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Rice: a common and severe cause of food protein-induced enterocolitis syndrome

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ABSTRACT

Objective: To examine and compare the characteristics of food protein-induced enterocolitis syndrome (FPIES) caused by rice and cow's milk/soy.

Design: Retrospective study of children presenting with FPIES to the Children's Hospital at Westmead, NSW, Australia, over a 16-year period.

Results: There were 14 children with 26 episodes of rice FPIES compared with 17 children with 30 episodes of cow's milk (n = 10) or soy (n = 7) FPIES. Children with rice FPIES were more likely to have FPIES caused by other foods (36%) than children with FPIES caused by cow's milk/soy (0%). Rice caused more episodes of FPIES before a correct diagnosis was made (median 4 (range 1–4) vs median 2 (range 1–4)) and triggered more severe reactions with higher rates of intravenous fluid resuscitation (42% vs 17%) than reactions caused by cow's milk/soy.

Conclusions: This study highlights the emerging importance of rice, a food commonly thought to be "hypoallergenic", as a significant trigger of FPIES. Paediatricians should be aware that rice not only has the potential to cause FPIES, but that such reactions tend to be more severe than those caused by cow's milk/soy.

Food protein-induced enterocolitis syndrome (FPIES) is classified as a non-IgE-mediated allergic disorder triggered by the ingestion of certain food proteins.¹ Children <12 months of age usually present with vomiting and/or diarrhoea ~2 h after ingesting the causative food. Some children present in a moribund state, with shock and metabolic acidosis.² Early literature on FPIES focused on cow's milk and soy, the two most common causes of FPIES.^{3–5} However, the range of food proteins documented to cause FPIES has expanded to include meats, vegetables and grains.^{2 6–10} Rice, a food generally considered to be of "low allergenicity", has been increasingly recognised as a cause of FPIES. The number of children reported in the literature with rice FPIES has increased from three in 1963–1989 to 25 in 1990–2007,^{2 7 9 11–13} with 19 of these cases being described in the last 7 years. There have been two series specifically examining children with rice FPIES, comprising four¹¹ and five¹³ cases; however, these cases were not compared with non-rice-induced episodes of FPIES.

The aim of this study was to examine the characteristics of children presenting with rice FPIES and determine whether there were any differences from those presenting with cow's milk and/or soy FPIES.

METHODS

This was a retrospective study of children presenting with FPIES to the Children's Hospital at

What is already known on this topic

- ▶ Misdiagnosis of food protein-induced enterocolitis syndrome (FPIES) is common, and children are often mistakenly diagnosed with sepsis or a surgical abdominal emergency.
- ▶ Cow's and soy milk are the most commonly reported triggers of FPIES.

What this study adds

- ▶ Rice, a food generally thought to be hypoallergenic, is emerging as one of the most common triggers of FPIES.
- ▶ Rice caused more severe reactions than cow's milk or soy as judged by the requirement for intravenous fluids.

Westmead, NSW, Australia, over 16 years (1992–2007). Possible cases of FPIES were identified from the hospital medical record database using the ICD-9 code, allergic gastroenteritis and colitis (558.3), and ICD-10 code, allergic and dietetic gastroenteritis and colitis (K52.2). Cases were also identified from electronically stored departmental letters written by allergists/immunologists. The Microsoft search option was used to scan letters for keywords (ie, food protein, enterocolitis, vomiting, diarrhoea, FPIES) to identify potential FPIES cases. Information on the first and any subsequent episode caused by rice and cow's milk and/or soy was recorded.

The criteria proposed by Sicherer *et al*² for the diagnosis of FPIES were used: (1) repeated exposure to the incriminated food elicited repetitive vomiting and/or diarrhoea within 24 h without any other cause for the symptoms; (2) no symptoms other than gastrointestinal symptoms elicited by the incriminated food; (3) removal of the offending protein from the diet resulted in resolution of symptoms, and/or a food challenge elicited vomiting and/or diarrhoea within 24 h of administration of the food. Cases were also differentiated into typical (ie, age ≤9 months of age) and atypical presentations (ie, >9 months of age at diagnosis or IgE antibody to causative food). A skin prick test (SPT) using standardised allergens (Hollister-Stier Laboratories, Spokane, Washington, USA) was performed to the food trigger in all cases. An SPT was considered to be positive if the mean wheal size was ≥3 mm.

Table 1 Characteristics of children with food protein-induced enterocolitis syndrome (FPIES) caused by rice or cow's milk/soy

Characteristic	Rice FPIES (n = 14)	Cow's milk (n = 7)/ soy (n = 10) FPIES	p Value
Male	8 (57%)	10 (59%)	0.93
Median (range) age at presentation (months)	5.3 (3–6)	5.5 (2–14)	0.97
Atopy at initial presentation			
At least one atopic disorder	7 (50%)	12 (71%)	0.24
Eczema	7 (50%)	11 (65%)	0.41
Asthma	0 (0%)	1 (6%)	1.0
IgE-mediated food allergy	1 (7%)	3 (18%)	0.61
FPIES to >1 food	5 (36%)	0 (0%)	0.01
Oat	1	–	–
Sweet potato	1	–	–
Banana	1	–	–
Soy	2	–	–

Data were analysed using Minitab for Windows. Continuous data were described as either mean (SD) or median (range) if not normally distributed. Differences between groups for categorical variables were determined using either the χ^2 analysis or Fisher exact test. The Mann–Whitney U test or Student t test was used for comparisons between non-parametric and parametric continuous variables, respectively. $p < 0.05$ was considered significant. The study was approved by the ethics committee at the Children's Hospital at Westmead.

RESULTS

Demographics

Over the 16-year period, there were 14 children with 26 episodes of rice FPIES, which were compared with 17 children with 30 episodes of cow's milk or soy FPIES. Other foods implicated in single cases included fish, chicken and lamb, and one child reacted to both sweet potato and oats. As no child had combined cow's milk and soy FPIES, children with episodes of rice FPIES were compared with those caused by cow's milk or soy. All 14 children with rice FPIES fulfilled the criteria set by Sicherer *et al.*² Two children with cow's milk FPIES were included in the study despite having only a single episode of FPIES and no diagnostic challenge, as the reactions were deemed typical of FPIES with both children developing profuse vomiting, lethargy and pallor 1–2 h after ingesting cow's milk for the first time. No other explanation for their symptoms could be found, SPTs to cow's milk were negative, and both improved after cow's milk was eliminated from their diet.

Table 1 presents the features of children presenting with rice versus cow's milk/soy FPIES. There was no significant difference between children with rice versus cow's milk/soy FPIES with respect to gender, age at initial presentation, and the presence of atopy at presentation ($p > 0.05$ for all comparisons; table 1).

Causative foods

Of the 14 children with rice FPIES, nine reacted only to rice. The other five children had FPIES caused by rice and another food protein (table 1). Children with rice FPIES were more likely to also have FPIES caused by another food than those reacting to

cow's milk/soy (table 1). All children had an SPT performed to the implicated food. One child had a 5 mm SPT to cow's milk, and all remaining children had a negative SPT to the causative food.

Comparison of rice and cow's milk/soy FPIES

There were no significant differences between rice and cow's milk/soy FPIES with respect to the time to reaction after ingestion of the causative food or the presenting clinical features (table 2). Rice caused more episodes before the diagnosis of FPIES was made than cow's milk/soy (table 2).

To examine whether FPIES episodes due to rice were more severe than those caused by cow's milk/soy, we compared rates of hospital presentations, administration of intravenous (IV) fluid for circulatory resuscitation, requests for abdominal imaging or surgical consultations and septic work-up evaluations (table 2). The only significant difference between the two groups was between the rates of IV fluid administration. Rice FPIES was significantly more likely to require IV fluid resuscitation than that caused by cow's milk/soy (table 2). The findings from those children who underwent a diagnostic challenge ($n = 8$) also tended to suggest that FPIES caused by rice was more severe. Thus four out of five children with positive rice challenges required IV fluid resuscitation compared with one of three who reacted to soy.

Children with rice episodes tended to have a higher white cell count on presentation (mean (SD) $20.9 (10.8) \times 10^9/\text{litre}$) than those with soy/cow's milk episodes ($14.5 (3.2) \times 10^9/\text{litre}$); however, this difference failed to reach significance ($p = 0.08$). There were also no significant differences between the two groups with respect to the time delay from presentation to blood being taken and the following test parameters at presentation: haemoglobin, haematocrit, neutrophil, platelet, lymphocyte or eosinophil counts ($p > 0.05$ for all comparisons; data not shown).

Table 2 Characteristics of rice versus cow's milk/soy food protein-induced enterocolitis syndrome (FPIES) episodes

Characteristic	Rice FPIES (n = 26)	Cow's milk/soy FPIES (n = 30)	p Value
No of episodes before correct diagnosis	4 (1–4)	2 (1–4)	0.02
Clinical features			
Time to reaction (h)	1.7 (1.2)	1.7 (1.1)	0.96
Vomiting	26 (100%)	30 (100%)	1.0
Diarrhoea	5 (19%)	9 (30%)	0.54
Lethargy	23 (88%)	25 (83%)	0.71
Pallor	18 (50%)	21 (70%)	0.95
"Atypical" presentation	2 (8%)	3 (10%)	1.0
Presentation to hospital	15 (58%)	18 (60%)	0.86
Markers of reaction severity*			
Abdominal imaging performed†	9 (35%)	9 (32%)	0.85
Request for surgical consultation	6 (23%)	5 (18%)	0.63
Septic work-up performed‡	7 (27%)	8 (29%)	0.89
IV fluid bolus on presentation	11 (42%)	5 (17%)	0.03

Values are median (range), mean (SD) or number (%).

*In two episodes of cow's milk/soy FPIES, information on investigations and/or consultations not available.

†Abdominal imaging = barium swallow, abdominal radiograph and/or abdominal ultrasound.

‡Septic work-up included full blood count and blood culture and/or lumbar puncture, IV, intravenous.

Table 3 Reported cases of rice food protein-induced enterocolitis syndrome (FPIES)

Study	No with rice FPIES	Rice as a proportion of reported FPIES (%)	Rice associated with other FPIES (n)				Rice + other non-grain food
			Rice alone	Rice + oat	Rice + barley	Rice + wheat	
This study	14	40	9	1	—	—	4
Nowak-Węgrzyn <i>et al</i> ⁸	10	23	2	6*	1†	—	2
Hojdak <i>et al</i> ¹³	5	—‡	5	—	—	—	—
Cavataio <i>et al</i> ¹¹	4	—‡	4	—	—	—	—
Fogg <i>et al</i> ⁷	3	3	0	2	—	—	1
Sicherer <i>et al</i> ²	1	5	1	—	—	—	—
Single case reports ^{9 12 14 21 22}	5	—‡	1	0	1	1	2
Total	42	—‡	22 (52%)	9 (21%)	2 (5%)	1 (2%)	9 (21%)

*Five children also reacted to at least one other non-grain food.

†This child also reacted to oats and other non-grain foods.

‡Only reported cases of rice FPIES.

DISCUSSION

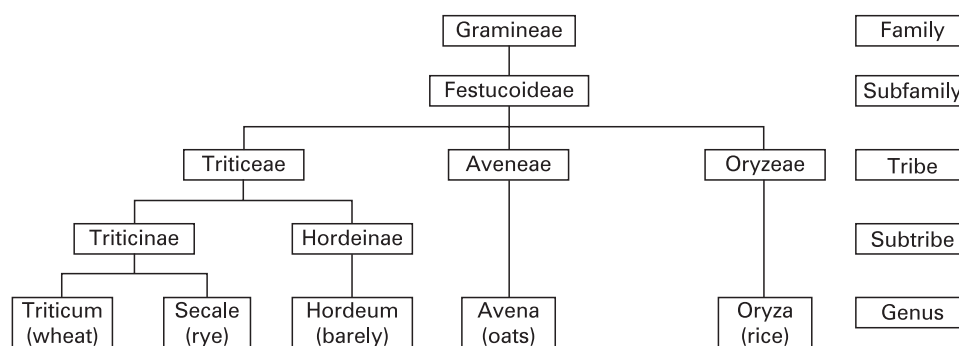
This study represents the largest reported series of children with rice FPIES (table 3). We found that rice was a more common trigger than either soy or cow's milk, and that rice caused more episodes and more severe reactions than cow's milk/soy. Almost 50 years ago, Ikola¹⁴ most likely described the first reported case of rice FPIES. The infant presented to hospital with vomiting, profuse diarrhoea and cyanosis, with a background history of failure to thrive. He was initially thought to have gut malrotation and underwent a non-diagnostic laparotomy. Subsequently it was noted that each time the infant was given rice, and on one occasion wheat, the same, severe, stereotypical gastrointestinal reaction would occur. SPTs to both rice and wheat were negative. Ikola¹⁴ concluded that the reactions to rice and wheat may represent a non-antibody-mediated immunological reaction. Since then, there has been an increasing number of reports of rice FPIES. Rice was the most common single trigger of FPIES in this study, compared with all other series, in which cow's milk or soy were the most common individual triggers.^{2 7 8}

Case reports and series of rice FPIES commonly reveal that such children tend to have multiple episodes, admissions and investigations, before a correct diagnosis is finally made.^{9 11 13} The study by Nowak-Węgrzyn *et al*⁸ of solid food FPIES included 10 children who reacted to rice. Seven had had more than one FPIES reaction to rice. Hospitalisation was common (5/10), as was FPIES to at least one other food protein (8/10). We made similar observations in our study. Children with rice FPIES had many more episodes before being correctly diagnosed than children with cow's milk/soy FPIES. All except one child in our series had had more than one FPIES reaction caused by rice (13/14). Hospitalisation was common (15/26), as was combined

FPIES reactions to rice and another food protein (9/14). A contributing factor to repeated episodes with rice may be that doctors perceive rice to be more hypoallergenic than cow's milk or soy and thus do not suspect it as an allergic trigger. Children with FPIES are often mistakenly diagnosed with sepsis or a surgical abdominal emergency.^{9 15} Septic evaluations were performed in 57% of children with solid food FPIES in the study of Nowak-Węgrzyn *et al*.⁸ In the present study, a third of episodes caused by rice had some form of abdominal imaging, 23% had a surgical consultation, and 27% of episodes had a septic work-up.

Although children with rice and cow's milk/soy FPIES had similar rates of hospital presentations, episodes triggered by rice necessitated resuscitation with IV fluids more often than episodes caused by cow's milk/soy, indicating that reactions to rice tended to be more severe. This has not been reported previously. The requirement for IV fluid resuscitation was also noted to be higher during diagnostic challenges with rice than with cow's milk/soy. Nowak-Węgrzyn *et al*⁸ found that solid food protein FPIES did not result in more severe reactions, on the basis of hospitalisations, episodes of shock and sepsis evaluations, compared with FPIES caused by cow's milk and/or soy ($p = 0.2$). However, rates of IV fluid administration were not presented and no sub-analysis of rice versus cow's milk and/or soy was performed.

The reasons for the predominance of rice in our series are not known. It may be that the increased exposure of the Australian population to rice is a contributing factor. Rice has become a common part of the Australian diet, with consumption doubling during the time frame of this study from ~5 kg/person/year in 1994 to 11 kg/person/year in 2004.¹⁶ Australian dietary guidelines in 2003 recommended rice as one of the first

Figure 1 Taxonomic relationships between cereals.²⁰

solids to be introduced into an infant's diet between the ages of 4 and 7 months.¹⁷ All children with rice FPIES in our series had their first reaction at 3–6 months of age. An Australian-based infant nutrition and dietary survey conducted in 2003 found that 88% of children under 5 years of age (n = 1761) had started regular solid intake by 6 months of age.¹⁸ Rice cereal was by far the most common first solid introduced in these children (70%), followed by pureed vegetables and fruit (19.8%), custard (4.1%) and other solid foods (5.9%).¹⁸ FPIES is not reported in exclusively breastfed infants and only occurs once food proteins are introduced into the infant's diet. A predominance of children from Asian or Indian backgrounds, where rice is often a large part of the diet, did not appear to be a contributing factor to the preponderance of rice FPIES. In 2001, 82% of the Australian population identified themselves as having Anglo-Saxon ancestry (ie, Australian, English, Irish and Scottish) compared with only 4% of Asian ancestry (Chinese and Vietnamese) and 1% with Indian ancestry. Although the numbers are very small, the proportion of children with rice FPIES with Indian or Asian ancestry (7%) does not differ significantly from the proportion of these ancestries in the Australian population (5%).¹⁹

It is an unresolved question as to whether children with rice FPIES are at increased risk of FPIES from other grains. There has only been one case in the literature of a child having FPIES caused by both rice and wheat.¹⁴ The low rate of concurrent rice and wheat FPIES is of interest. In our series, all children with rice FPIES were documented to have had tolerated wheat by 12 months of age, which was introduced into their diet either before (n = 2) or, in most cases, after (n = 12) their reaction to rice. Nowak-Węgrzyn *et al*⁸ did not find any child with combined rice and wheat FPIES, and postulated that, because wheat introduction is typically delayed, this practice may avoid sensitisation or reactions in children with FPIES during a possible period of susceptibility to other food proteins.⁸ Of the 28 cases of rice FPIES reported before the present study, FPIES caused by oats was also present in nine (table 3). However, this finding is heavily dependent on the report of Nowak-Węgrzyn *et al*,⁸ in which six of the 10 children with rice FPIES were also recorded as having FPIES cause by oats. We did not confirm this observation; only one out of 14 children (7%) with rice FPIES had FPIES caused by oats. The issue of the risk of FPIES caused by oats in rice-sensitive children requires further investigation. If an increased sensitivity to oats is confirmed, an explanation may lie in the taxonomic relationship between rice and the other grains. Rice, oats, barely, rye and wheat are all genetically related and come from the same subfamily Festucoidae (fig 1).²⁰ However, wheat, rye and barely are more closely related to one another, belonging to the same tribe Triticeae, and are more genetically distant from rice and oats.²⁰ Children with rice or oats FPIES may therefore be less likely to have cross-reactions with more distantly related cereals, such as wheat, rye and barely.

In conclusion, this study highlights the emerging importance of rice as a significant trigger of FPIES. Awareness of the entity

is fundamental, as the clinical presentation is often confused with an intra-abdominal surgical emergency or sepsis. Multiple presentations before the true diagnosis is established are the norm. Early diagnosis would eliminate repeated reactions and unnecessary investigations. Paediatricians should be aware that rice not only has the potential to cause FPIES, but that such reactions may be more severe than those caused by cow's milk/soy.

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