

Multiple food protein intolerance of infancy or severe spectrum of non-IgE-mediated cow's milk allergy?—A case series

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Clinical Implications

- This series describes an uncommon but complex presentation of what is presumed to be a severe form of non-IgE mediated cow's milk allergy but may represent a new syndrome. Infants become asymptomatic on amino acid based formula, however introduction of solids is extremely difficult with symptoms returning with most solid foods.

TO THE EDITOR:

Non-IgE-mediated cow's milk allergy usually presents in the first year of life and is often associated with soy intolerance. Treatment requires cow's milk elimination and replacement with medicalized formula—usually extensively hydrolyzed formula as first line, if intolerant to soy and older than age 6 months. Between 10% and 20% of infants with this condition require transition to a second-line treatment formula that is amino acid-based to become symptom free.¹ In this group of infants we have noted a subset with a more extreme presentation who although asymptomatic on a diet consisting of amino acid-based formula (AAF) alone become symptomatic with the introduction of most solid foods. It is unclear whether this condition is a complication of severe non-IgE-mediated cow's milk allergy, a failure of generalized oral tolerance, a chronic form of food protein-induced enterocolitis syndrome (FPIES), or simply due to the development of a fermenting pattern of gastrointestinal dysbiosis.

Here, we describe a consecutive case series of these patients ascertained by review of consecutive patients referred to the allergy dietitian (V.McW.) between January 2008 and December 2013 in the Department of Allergy and Clinical Immunology, Royal Children's Hospital Melbourne, Australia. Patients were eligible if they fulfilled the following criteria:

1. Non-IgE-mediated cow's milk allergy and soy allergy commencing in infancy and requiring treatment with AAF or extensively restricted maternal diet for breast-fed infants.
2. Asymptomatic on AAF alone.
3. Gastrointestinal symptoms (diarrhea, vomiting, abdominal distension, and severe irritability) with introduction of a broad range of foods.

Chart review and a questionnaire-guided interview with all contactable families were completed after informed consent to ascertain long-term outcomes for this group of patients. Ethics

approval was obtained from the Royal Children's Hospital Institutional Review Board (HREC no. 33213A).

Thirty-eight patients were identified, and 24 (63%) could be contacted and consented to participate in follow-up (males, 75%; white, 100%). Demographic and clinical features are summarized in Table 1. All patients had more than 1 symptom at presentation, with 75% (18 of 24) experiencing 3 to 4 symptoms. Irritability was the most commonly reported symptom by 79% (19 of 24). Eighteen participants (75%) had skin prick testing or specific IgE test performed. Two participants were sensitized, one to egg, wheat, and cashew and the other to peanut and egg. Three (12.5%) participants had coexisting rice FPIES. Five participants had gastroscopy and biopsies performed and results for all were normal. Seventeen participants (71%) had received antibiotics and 14 (58%) protein pump inhibitor medication in the first 12 months. Four (16.6%) had an older sibling with a history of the same syndrome.

Despite extensive allergy specialist dietitian support, 50% (12 of 24) patients were unable to include more than 5 individual foods in the first 12 months. There was no identified pattern of symptom-inducing foods, with a wide range of fruits, vegetables, grains, and meats reported to cause symptoms (Figure 1).

The mean age at follow-up was 2.5 years (1–4 years). Of those contactable at follow-up (n = 24), only 12.5% (3 of 24) reported complete resolution. All the 3 participants were older than 2.5 years and had irritability and sleep disturbance as the only symptoms reported at initial diagnosis. Twenty-two (91.6%) reported ongoing diarrhea, abdominal pain, and/or distension and continued to exclude 1 to 6 foods. Cow's milk and soy were the most common foods excluded from the diet. Fourteen (58.3%) participants remained on AAF and 3 (12.5%) on protein pump inhibitor medication at follow-up. As per our standard clinical practice, in the context of negative allergy testing results, all food reintroductions were via home-based challenge protocol. Foods were introduced in a graded manner over a period of a week. Patients are reviewed by the allergy dietitian via telephone and if reactions occur the food continues to be excluded. If the food is tolerated, it can be incorporated into the diet. The 3 cases of rice FPIES and the IgE-sensitized participants had all successfully reintroduced foods after hospital-based challenges by follow-up. Growth was reported as normal for 96% (23 of 24) of participants at follow-up.

This series describes an uncommon but complex presentation of what is currently presumed to be a severe form of non-IgE-mediated food allergy although it may represent a new syndrome. Infants remain on very limited diets consisting mainly of AAF in the first 12 months. Many experience ongoing symptoms and diet restrictions up to age 4 years. This presentation is consistent with a previously described condition termed multiple food protein intolerance.^{2–6} The term “multiple food protein intolerance” is outdated based on current classifications of food allergy, and we feel that it does not represent the full pathophysiology of this presentation.⁷ Although it is plausible that a very severe form of food hypersensitivity reaction that involves a wide range of foods is occurring, our understanding of the interplay of other factors in oral tolerance has evolved and there may be other reasons why foods in general or such a wide range of foods result

TABLE I. Summary of (A) demographic and (B) clinical features at initial diagnosis and (C) clinical features at follow-up

Characteristic	Number (n = 24)	%
A. Demographic features at initial diagnosis		
Sex: male	20/24	75
COB, Australia		
Child	24/24	100
Mother	23/24	95.8
Father	24/24	100
Birth details (mode and location)		
Cesarean section delivery	11/24	45.8
Metropolitan Melbourne	12/24	50.0
Rural town	10/24	41.6*
Farm	2/24	8.4
Antibiotic use		
Pregnancy	7/24	29.2
Maternal breast-feeding	5/24	20.8
Infant in the first 12 mo	17/24	71
Feeding history		
Breast-feeding duration (mo), mean (range)	5.5 (0-24)	—
Age AAF introduction (mo), mean (range)	4.7 (1-10)	—
Childcare in the first 12 mo	2/24	8.3
Family history		
First-born children	6/24	25
Sibling with MFPI†	4/24	16.6
Family history of allergic disease‡	6/24	37.5
Family history of IgE-mediated food allergy§	1/24	4.2
Family history of non-IgE-mediated food allergy	2/24	8.3
Family history of IBD/IBS¶	4/24	16.7
Family history of celiac disease	0/24	0
B. Clinical features at initial diagnosis		
Age at initial RCH appointment (mo), mean (range)	11.2 (8-13)	—
Symptoms at presentation		
Irritability	19/24	79.2
Eczema	14/24	58.3
Sleep issues	13/24	54.2
Diarrhea	11/24	45.8
Poor growth#	7/24	29.2
Vomiting	7/24	29.2
Abdominal distention	3/24	12.5
Investigation results at diagnosis		
Positive SPT result (>3 mm)	2/16	12.5
Positive specific IgE level (>0.35 kU/L)	0/2	0
Abnormal full blood cell count	0/9	0
Low serum zinc (<10 µmol/L)	3/9	33.3
Gastroscopy**	5	20.8
Abnormal macroscopic findings	0/5	0
Abnormal microscopic findings	0/5	0
Elevated breath hydrogen test (fructose and lactose)	0/2	0

(continued)

TABLE I. (Continued)

Characteristic	Number (n = 24)	%
Abnormal fecal calprotectin (>50 µg/g)	0/10	0
<i>Clostridium difficile</i> cytotoxin A identified in stool	1/8	12.5
Celiac genotype positive	2/4	50
Celiac antibody screen positive	0/9	0
Elevated total serum IgE level (>100 Ku/L)	2/9	22.2
Low total IgA level (<0.2 g/L)	3/9	33.3
Coexisting conditions at diagnosis		
Gastroesophageal reflux, prescribed proton pump inhibitor medication	14/24	58.0
FPIES	3/24	12.5
IgE-mediated food allergy/sensitization	2/24	8.3
C. Symptoms and features at follow-up		
Age at follow-up (y), mean (range)	2.5 (1-4)	
Resolution of symptoms at follow-up	324	12.5
Continued use of AAF	14/24	58.3
Ongoing diet restriction required	22/24	91.6
Cow's milk	16/24	66.7
Soy	14/24	58.3
Wheat	3/24	12.5
Rice/oat	2/24	8.3
Other (pork, beef, additives/preservatives)	3/24	12.5
Poor growth#	1/24	4.2
Infant sleep intervention††	8/24	33.3
Speech therapy for feeding issues	2/24	8.3

COB, Country of birth; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MFPI, multiple food protein intolerance; RCH, Royal Children's Hospital; SPT, Skin prick test.

*Victorian population ~5.6 million, with 70% of population born in metropolitan Melbourne.

†Sibling with MFPI.

‡Parent or sibling with asthma, eczema, and rhinitis.

§Parent or sibling with IgE-mediated food allergy.

||Parent or sibling with non-IgE-mediated food allergy.

¶Parent or sibling with IBD or IBS.

#Weight <2 centiles from length, World Health Organization growth charts.

**Gastroscope passed to second part of duodenum and biopsies obtained from duodenum, stomach, and oesophagus.

††Inpatient admission to a postnatal health facility for assistance with infant sleep issues and unsettledness.

in symptom exacerbation. A limitation of this study is the retrospective nature of the data collection. Corroboration of this syndrome in other centers and prospective studies using uniform diagnostic testing methods would be valuable including exploration of mechanisms involved in oral tolerance development.

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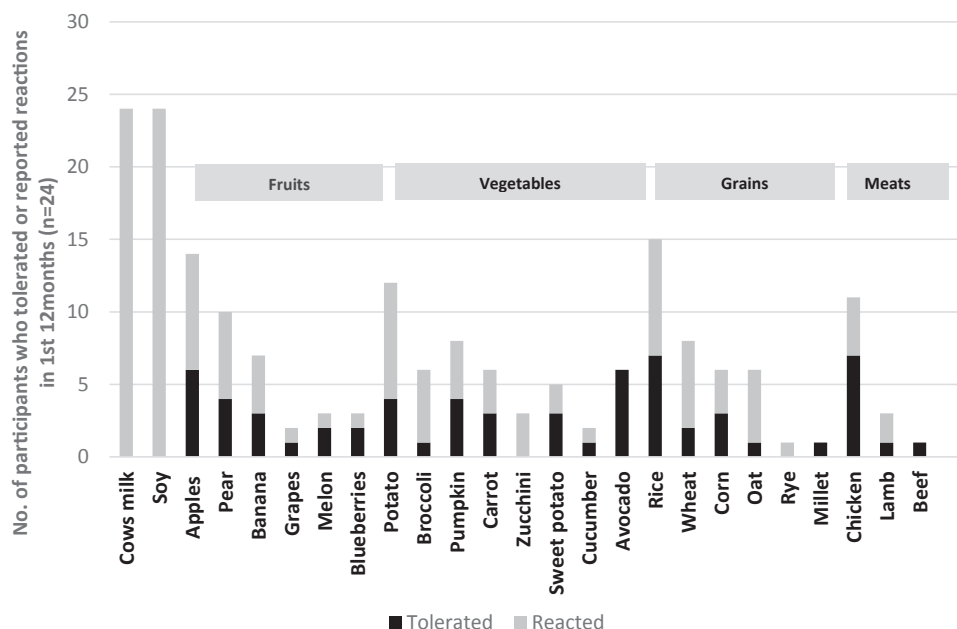


FIGURE 1. Summary of foods tolerated and reported to cause reactions up to age 12 months.

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Conflicts of interest: V. McWilliam has received lecture fees from Danone/Nestle, Nutricia, and Abbott. R. Heine has received lecture fees from Nestle Nutrition Institute and Nutricia Danone Australia and is on the boards for Nestle Nutrition Institute Oceania, Nutricia Danone Australia. M. L. K. Tang is on the Nestle Nutrition Institute Medical Advisory Board, Oceania and the Danone Nutricia Advisory Board, ANZ; a Global Scientific Advisory Board Member; has received lecture fees from Danone Nutricia; has a patent on "A method for inducing tolerance"; and receives royalties as the coauthor of the book *Kids Food Allergies for Dummies*. K. J. Allen has received speakers honoraria from Nestle, Wyeth, Nutricia, AspenCare, Danone, Abbott, Alphafarm, Pfizer, and ThermoFisher and is on the Ilhan Food Allergy Foundation board.

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