Fecal eosinophil-derived neurotoxin in cow's milk-sensitive enteropathy: a case report

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Fecal eosinophil-derived neurotoxin in cow's milk-sensitive enteropathy: a case report

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Running title: Fecal EDN in cow's milk enteropathy

To the Editor,

Food allergy reactions can be divided into IgE mediated, non-IgE mediated, or a combination of both.[1,2] Non-IgE-mediated food allergies include food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis, and food protein-induced enteropathy. On the other hand, mixed IgE- and non-IgE-mediated reactions lead to eosinophilic gastroenteropathies including eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis.

Food protein-induced enteropathy is a rare disorder characterized by chronic diarrhea, steatorrhea, weight loss and growth failure. Similar to FPIES, it occurs mostly in young infants and is usually diagnosed based on clinical features, response to an elimination diet, and an oral food challenge test.[1] Examination of jejunal biopsy specimens from patients with food protein-induced enteropathy has identified varying degrees of villous atrophy with crypt hyperplasia and inflammation.[3,4] However, no laboratory tests have been developed to confirm this diagnosis in a clinical setting. In a recent study, we identified one potential fecal biomarker, eosinophil-derived neurotoxin (EDN), showing significant elevation after the ingestion of the causative foods in FPIES patients.[5] Such fecal biomarkers have yet to be fully characterized in other types of gastrointestinal food allergies. As certain features of FPIES overlap those of food protein-induced enteropathy, we investigated whether fecal EDN is also elevated after ingestion of the causative food in a patient with food protein-induced enteropathy.

An 8-month-old Japanese boy was referred to our hospital for evaluation of protein-losing enteropathy. Shortly after a cow’s milk-based formula was used to supplement breast-feeding at 7 months of age, the patient developed chronic diarrhea and

occasional vomiting. He had no history of allergies or gastrointestinal diseases. Physical examination showed lower leg edema. Laboratory studies revealed hypoproteinemia (3.7 g/dL), hypoalbuminemia (1.7 g/dL), low serum immunoglobulin G (IgG, 410 mg/dL), and hypocalcemia (7.8 mg/dL). His white blood cell count was 9800/μL with 29% neutrophils, 50% lymphocytes, and 2% eosinophils. The patient was negative for anemia (hemoglobin 11.5 g/dL) and proteinuria. His serum IgE level was slightly elevated at 31 IU/L, and low levels of allergen-specific IgE were detected: class 2 for β-lactoglobulin; class 1 for cow's milk; and class 0 for casein, α-lactalbumin, egg, wheat and soy. Immunophenotypic analysis of the lymphocytes exhibited a normal percentage of $CD3^+$ T cells and ratio of $CD4^+$ to $CD8^+$ T cells, and no selective loss of naive T cells (data not shown). His diarrhea was positive for Sudan III staining indicating steatorrhea, and positive occult blood testing. Abdominal computed tomography revealed diffuse thickening of the small intestine wall (Figure 1). After elimination of cow's milk protein and introduction of an extensively hydrolyzed casein formula, his gastrointestinal symptoms were rapidly improved, suggesting the possible diagnosis of cow's milk-sensitive enteropathy. We did not perform an endoscopic examination which would certainly require general anesthesia in infants. The serum levels of total protein and albumin had improved to 5.5 g/dL and 2.6 g/dL, respectively, at 14 days of hospitalization.

An oral food challenge test was performed in the hospital to confirm the diagnosis at 11 months of age, after informed consent was obtained from the parents. According to the guideline of FPIES by Powell et al., the patient was given a cow's milk-based formula (0.38 g protein/kg body weight) over a period of 30 min.[6] He developed diarrhea 24 h

after the ingestion. No vomiting was observed. Of note, a significant increase in fecal EDN was demonstrated in the diarrhea (Figure 2). The levels of fecal calprotectin and IgA were not elevated after the ingestion (data not shown). The patient was diagnosed with cow's milk-sensitive enteropathy and the elimination of cow's milk protein continued, resulting in no episodes of enteropathy. At 18 months of age, we performed the same challenge test again in order to assess potential development of tolerance. The patient did not exhibit any gastrointestinal symptoms during the 2 days after the ingestion of a cow's milk-based formula, resulting in a termination of cow's milk elimination from the diet (Figure 2). He is now 8 years old and has tolerated cow's milk without any reaction.

Before the oral challenge test at 11 months of age, no elevation of fecal EDN level was demonstrated in the patient, likely because it was performed 3 months after initiation of cow's milk elimination. We did not measure fecal EDN at the acute phase of enteropathy due to the availability of the sample. In contrast, a marked increase in fecal EDN was demonstrated 24 h after ingestion of cow's milk protein, which was consistent with a positive challenge test. The kinetics was quite similar to those of FPIES.[5] It is well known that most of patients with food protein-induced enteropathy outgrow their symptoms after elimination of causative foods by 2 to 3 years of age.[1,2] In fact, the follow-up challenge test indicated development of tolerance in our patient at 18 months of age. Interestingly, he did not show any increase in fecal EDN at the follow-up challenge test. Taken together, these results suggest the potential of fecal EDN as a useful marker for both diagnosis and assessment of tolerance in food protein-induced enteropathy.

A lack of endoscopic and histological findings did not allow us to rule out the possibility that protein-losing enteropathy in our patient was due to eosinophilic gastroenteropathy, which might share clinical and immunopathogenic features with non-IgE-mediated food allergies.[7] Further studies evaluating clinical and pathophysiological features of non-IgE-mediated food allergies are necessary to elucidate the diagnostic role of fecal biomarkers in gastrointestinal food allergies.

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Figure Legends

Fig. 1

Contrast-enhanced computed tomography of the abdomen showing diffuse thickening of small intestine wall.

Fig. 2

Fecal eosinophil-derived neurotoxin (EDN) levels before and after the ingestion of cow's milk protein. Shaded areas represent the ranges of the normal values.

Figure 1

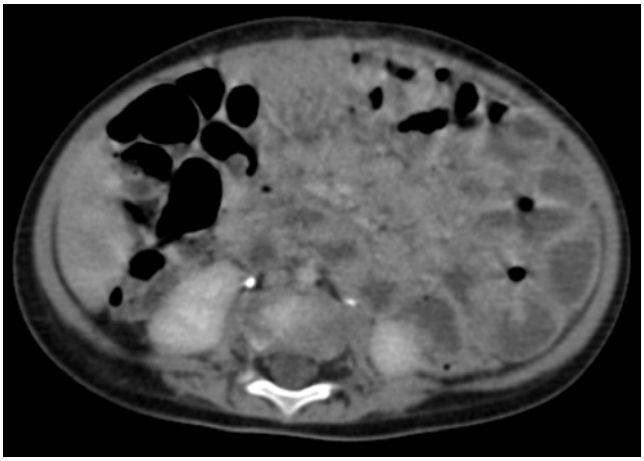
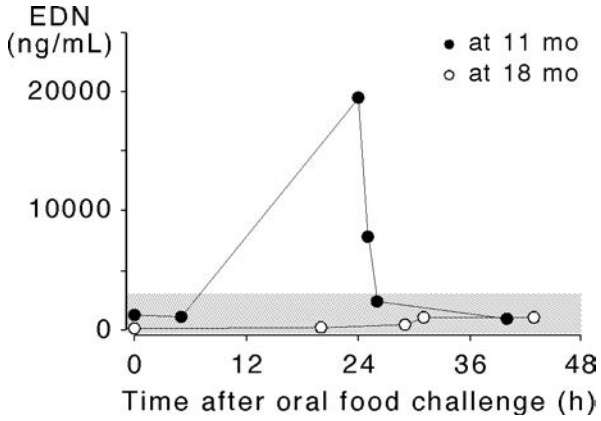


Figure 2


EDN
(ng/mL)
20000
10000
0
at 11 mo
at 18 mo
0
12
24
36
48
Time after oral food challenge (h)