



## SHORT REPORT

# Rice protein-induced enterocolitis syndrome

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**KEYWORDS**Food protein-induced enterocolitis syndrome;  
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Allergy**Summary**

**Background & aims:** Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergic reaction, usually to cow's milk or soy protein. The aim is to present a series of infants with enterocolitis syndrome developed after rice ingestion. To our knowledge, the issue has only once been described in patients from Europe.

**Methods:** Data on five patients were retrospectively analyzed. The patients presented with vomiting, diarrhea and dehydration; therefore, allergy was not considered as a diagnosis and the patients underwent broad diagnostic evaluation. Finally, an open food challenge was performed for suspicion of rice allergy.

**Results:** Detailed clinical and laboratory findings are presented. As all patients had symptoms which could have been indicative of a broad spectrum of diseases, a median of two hospitalizations was needed to establish the diagnosis. When the rice protein-induced enterocolitis syndrome is suspected all patients should undergo open food challenge test, as no other diagnostic procedure can confirm the diagnosis.

**Conclusion:** This report shows that even hypoallergenic foods such as rice may cause FPIES and should be considered in the differential diagnosis of profuse vomiting and prostration in infants introduced to some kind of rice protein.

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**Introduction**

In general, food allergy is a spectrum of disorders that result from an aberrant immune response to

dietary antigens, which can be either IgE-mediated or non-IgE-mediated. In IgE-mediated food allergy, T-cell-directed antigen-specific IgE production leads to sensitization, and re-exposure to the same antigen results in the release of mediators causing allergic reaction. The second, non-IgE-mediated mechanism results from direct T cell antigen response, mediated by proinflammatory cytokines

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and leading to a variety of chronic responses.<sup>1</sup> One of these non-IgE-mediated reactions, very infrequently described, is food protein-induced enterocolitis syndrome (FPIES).<sup>2</sup> Clinical presentation of FPIES is characterized by profuse vomiting and prostration that lead to dehydration and sometimes shock. Symptoms commonly begin 2–4 h after ingestion of the incriminated protein and, therefore, represent an allergic reaction with delayed onset. The diagnosis is based on clinical criteria and oral challenge. Although mostly caused by cow's milk or soy protein, some authors have described similar reaction to solid food protein.<sup>2–4</sup>

The aim of this report is to present a series of infants with enterocolitis syndrome developed after ingestion of rice protein, which has, to our knowledge, only once described in patients from Europe.<sup>5</sup>

bolic disease, etc.). Upon admission and treatment of life-threatening symptoms, all patients underwent broad diagnostic evaluation to exclude different infectious, neurological and metabolic diseases. Eosinophil count, total IgE, RAST to food protein, Hemocult testing and skin prick tests were obtained for suspicion of allergy. Finally, rice protein was incriminated and all five patients underwent an open food challenge. For open food challenge all patients received rice cereals mixed with water. At the beginning a very small amount of food (only few drops) was given and every half an hour an amount of food was increased. The patients remained under close observation for 8–10 h. Expecting a severe positive reaction, the test was performed after obtaining an informed consent and with all due precautions (venous access, emergency equipment, and constant surveillance).

## Material and methods

We reviewed medical records of five patients referred to the Referral Center of Pediatric Gastroenterology and Nutrition, Zagreb Children's Hospital, for treatment of severe dehydration and prostration due to the then unknown cause (differential diagnosis included seizures, sepsis, meta-

## Results

Detailed clinical and laboratory findings are presented in Table 1. Patients were 5–6 months old, and it was their first to third hospitalization. By the time of admission, all patients were breastfed, in one a cow's milk formula was also introduced, and all had tried different fruits. It is important to

**Table 1** Clinical presentation of patients with rice induced FPIES.

| Patient | Age at diagnosis (months) | History of family atopy | Onset of the symptoms (hours after ingestion) | Symptoms                                            | Breast feeding                              | No. of hospitalization |
|---------|---------------------------|-------------------------|-----------------------------------------------|-----------------------------------------------------|---------------------------------------------|------------------------|
| 1       | 5                         | No                      | 2                                             | Vomiting, diarrhea, dehydration, acidosis, lethargy | Yes (2 months), Cow milk formula introduced | 2                      |
| 2       | 6                         | No                      | 1                                             | Vomiting, diarrhea, acidosis, cyanosis, dehydration | Yes (2 months), Cow milk formula introduced | 2                      |
| 3       | 6                         | No                      | 3                                             | Vomiting, diarrhea, lethargy, dehydration           | Yes                                         | 1                      |
| 4       | 6                         | No                      | 1                                             | Vomiting, diarrhea, dehydration                     | Yes                                         | 2                      |
| 5       | 6                         | No                      | 2                                             | Vomiting, diarrhea, dehydration, lethargy           | Yes                                         | 3                      |

**Table 2** Laboratory findings.

| Patient | Prick skin test to rice | RAST to rice | Eosinophils (%) | Hemoccult | Open challenge test | Rice reintroduction     |
|---------|-------------------------|--------------|-----------------|-----------|---------------------|-------------------------|
| 1       | Negative                | Negative     | 5               | Positive  | Positive            | Lost to follow up       |
| 2       | Positive                | Negative     | 12              | Positive  | Positive            | At age 3 years          |
| 3       | Negative                | Negative     | 8               | Positive  | Positive            | At age 3 years          |
| 4       | Negative                | Negative     | 40              | Positive  | Positive            | Still on rice-free diet |
| 5       | Negative                | Negative     | 5               | Positive  | Positive            | Still on rice-free diet |

emphasize that symptoms, which included severe vomiting, diarrhea and dehydration in all patients, acidosis in two and lethargy in three patients, occurred after rice was introduced for the first time. Two patients were treated at intensive care unit due to very severe symptoms of dehydration, acidosis and lethargy, which initially were not ascribed to food hypersensitivity. Before admission to our unit, patient No. 5 was treated with antibiotics on two occasions, because she was misdiagnosed with infective enterocolitis (high leukocyte count, leukocytes in stool). All patients had elevated eosinophil count and positive occult blood in stool. Skin prick test was positive in one patient (patient No. 2). Specific IgE antibodies to rice were negative in all patients, whereas IgE level was elevated in only one patient (patient No. 4). All patients developed profuse vomiting and dehydration requiring fluid resuscitation within 2–3 h of rice challenge (Table 2). The patients remained free from symptoms when rice was excluded from their diet. In two patients rice was reintroduced at the age of 3 years, without any complications. Two patients, now aged 10 and 18 months, are still on rice-free diet. One patient has been lost for follow-up; the last control visit was performed at the age of 17 months when she was still on rice-free diet.

## Discussion

Rice as an allergen has been rarely described in the USA and Asia<sup>2–4,6–8</sup> and, to our knowledge, only one series of four patients with rice-induced FPIES has been reported in Europe.<sup>5</sup> The patients reported here presented with a rare, rice-induced enterocolitis syndrome. At presentation, neither the clinical condition was recognized as an allergic reaction, nor was rice detected as the cause. However, thorough medical history, laboratory results and food challenge demonstrated a cell-mediated, non-IgE-related allergic reaction to rice

protein in all five patients. Two hospitalizations (median) were required to establish the true nature of the disease. This could be explained by the fact that rice is rarely considered as an allergen in Europe; that FPIES is an infrequent allergic reaction; and that symptoms may be quite misleading, suggesting a life-threatening disease such as sepsis or metabolic syndrome rather than a food-induced reaction. As shown by our report, determination of specific IgE, total IgE count and skin prick test to rice had little diagnostic value. However, these should not be totally ignored as one patient had positive skin prick test to rice and elevated total IgE count each.

FPIES is the most severe form of non-IgE-mediated gastrointestinal food allergy in infants. It is the result of the generation of T cells that respond directly to the incriminated protein and is mediated by cytokines leading to allergic reaction with eosinophilic infiltration and increased vascular permeability. The immunopathology is unknown; it has been suggested that food antigen-induced secretion of TNF $\alpha$  from local mononuclear cells may be responsible for diarrhea and hypotension.<sup>9</sup> Vomiting and blood positive diarrhea (in our patients, all Hemoccult tests were positive) can lead to dehydration and shock.<sup>3</sup> Acidemia, methemoglobinemia and sepsis-like picture, including elevated white blood cell counts, can also be a part of the clinical picture. In fact, this was the case in patients No. 1 and No. 2, who had to be treated at intensive care unit for severe acidosis and dehydration. Protein readministration in open challenge results in delayed profuse vomiting and late-onset diarrhea, being therefore a key diagnostic procedure.<sup>1</sup>

Although FPIES is typically caused by cow's milk or soy protein,<sup>10</sup> there are an increasing number of reports on other proteins such as sweet potato, barley, peas, chicken, rice, and oat.<sup>2</sup> A case of male infant with rice intolerance, depressed levels of complement and central nervous system reaction during the first 6 months of life is one of the first

reports identifying rice as a cause of allergic reaction.<sup>11</sup> There are even reports of severe anaphylactoid reaction to rice with negative RAST and skin prick tests.<sup>4</sup> However, larger series of patients with FPIES identified rice to be a very rare cause of allergic reaction, with the identical clinical presentation as to cow's milk or soy.<sup>3</sup> Nowak-Węgrzyn et al.<sup>2</sup> presented 14 cases with FPIES to solid foods, among them two patients allergic to rice. It should be emphasized that, unlike our patients, children in these series had allergic reaction to multiple food proteins. Still, when a patient presents with allergy to one food protein, all others should be introduced with extreme caution, slowly, one at the time.<sup>12</sup>

In conclusion, we have shown that even hypoallergenic foods such as rice may cause FPIES in its full-blown clinical picture and should, therefore, be considered in the differential diagnosis of profuse vomiting and prostration in infants introduced to some kind of rice proteins.

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