

Cow's milk protein is often tolerated by children with oat-induced FPIES

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Clinical Implications

- A better understanding of presenting signs and symptoms, triggers, and predisposing factors may lead to prompt diagnosis and targeted management of food protein-induced enterocolitis (FPIES). Cow's milk oral food challenges may be considered in patients with oat-related FPIES in the first year of life.

TO THE EDITOR:

Food protein-induced enterocolitis (FPIES) is an under-recognized non-IgE-mediated reaction to food, primarily affecting the gastrointestinal system.^{1,2} The most common presenting symptoms include repetitive vomiting, diarrhea, dehydration, and/or lethargy 1 to 3 hours after ingestion of the triggering allergen.³ Cow's milk (CM) and soy have been reported as the most common triggers, whereas solid food allergens not typically associated with food allergy, such as rice and vegetables, may also trigger FPIES.^{1,4} The first onset of symptoms typically occurs during infancy.¹ There is no definitive diagnostic test for FPIES apart from confirmation by observed oral food challenge (OFC). Diagnosis is more commonly made by recognition of a constellation of characteristic symptoms as described above.^{1,5} Advice given to families regarding food introduction and course of disease is primarily limited to retrospective chart reviews. Our typical advice is to avoid other common FPIES triggers until at least 1 to 2 years of age. If symptom free for at least 1 year, common FPIES triggers are challenged in clinic, introducing a characteristic food from each group with allowance for other foods in that group to be introduced at home (ie, if a CM challenge is passed in clinic, then soy may be introduced at home). We conducted a retrospective chart review to further characterize triggers, predisposing factors, symptoms, and management outcomes in an effort to better understand the natural history, common triggers, and more appropriate methods of food introduction in FPIES.

All patients referred to the Children's Medical Center Food Allergy Center (FAC) diagnosed with FPIES from September 1, 2009, to December 19, 2014, were identified using International Classification of Diseases, Ninth Revision Codes for Enterocolitis (558.9), Food Allergy (995.7), and FPIES (558.3). Search queries returned 852 records and a diagnosis of FPIES was confirmed by history in 39 patients. Demographic data, presenting symptoms, trigger food(s), predisposing factors, growth parameters, and OFC were collected and analyzed. Statistical analysis was performed using the χ^2 test and Mann-Whitney *U* test.

The average age of symptom onset was 5 months (1-12 months). Age at diagnosis was 12 months (1-48 months). All patients were born full-term except 1 patient born at 36 weeks estimated gestational age. All patients presented with a history of

vomiting. Other common symptoms included diarrhea (48.7%) and lethargy (59%) (Table I). Of the 39 patients, 14 required an emergency room visit or hospitalization for FPIES symptoms (Table I). The most common food triggers overall were rice (59%), oat (35.9%), CM (30.8%), and soy (12.8%). The most common first food to cause a reaction included rice (38.5%), CM (25.6%), and oat (15.4%). Patients with oat FPIES were unlikely to also have a CM trigger (Table II). Only 1 of 14 patients with oat FPIES also had a history of CM FPIES (this patient had negative skin testing to CM). Any patients with oat FPIES who had previously tolerated CM were instructed to continue ingesting CM. Of these, 4 were tolerating CM before an oats reaction, 2 had CM successfully introduced at 10 and 12 months of age after reacting to oats, and 3 patients tolerated CM at unknown age of introduction. If CM had not been previously introduced and avoidance of CM was not recommended, it was introduced as an observed OFC between ages 6 to 22 months depending on parental preference.

Most patients were breastfed (76.9% at any point in time, 43.6% at first clinic visit, 64.2% of patients with oat FPIES), vaginally delivered (59%), and had a family history of atopy (74.4%) with 46.2% having a history of atopy at presentation (Table I). Supplemental formula was advised for 15 patients (38.5%), the most common type ingested being elemental formula (23%) (Table I). IgE testing was completed for 7 patients (4 positive for milk IgE, 2 positive for egg IgE, and 1 positive for soy IgE). Most patients were between the 25th and 50th growth percentiles for weight and length at presentation. Growth parameters were not significantly changed at follow-up visits an average of 7.9 months after the first visit (0.25-39.5 months). The average age of recommended reintroduction of food triggers was 24 months (12-72 months). We performed 28 OFC (11 for trigger foods and 17 for nontrigger foods) in 16 patients at the FAC. All challenges were passed.

Most concerning from our data is delayed diagnosis. The average time from initial symptoms to diagnosis was 7.1 months (0-24 months), suggesting poor recognition of FPIES by primary care and emergency providers. More than one-third of patients sought emergency care, which underscores the importance of educating emergency providers about the diagnosis of FPIES.

In our cohort, rice, oat, and CM were the most common triggers. Less typical allergens (sweet potato, mango, banana, and avocado) also triggered reactions. Atopic history, family history of atopy, vaginal delivery, and breastfeeding are common among our patients with FPIES.

Our data demonstrate that patients with oat triggers were unlikely to also have a CM trigger. This relationship has not been explicitly explored previously. In another study, it was reported that 64% of patients with solid-food FPIES also had a history of CM and/or soy FPIES.⁶ In a 2013 review, Jarvinen and Nowak-Węgrzyn⁶ cited that approximately one-third of patients with CM or soy FPIES go on to develop solid-food FPIES. Our findings suggest that CM is likely tolerated by most children with oat FPIES; however, because many subjects were not challenged to milk before 1 year of age, it is possible that they may have already outgrown a milk FPIES reaction. We think this is unlikely because only 1 of the children who had independently introduced CM had

TABLE I. Demographics, clinical features of FPIES reactions, and pertinent past medical history

Demographics, presenting symptoms, and use of supplemental formula	N = 39 n (%)
Male	20 (51.3)
Vomiting	39 (100.0)
Diarrhea	19 (48.7)
Lethargy	23 (59.0)
Poor weight gain	3 (7.7)
Hypotension	2 (5.1)
ER visits/hospitalizations	14 (35.9)
History of atopy	18 (46.2)
Family history of atopy	29 (74.4)
Vaginal delivery (SVD)	23 (59.0)
Breast fed	30 (76.9)
Whole cow's milk protein infant formula	2 (5.1)
Partially hydrolyzed formula	1 (2.6)
Extensively hydrolyzed formula	6 (15.4)
Elemental formula	9 (23.1)
Advised to supplement with extensively hydrolyzed or elemental formula by FAC	15 (38.5)*

ER, Emergency room; FAC, food allergy center; FPIES, food protein-induced enterocolitis; SVD, spontaneous vaginal delivery.

*Some patients were switched from one type of formula to a different type during the time period of our review.

TABLE II. Patients with oat trigger vs without oat trigger: comparison of cow's milk triggers by parental history, family history of atopy, and provider's recommendation to avoid cow's milk

	Oat trigger (N = 14) n (%)	No oat trigger (N = 25) n (%)	P value
Cow's milk trigger	1 (7.1)	11 (44.0)	.02
Family history of atopy	13 (92.9)	16 (64.0)	.048
Cow's milk avoidance	4 (28.6)	18 (72.0)	<.01

a reaction. In US cohorts, patients reactive to oat are also typically reactive to rice, and 40%-50% of patients with grain FPIES react to 2 or more grains.^{7,8} Based on our data, OFC to CM may be considered during the first year of life in oat FPIES or other solid FPIES. Further studies will better characterize this relationship, management outcomes, growth patterns, and the development of IgE-mediated food allergies later in life. These studies are needed

to help establish additional guidelines and new management tools for food introduction in patients with FPIES.

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