Food protein-induced enterocolitis syndrome to peanut with early introduction: a clinical dilemma

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Clinical Implications

- Peanut is an infrequently described trigger of food protein-induced enterocolitis syndrome (FPIES) in infants. We report 3 cases of peanut-induced FPIES after guideline-recommended early introduction, suggesting that clinicians should be watchful for this previously rare event.

TO THE EDITOR:

The Learning Early About Peanut Allergy (LEAP) study and Addendum Guidelines for the Prevention of Peanut Allergy spurred a dramatic shift in the approach to peanut introduction in early childhood.[1,2] Recommendations now encourage peanut introduction to infants as early as 4 to 6 months to reduce the risk of developing peanut allergy. For high-risk infants, guidelines advise to strongly consider evaluation for peanut sensitization and, if necessary, oral food challenge (OFC) to assess if peanut may be introduced. The following cases exemplify infants who, on early introduction, had delayed reactions to peanut, consistent with food protein-induced enterocolitis syndrome (FPIES) (Table I).

Patient 1 was an 11-month-old male with moderate atopic dermatitis who previously had specific IgE (sIgE) and skin prick testing (SPT) at 6 months that showed sensitization to peanut, tree nuts, egg, and milk, none of which had been introduced. At 11 months, peanut testing showed SPT wheal 0 mm, sIgE 2.76 kU/L, and Ara h2 <0.10 kU/L. He underwent a 1 g OFC to peanut at 13 months with no initial symptoms, and later fell asleep. Approximately 1.5 hours after the last ingested dose, he awoke and had 3 episodes of emesis, the last episode concomitant with pallor and perioral cyanosis. Each episode was treated with intramuscular (IM) epinephrine, which did not curtail vomiting, but facial coloring improved after the third dose. He was transferred to the emergency department for ongoing observation and treated with intravenous (IV) fluids and methylprednisolone before discharge 5 hours later. Repeat SPT to peanut the next month remained negative. He had another OFC to 1 g peanut at 17 months that resulted in vomiting 2.5 hours later. He was treated with IV fluids, ondansetron, and methylprednisolone, with quick resolution of symptoms.

Patient 2 was a 6-month-old female with mild atopic dermatitis who tried peanut at home on multiple occasions. After initial peanut ingestion (<0.5 g), she experienced emesis and eczema exacerbation approximately 6 hours later. On 2 subsequent occasions of eating less than 0.5 g peanut protein, she had localized rash in typical eczema distribution and contact erythema around her mouth and neck. Peanut (1 g) ingested on a fourth occasion resulted in 4 episodes of emesis 2.5 hours after ingestion. Treatment with IM epinephrine did not appear effective, as she had 2 additional episodes of emesis accompanied by lethargy. Subsequent testing showed peanut SPT 3 mm, sIgE 1.88 kU/L, and Ara h2 1.90 kU/L. The patient was then challenged to 100 mg of peanut protein at 7 months and approximately 2.5 hours after ingestion, and had >10 episodes of emesis occurring every 5 to 10 minutes and increased fatigue. Diarrhea ensued 6 hours later.

Patient 3 was a 48-month-old female who initially introduced peanut at age 4 months. She ate peanut an unclear number of times before 9 months, when she experienced repetitive emesis with pallor and lethargy 4.5 hours after ingestion of peanut butter on 3 consecutive occasions. She was diagnosed with peanut-triggered FPIES (PN-FPIES) at another referral center, with peanut sIgE 4.10 kU/L at 13 months of age (SPT not performed). She strictly avoided peanut until 46 months of age, when repeat testing demonstrated sIgE 0.58 kU/L. The next month she was given peanut (>1 g) by her parent, and had repeated emesis and lethargy starting 4 hours after ingestion, lasting for approximately 5 hours, with resolution after rehydration at home.

FPIES is a non−IgE-mediated food allergy that is clinically diagnosed yet poorly understood. It typically manifests in the first year of life, frequently resolving in early childhood.[3] The hallmark feature of acute FPIES is repetitive emesis, often delayed 1 to 4 hours after ingestion of the offending food. Other clinical features include diarrhea, lethargy, pallor, cyanosis, hypotension, and hypothermia.[3] Symptom onset is often correlated with timing of food introduction.[3] Although cow's milk and soy are the most common triggers during food introduction in infants, FPIES can be triggered by solid foods traditionally thought to be of low allergenicity. These include grains (oat, rice, barley, also wheat), and less frequently, poultry and vegetables (sweet potato, white potato). FPIES to legumes (green beans, pea, string beans, peanut) has also been described.[4,5]

Few studies have addressed the prevalence of FPIES, which is likely underestimated in the United States and worldwide. PN-FPIES appears to be rare.[4,6-9] In a review of 462 US FPIES cases, only 1.9% had PN-FPIES,[6] and peanut was not mentioned as a causative food in a retrospective studies of 66 Italian FPIES cases[7] or 35 FPIES cases in Australia.[9] In the LEAP trial, 1 of 9 patients who discontinued peanut consumption did so because of PN-FPIES.[1] It is possible that PN-FPIES has been rarely reported because of previous practices of delayed peanut introduction and avoidance during a period of susceptibility. Whether the cases presented here represent increased incidence versus heightened awareness in our practice is uncertain, but, with early introduction, we hypothesize a greater occurrence of PN-FPIES.

Most patients in previous FPIES reports have had negative serum-IgE and SPT to triggering foods.[5-9] Interestingly, all 3 of the aforementioned infants with PN-FPIES had IgE sensitization

TABLE I. Clinical features of children with FPIES reactions to peanut

	1	2	3
Sex	M	F	F
Age at peanut introduction (mo)	13	5	4
Age at peanut reaction(mo)	13* 17*	6* 7*	9† 47†
Quantity of peanut ingested	1 g 1 g	1 g 100 mg	Unknown >1 g
Reaction symptoms	Repetitive emesis 1.5 h after ingestion, pallor, perioral cyanosis (13 mo) Emesis ×1 2.5 hours after ingestion (17 mo)	Repetitive emesis 2.5 h after ingestion, lethargy, diarrhea	Repetitive emesis 4.5 h after ingestion, pallor, lethargy
Age at testing (mo)	11 14	6	13 46
SPT (wheal, mm)	0 (11 mo) 0 (14 mo)	3	N/A
sIgE peanut (kU/L) (age)	4.61 (6 mo) 2.76 (11 mo) 2.37 (14 mo)	1.88 (6 mo)	4.10 (13 mo) 0.58 (46 mo)
Peanut component testing (kU/L)			
Ara h 1	0.39 (11 mo)/0.86 (14 mo)	<0.10	–
Ara h 2	<0.10/<0.10	1.90	–
Ara h 3	0.16/0.44	<0.10	–
Ara h 8	<0.10/<0.10	<0.10	–
Ara h 9	<0.10/<0.10	<0.10	–
Comorbidities	Atopic dermatitis, wheeze, feeding aversion	Atopic dermatitis	Atopic dermatitis
Known IgE reaction or sensitivity to other foods	Reaction to sesame (SPT 10 mm, sIgE 4.36) No history of ingestion but sensitization (SPT, sIgE) to cow's milk, egg, cashew, almond	N/A	N/A
Other known FPIES triggers	None	None	None
Milk source	Exclusively breastfed for first 12 mo	Exclusively breastfed	Breastfed (infancy) + Cow's milk

FPIES, Food protein-induced enterocolitis syndrome; *OFC*, oral food challenge; *SPT*, skin prick testing.
*OFC.
†Historical data.

to peanut, which presents unique concerns. Peanut exposure during infancy is hypothesized to prevent the development of IgE-mediated peanut allergy in some children, but may not be possible in children with PN-FPIES. It remains unclear whether PN-FPIES follows the same clinical course as FPIES to other foods, where IgE sensitivity is associated with the risk of persistent disease.[3]

Providers who perform peanut OFCs in infants to rule out IgE-mediated allergy should be aware of possible FPIES reactions. Families should also be educated on signs and symptoms of a delayed presentation after the OFC and with subsequent exposures to peanut at home. FPIES reactions may not occur until second, third, or subsequent feedings. Timing of rechallenge should be carefully considered in infants who require complete peanut avoidance due to FPIES. Updated skin and sIgE testing will help practitioners be prepared for immediate reactions. It remains to be seen if larger numbers of infants undergoing peanut challenges will lead to increased identification of PN-FPIES.

Further study is necessary to determine whether conditions such as atopic dermatitis, sensitization to peanut and/or other foods, or other factors are predictors for the risk of PN-FPIES. Understanding early mechanisms of tolerance may help clarify how IgE sensitivity and FPIES develop at an early age. Future research could investigate if infants with FPIES and IgE sensitization go on to develop IgE-mediated reactivity to peanut, and if there is any role for novel forms of immunotherapy that bypass the GI tract (ie, epicutaneous). Moving forward, it will be important to identify incidence of PN-FPIES among infants, closely monitor for these delayed reactions, and develop cohesive counseling recommendations and guidelines.

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