Extensively Hydrolyzed Formula (MA-mi) Induced Exacerbation of Food Protein-Induced Enterocolitis Syndrome (FPIES) in a Male Infant

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ABSTRACT

Background: Food protein-induced enterocolitis syndrome (FPIES) is a severe, cell-mediated food allergy in which digestive symptoms such as severe vomiting and diarrhea are induced by cow’s milk and/or soy protein in infants. Generally, a food-specific IgE is not detected, and FPIES may be caused by inadvertent exposure to allergenic foods.

Case Summary: The patient in our case was a male infant in whom vomiting had been induced by ingestion of a cow’s milk-based formula and bloody diarrhea had been caused by ingestion of breast milk during the neonatal period. Accidental ingestion of a new and extensively hydrolyzed casein/whey formula, MA-mi, caused watery diarrhea at 8 months of age, and FPIES was diagnosed based on these symptoms. In antigen-specific lymphocyte stimulation tests, New MA-1 was negative, but MA-mi and cow’s milk antigens were positive. The only causative antigens were derived from cow’s milk, and the symptoms were not induced by another extensively hydrolyzed casein formula, New MA-1. The patient grew and developed normally thereafter, and no symptoms were induced by solid food during the course of the condition.

Discussion: MA-mi is likely to be used increasingly for allergic infants, but it is not necessarily a substitute for other hydrolyzed milk formulae in all cases, and care should be taken regarding its use and possible misuse.

KEY WORDS

cow’s milk, food allergy, food protein-induced enterocolitis syndrome

INTRODUCTION

FPIES is a severe, cell-mediated food allergy, in which ingestion of causative food induces enterocolitis symptoms, such as protracted vomiting and diarrhea, and elimination of the causative food resolves the symptoms. A cow’s milk-based formula induces symptoms during the neonatal period in many cases, but ingestion of an extensively hydrolyzed formula is generally possible. Here, we describe the case of a male infant with FPIES in whom symptoms were not induced by an extensively hydrolyzed casein formula, New MA-1, but were exacerbated by a new extensively hydrolyzed casein/whey formula, MA-mi.
was referred to the Surgery Department of our hospital at 3 months of age, he was followed up at the outpatient clinic because bloody diarrhea had tended to improve. At 5 months of age, bloody diarrhea was exacerbated due to acute gastroenteritis (Fig. 1), and he was referred to our department.

An initial physical examination in our department, revealed no abnormalities. Elevation of peripheral eosinophils (2236/mm$^3$) and ECP (63.5 $\mu$g/L) were noted in laboratory findings (Table 1), but tests for food-specific IgE and histamine release were negative and there were no findings suggesting IgE mediated food allergy. Since the general condition of the patient was normal, we proposed concomitant nourishment with New MA-1 and breast milk and he was followed as an outpatient. However, bloody diarrhea persisted, and thus breast feeding was discontinued; the patient was nourished with only New MA-1 and bloody diarrhea resolved on the following day. Food allergy was tentatively diagnosed, elimination of cow's milk and eggs was instructed, and he was followed as an outpatient. No anti-allergic drugs were used. At this point, the infant had ingested rice and sweet potatoes, and he was able to eat soybeans (tofu) at 6 months of age. The clinical course was good thereafter without exacerbation of symptoms. At 8 months of age, he was fed MA-mi that had been purchased by mistake, and watery diarrhea accompanied by a bad temper appeared 5 hours after ingestion. Since watery diarrhea was similarly noted 5 hours after ingestion of MA-mi on the following day, feeding with MA-mi was discontinued, and the milk formula was changed to New MA-1; subsequently the fecal condition improved. The infant did not receive breast milk during this period. In antigen-specific lymphocyte stimulation tests (Table 2), New MA-1 was negative, but MA-mi and cow's milk antigens were positive, so watery diarrhea after ingestion of MA-mi was thought to be an immunological reaction. Since these findings met Powell's diagnostic criteria, a diagnosis of FPIES was made for this patient. At 1 year and 3 months of age, his only food restriction is cow's milk and he had normal growth and development. We planned to slowly introduce cow's milk into his diet.

**PATHOLOGICAL FINDINGS**

In antigen-specific lymphocyte stimulation tests (Table 2), the result of New MA-1 was negative, but the results of MA-mi and cow's milk antigens were positive.
FPIES Induced by MA-mi

**Table 2 Results of Antigen Specific Lymphocyte Stimulation Tests**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Counts (cpm)</th>
<th>S.I. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>① new MA-1</td>
<td>2637</td>
<td>105</td>
</tr>
<tr>
<td>② MA-mi (casein hydrolysate)</td>
<td>4469</td>
<td>178</td>
</tr>
<tr>
<td>③ MA-mi (whey protein hydrolysate)</td>
<td>3804</td>
<td>152</td>
</tr>
<tr>
<td>④ MA-mi (①+③)</td>
<td>5241</td>
<td>209</td>
</tr>
<tr>
<td>⑤ casein</td>
<td>8175</td>
<td>327</td>
</tr>
<tr>
<td>⑥ whey protein</td>
<td>5962</td>
<td>238</td>
</tr>
<tr>
<td>⑦ cow’s milk protein (⑤+⑥)</td>
<td>8455</td>
<td>338</td>
</tr>
<tr>
<td>⑧ control</td>
<td>2498</td>
<td></td>
</tr>
</tbody>
</table>

Examination was carried out at 10 months of age. Using the following antigens (with no additives) provided by the manufacturers, thymidine uptake was measured using autologous plasma for culture. The measurements were performed by a laboratory testing company. The result of new MA-1 was negative. The results of MA-mi and cow’s milk protein were positive.

Antigen ①: casein hydrolysate combined in new MA-1
Antigen ②: casein hydrolysate combined in MA-mi
Antigen ③: whey protein hydrolysate combined in MA-mi
Antigen ④: mixture of antigen ② and ③ at the same proportion as in the product
Antigen ⑦: mixture of antigen ⑤ and ⑥ by a ratio 4 to 6 as a cow’s milk formula

**DISCUSSION**

FPIES is a symptom complex of severe vomiting and diarrhea caused by cell-mediated allergy. Symptoms typically occur within several hours after ingestion of the causative food, repeated exposure to which may elicit bloody diarrhea, dehydration and developmental retardation; these symptoms may lead to shock in severe cases.5,7,12 Cow’s milk and soybeans are the causative foods in many reports, but cases of solid food-FPIES induced by foods such as rice, wheat, chicken and vegetables, have also been reported.8,11

Generally, if the results of skin-prick tests and radioallergosorbent tests (RASTs) for food antigens are negative, FPIES may be suspected based on the typical clinical symptoms. The condition is often diagnosed based on resolution of the symptoms by removal of the causative food, and reappearance of the symptoms with ingestion of the causative food. Patients with FPIES caused by antigens from cow’s milk are able to ingest extensively hydrolyzed milk, but some cases require an amino-acid based formula. Although involvement of allergens of cow’s milk passed in maternal breast milk has been suspected in the pathology of FPIES, Sicherer12 reported that breast milk may have a role in protecting against or delaying the onset of FPIES and that breast milk antigen-induced FPIES is unlikely. However, our case included vomiting after ingestion of a cow’s milk-based formula, watery diarrhea after ingestion of MA-mi, and bloody diarrhea after ingestion of breast milk alone, suggesting the involvement of breast milk antigens.13,14 Differentiation from proctitis is necessary if breast milk is thought to be involved in symptom development;14 however, FPIES was diagnosed based on enterocolitis symptoms in our case.

The choice of baby food and timing of initiation of feeding of baby food are of importance in follow-up of children with FPIES. Our patient had no problem with ingestion of other foods, including soybeans, but about half of FPIE cases are reported to be caused by soy antigen.7,12 In some reports,12 development of FPIES is a risk factor for later development of solid food-FPIES, and initiation of feeding with baby food should be delayed. In Japan, the incidence of FPIES induced by foods other than cow’s milk is unclear at present, and an investigation of the appropriate timing of initiation of feeding with baby food, including soybeans and grains, is required in a large number of FPIES patients.

In our case, ingestion of New MA-1 was possible, but watery diarrhea developed following ingestion of MA-mi. We regarded this as a symptom of FPIES, even though a cow’s milk-based formula containing whey protein hydrolysate can also elicit diarrhea through a non-immunological intolerance reaction, even in healthy infants.15 However because of recurrent episodes of symptoms accompanied by a bad temper at a fixed time (5 hours after ingestion of MA-mi) and positive findings for antigen-specific lymphocyte stimulation tests, the watery diarrhea was thought to have occurred through an immunological reaction. MA-mi is a cow’s milk-based formula prepared by enzyme hydrolysis and ultrafiltration of cow’s milk protein, which reduces the antigenicity of casein and whey protein. The immunogenic capacity and reactivity of MA-mi are very low, and no differences in antigenicity have been noted between MA-mi and new MA-1 in in-vitro or animal studies, suggesting that MA-mi could be useful for infants with food allergy, regardless of IgE-dependent or -independent allergy. MA-mi is also easy to ingest because of the good taste due to the low free amino acid content. However, its molecular weight distribution is slightly high, with a maximum molecular weight of approximately 2000, compared with approximately 1000 in new MA-1. Moreover, a difference was detected on lymphocyte stimulation tests between new MA-1 and MA-mi, suggesting that tolerance to the 2 products is not necessarily the same in clinical cases. For the continued use of MA-mi for infants with severe allergy (particularly, allergy with systemic symptoms), further consideration, such as supervision by a physician, is necessary. MA-mi was marketed in fall 2005, and it is often confused with MA-1, given the similarity of the names of these products. Therefore, parents may use MA-mi by mistake, and in our case the patient’s parents purchased MA-mi immediately after its introduction, believing it to be the same product as New MA-1. Feeding of MA-mi to allergic in-
fants is likely to increase, but our case shows that it is not necessarily a substitute for other products; therefore, an adequate explanation to parents may be necessary to avoid mistakes in the feeding of infants.

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**REFERENCES**