopically confirmed. This suggests that the hydrolyzed protein formula or ED may have a therapeutic advantage in nutritional management in patients with SBS. However, the long-term use of ED is sometimes thought to induce intestinal and colonic mucosal damage, thus resulting in the mucosal atrophy.^{10,11} This mucosal atrophy also might induce the increase of permeability to macromolecules digested from consumed food. When cow's milk was first consumed after the long-term use of ED, cow's milk protein might enter into the microcirculation and induce CMA. Furthermore, in the low-birth-weight infants, the presence of intestinal prematurity might also result in an increase of intestinal permeability.¹² Therefore, ED might not be an appropriate formula in ESBS patients if it is used over a prolonged period. In addition, the long-term use of ED itself might be a risk factor for food allergy when cow's milk or other feeding is initiated.

In the first patient, the specific antigen test for food after the cow's milk was positive for soybean protein, in addition to cow's milk protein (Table 1). In this patient, only ED, which is composed of a soybean based amino acids, was used before cow's milk was introduced. This ED contained a small amount of soybean oil and was sometimes contaminated with a slight volume of soybean protein,¹³ while the cow's milk did not contain soybean protein. In addition, a similar clinical course after the long-term use of this ED was reported in two infants with chronic diarrhea in Japan.¹⁴ Furthermore, Mazon et al. showed the possibility of the existence of other food allergies in SBS patients, as well as CMA.⁹ Therefore, this increase of serum IgE level for soybean protein might indicate that the ED should be also carefully used in ESBS if it is used over a prolonged period because the long-term use of ED itself might be partly related to the occurrence of CMA in patients.

Based on the findings of these cases, when ED has been used for over 3 months, clinician might be aware of the possibility for food allergy, especially for CMA, at the time when the cow's milk or other feeding is started in infants with ESBS. In addition, we consider that testing for food allergy, including CMA, should be done in patients with SBS, especially with ESBS, before and after cow's milk is started. A recent study showed that the skin prick tests or serum specific IgE antibodies did not reveal any positive findings in approximately 50% of the patients with food allergy.⁴ Therefore, if the detection tests resulted in a negative

finding, then the clinicians treating SBS keep the possibility of a food allergy in mind when making a differential diagnosis. We experienced only 2 ESBS patients with CMA. Further multicentric studies in a larger group of patients will thus be necessary in order to elucidate the occurrence rate and the pathology of CMA in ESBS.

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