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Food protein-induced enterocolitis syndrome (FPIES) after multiple tolerant ingestions

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Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy. Acute FPIES reactions involve repetitive emesis 1-4 hours after food trigger ingestion and may be associated with lethargy, diarrhea, dehydration, hypotension, and metabolic derangements. (1) Approximately 5-30% of patients with FPIES have specific IgE to the implicated food, termed atypical FPIES. (2) The pathophysiology of FPIES remains poorly understood; a cell-mediated mechanism has been postulated. The phenotype of patients with persistent FPIES has not been well-characterized but may involve multiple food triggers, atypical FPIES, seafood triggers, and/or more severe reactions.[1]

A small percentage of individuals with IgE-mediated food allergy may react on subsequent ingestion despite passing an oral food challenge (OFC). (3-5) Recurrent FPIES has also been reported to poultry, fish and egg on the first subsequent ingestion at home after a negative FPIES OFC. (6-8) Additionally, FPIES to one type of fish after tolerating that fish on two previous occasions in someone with FPIES to a different fish has been reported.(9) Here, we

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present five patients who developed FPIES after previously tolerating significant amounts of the implicated food proteins (1-5 g) on **many occasions** (Table 1). Cases 1 and 2 previously had FPIES, tolerated the food at a FPIES OFC, and developed recurrent FPIES after several asymptomatic ingestions. Cases 3-5 involve new FPIES reactions despite previous prolonged tolerance.

Case 1

A 5-year-old male with FPIES to oat, mango and green beans, as well as asthma, atopic dermatitis (AD) and rhinitis (no aeroallergen testing performed) first reacted to oat at age 6 months with 7-8 episodes of emesis and lethargy 2 hours after consuming oatmeal. He had avoided oat since this reaction and subsequently passed a FPIES oat OFC (5 g oat protein) at age 4 years. After the challenge, he consumed oat daily for 7 days. On day 8, he developed recurrent emesis and lethargy 2.5 hours after consuming oat, consistent with recurrent FPIES.

Case 2

A 6-year-old male with FPIES to milk, IgE-mediated food allergies, AD and allergic rhinitis developed vomiting and lethargy 1 hour after trying milk-based formula for the first time in infancy and again at 6 months of age after ingesting cow's milk yogurt. At 11 months of age, he was given 3 oz of cow's milk yogurt, which was tolerated every day for 2 months. Then he tried 8 oz of whole milk and developed recurrent emesis 1 hour after ingestion. At 2 years of age, the child tolerated 8 oz of cow's milk. He consumed a variety of dairy products daily for at least 6 months followed by pizza and 8 oz of milk with cereal at least once per week for several years. However, he returned to clinic at 6 years of age after he developed 2 episodes of large volume, projectile vomiting 2 hours after consuming pizza and 8 oz of milk, consistent with recurrent FPIES.

Case 3

An 18-year-old female with severe AD, FPIES to soy and multiple IgE-mediated food allergies with no prior poultry exposure passed an OFC to 3 oz of cooked turkey. She consumed turkey 4-5 times before returning 2 weeks later for an OFC to chicken. About 90 minutes after consuming a total of 3 oz of cooked chicken, she had repetitive emesis over 3 hours. CBC revealed leukocytosis (18.9×10^3) with neutrophilia (16.4×10^3). The diagnosis of FPIES was suspected. In retrospect, the patient recalled vomiting a couple hours after eating turkey 4 days before the chicken OFC. These two reactions were felt to be consistent with FPIES to poultry.

Case 4

A 9-month-old female with FPIES to cow's milk and AD tolerated 3.5 g peanut protein on six occasions since 8 months old and also tolerated scrambled egg on one occasion. 2 days since she last ate peanut, she had one scrambled egg with one tablespoon of peanut butter (~3.5 g peanut protein) and developed repetitive emesis 2 hours after ingestion. The patient subsequently re-tried peanut butter (2 g peanut protein) with repetitive emesis and lethargy

2 hours later. She tolerated scrambled egg (full serving) at 12 months old, consistent with FPIES to peanut.

Case 5

A 7-month-old male with AD presented after a reaction to peanut. Skin and serum IgE tests were positive for peanut but negative for cashew. Cashew was introduced within 1-2 weeks, and up to 1 tsp cashew butter was tolerated 12 times at home. At age 8 months, he developed multiple episodes of profuse, repetitive emesis with lethargy that occurred 2-4 hours after consuming 1 tsp cashew butter on 2 occasions, 3 days apart, concerning for FPIES to cashew. Almond, hazelnut, and walnut have since been introduced without issue.

Cases 1-2 demonstrate that it is possible for children to develop recurrent FPIES reactions to the same food after passing a FPIES challenge, despite continued, regular ingestion. Case 2 is particularly unusual as the child tolerated cow's milk for years prior to developing symptoms, albeit with decreasing regularity. Cases 3-5 suggest that children may develop FPIES despite multiple tolerant ingestions over a prolonged period, including 1 case in a teenager, and with lower-risk FPIES foods (peanut, tree nuts).

Development of FPIES after multiple tolerant ingestion is rare. We estimate <10 cases in 5 years at two large tertiary referral centers. Risk factors remain unclear, although all patients were highly atopic. Additionally, optimal challenge and home reintroduction practices remain to be defined. Dr. Sampson anecdotally reports 2 children with an increase in the post-challenge absolute neutrophil count despite tolerating the food during an FPIES challenge, who later reacted at home. The children later underwent repeat OFC, tolerated the food, and demonstrated no neutrophilia on post-OFC CBC. This may suggest that post-challenge neutrophilia (despite tolerating the food) could serve as a useful biomarker to predict recurrent reactions or incomplete resolution of FPIES, although further studies are needed to verify. Given the potential risk of recurrent FPIES symptoms after a passed challenge, although rare, it may be prudent to encourage families to maintain access to emergency medications, including anti-emetics (ondansetron), at home.

References

1. Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2017 Apr;139(4):1111–1126.e4. [PubMed: 28167094]
2. Nowak-Wegrzyn A, Berin MC, Mehr S. Food Protein-Induced Enterocolitis Syndrome. J Allergy Clin Immunol Pract. 2020 Jan;8(1):24–35. [PubMed: 31950904]
3. Bird JA, Leonard S, Groetch M, Assa'ad A, Cianferoni A, Clark A, et al. Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report. J Allergy Clin Immunol Pract. 2020 Jan;8(1):75–90.e17. [PubMed: 31950914]
4. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: Resolution and the possibility of recurrence. J Allergy Clin Immunol. 2003 Jul;112(1):183–9. [PubMed: 12847497]
5. Busse PJ, Nowak-Wegrzyn AH, Noone SA, Sampson HA, Sicherer SH. Recurrent peanut allergy. N Engl J Med. 2002 Nov 7;347(19):1535–6. [PubMed: 12421906]

6. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr. 1998 Aug;133(2):214–9. [PubMed: 9709708]
7. Miceli Sopo S, Fantacci C, Bersani G, Romano A, Monaco S. Loss of tolerance for fishes previously tolerated in children with fish food protein induced enterocolitis syndrome. Allergol Immunopathol . 2018 Jul;46(4):394–6.
8. Argiz L, Infante S, Machinena A, Pascal M, Echeverria L, Barni S, et al. Reactions on re-exposure following negative and inconclusive follow-up food challenges in children with acute FPIES. J Allergy Clin Immunol Pract. 2020 Oct;8(9):3228–3231.e3. [PubMed: 32534148]
9. Weisz G, Cross S, Grimshaw K, Erlewyn-Lajeunesse M. False tolerant food challenges in children with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract. 2021 Mar;9(3):1418.

Clinical implications:

We present five patients who developed FPIES to various foods despite multiple previous tolerant ingestions. Optimal challenge and home reintroduction practices remain to be defined, but post-challenge neutrophilia may be a biomarker to help identify at-risk patients.

Table 1

Summary of Cases

Case	Implicated food	Amount of implicated food previously tolerated	Previous FPIES diagnosis to implicated food	Skin Testing	Serum IgE Testing	Age of first reaction	Age of Recurrent Reaction	Sex	Comorbidities
1	Oat	5 g protein with subsequent daily ingestion x 7 days	Yes	-	-	6 months	5 years	M	FPIES to mango and green beans; atopic dermatitis; rhinitis
2	Cow's milk	4 years of regular consumption	Yes	-	Casein IgE 1.4 kU/L *; milk IgE 4.5 kU/L *	6 months	6 years	M	FPIES to milk; IgE-mediated food allergies; atopic dermatitis; allergic rhinitis
3	Turkey	3 ounces cooked x 4-5	No	-	Turkey IgE 0.36 kU/L *; Chicken IgE 0.66 kU/L *	18 years	-	F	FPIES to dairy; atopic dermatitis
4	Peanut	3.5 g protein x 6 days	No	Peanut – 0 mm ** Egg – 2 mm **	Peanut 0 kU/L **; Egg 0 kU/L **	9 months	-	F	FPIES to dairy; atopic dermatitis
5	Cashew	~1 g protein x 12 days	No	Cashew – 0 mm *,**	Cashew 0 kU/L *	8 months	-	M	IgE-mediated food allergy to egg, peanut, sesame and mustard; atopic dermatitis

* Testing performed prior to challenge

** Testing performed after reaction