

Food-dependent exercise-induced anaphylaxis to soybean

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Clinical Implications

- Food-dependent exercise-induced anaphylaxis (FDEIA) triggered by soybean is a rare and challenging diagnosis due to the ubiquity of soy in processed foods and relative insensitivity of commercial extracts. If the history is suggestive of FDEIA, an examination of secondary soy ingredients may be useful.

TO THE EDITOR:

Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare (estimated prevalence of 0.02%) but likely underreported cause of anaphylaxis.¹ Patients have no difficulty eating the triggering food alone but can experience severe reactions if followed by exercise. Wheat is the most common food trigger of FDEIA with nuts, grains, and shellfish also implicated.¹ Soybean-induced FDEIA is a rare and challenging diagnosis. Previous case reports suggest that soybean may be tolerated in some forms but not others,² or hidden in processed foods such as canned tuna.³ To complicate matters further, soy commercial extracts for skin prick testing significantly vary between suppliers⁴ and are relatively insensitive predictors of clinical reactivity.⁵

We present a case of a 13-year-old boy with allergic rhinitis and peanut allergy who presented with 3 severe reactions over a 2-year period. All 3 episodes occurred after eating a school cafeteria-prepared lunch and playing basketball almost immediately afterward for 20 to 30 minutes as was his normal routine. On each occasion, symptoms of shortness of breath, wheezing, facial swelling, flushing, waist-line erythema, and pruritus occurred that resolved within minutes of epinephrine, diphenhydramine, and albuterol administration given at school.

Patients with FDEIA should demonstrate sensitization to the culprit food by either skin prick testing, specific IgE testing, or both.¹ This patient reported eating a breaded chicken patty, breaded chicken nuggets, and breaded popcorn shrimp respectively before each episode. Skin prick and specific IgE testing were performed to identify potential food triggers (Table 1). Chicken and shrimp were tested as these were the main ingredients in the reported foods eaten before reacting. Egg was tested because he had a history of egg allergy that he had outgrown. Wheat was tested because all 3 episodes involved food that was breaded, and wheat is the most common FDEIA trigger. After skin testing, we performed separate challenges in which the patient ate large amounts (2-3 servings) of each food (chicken, shrimp, egg, and wheat) after aspirin pretreatment (10 mg/kg), followed by strenuous exercise to maximize test sensitivity.^{1,6,7}

After demonstrating negative challenges to these foods, we investigated secondary ingredients in the processed foods served in the school cafeteria. An examination of ingredients in the

particular breaded chicken patty and chicken nuggets served revealed soy as the third ingredient, whereas the breaded shrimp had soy as a minor (contains less than 2%) ingredient (Figure 1). We therefore investigated the possibility that these reactions were caused by soy, a food that he had previously eaten many times without incident.

Skin prick testing to commercial soy (GREER) was negative with a wheal of 2×2 , but puddle testing to edamame was positive with a wheal of 11×10 . In puddle testing, the food is homogenized in a small slurry of sterile saline and the applicator is dipped in this mixture. Puddle testing was used in this situation given the potential to miss layers or ingredients when lancing the food directly in prick-to-prick testing. Although direct testing of processed foods, such as with puddle testing, is not validated and can cause irritant reactions, the most recent food allergy practice parameters maintain that puddle testing can be used when commercial testing is not available or is relatively insensitive such as to fruits and vegetables.⁸ The discrepancy between testing of commercial soy and fresh edamame in our case is consistent with previous reports suggesting that commercial extracts for soy significantly vary between suppliers⁴ and are relatively insensitive predictors of clinical reactivity. In a multicenter double-blind placebo-controlled study, prick-to-prick testing with soybean flour was found to be superior to commercial soy extract in predicting clinical reactivity.⁵ We also puddle tested 2 processed breaded chicken products and found that the patient exhibited skin prick test reactivity to a chicken patty but not to a chicken nugget preparation (Table 1). The only notable ingredient contained in the chicken patty and not the nuggets was soy.

A soy challenge with edamame performed as described above resulted in more severe swelling and hives (compared with his previous reactions) during exercise. Although he had exhibited a negative methacholine challenge during the evaluation, the patient demonstrated a significant decline in forced expiratory volume in 1 second to 61% predicted that increased after epinephrine administration and nebulized albuterol treatment to 86% predicted. Laboratory tests drawn immediately after the reaction demonstrated an increased tryptase level from 2.76 at baseline to 14.7 mcg/L, and a 24-hour urinary leukotriene E₄ collected after his reaction was elevated at 219 pg/mg creatinine (normal < 104 pg/mg). An elevated tryptase level is an important feature distinguishing FDEIA from food allergy-induced anaphylaxis where levels typically do not change after reactions.⁹ Specific IgE testing was negative for soy Gly m 4, but positive to components Gly m 5 (8.41 kUA/L) and Gly m 6 (6.95 kUA/L), which have been associated with severe soy-induced anaphylaxis (Table 1).¹⁰

This case highlights some of the difficulties in identifying soy in processed foods as a trigger for FDEIA. If there is a high index of suspicion for FDEIA based on history of exercise-induced anaphylaxis soon after eating, the identification of a consistent food trigger may not be apparent without a direct examination of ingredients in the foods eaten. After major food ingredients have been ruled out, a close examination of secondary ingredients such as soy found ubiquitously in processed foods is warranted. Even the relatively small amount of soy found in many processed foods can trigger anaphylaxis as occurred, in this patient, after eating a

TABLE I. Food allergy testing

	Skin prick test (wheal)	Specific IgE (kUA/L)
Saline (negative control)	Negative	
Histamine (positive control)	5 × 4	
Peanut	38 × 15	93.10
Egg white	25 × 5	1.58
Chicken	3 × 2	<0.35
Shrimp	5 × 3	<0.35
Wheat	Negative	1.89
Soybean commercial	2 × 2	9.33
Soybean pudding (edamame)	11 × 10	
Soybean component Gly m 4		<0.35
Soybean component Gly m 5		8.41
Soybean component Gly m 6		6.95
Chicken pudding (breaded patty) <i>contains soybean</i>	10 × 7	
Chicken pudding (breaded nuggets) <i>does not contain soybean</i>	Negative	

Chicken Nuggets	Chicken Pattie	Popcorn Shrimp
Chicken Breast With Rib Meat, Water, Isolated Soy Protein, Textured Soy Protein Concentrate, Sugar, Sea Salt . . .	Chicken Breast with Rib Meat, Water, Soy Protein Concentrate, Isolated Soy Protein, Salt, Sodium . . .	Shrimp, Bleached Wheat Flour, Vegetable Oil (Contains One Or More Of The Following: Soybean Oil, Water, Wheat Flour, Contains 2% Or Less Of: Modified Corn Starch, Yellow Corn Flour, Salt, Partially Hydrogenated Soybean Oil, Soy Flour, Spices . . .
Contains: Soy, Wheat	Contains: Wheat, Soy	Contains: Shrimp, Wheat, Milk, Soy, Egg

FIGURE 1. Partial ingredient lists for the 3 implicated foods in our patient's reactions. All soy containing ingredients are included and highlighted.

breaded shrimp product containing soy as a minor ingredient. Skin prick testing for the suspected food should be performed with commercial extracts followed by pudding or prick-to-prick testing if negative especially if screening for soy-induced FDEIA as this may be missed with commercial soy extracts.

At this time, avoidance is the cornerstone of FDEIA management, and evidence for preventative therapy is currently only based on small case series.¹ Therefore, we advised our patient to carry an epinephrine autoinjector, not to exercise alone, and to avoid soy ingestion for at least 4 hours before exercise or when taking nonsteroidal anti-inflammatory drugs. As our patient was an avid athlete, he opted to eliminate soy from his diet entirely and continued to exercise daily several months later without any further reactions.

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REFERENCES

1. Feldweg AM. Food-dependent, exercise-induced anaphylaxis: diagnosis and management in the outpatient setting. *J Allergy Clin Immunol Pract* 2017;5:283-8.
2. Adachi A, Horikawa T, Shimizu H, Sarayama Y, Ogawa T, Sjolander S, et al. Soybean beta-conglycinin as the main allergen in a patient with food-dependent exercise-induced anaphylaxis by tofu: food processing alters pepsin resistance. *Clin Exp Allergy* 2009;39:167-73.
3. Navratil M, Pavic I, Pastar Z, Caleta D. Exercise-induced anaphylaxis after ingestion of sandwich with soy containing canned tuna: case report. *Acta Dermatovenol Croat* 2011;19:176-9.
4. Herian AM, Bush RK, Taylor SL. Protein and allergen content of commercial skin test extracts for soybeans. *Clin Exp Allergy* 1992;22:461-8.
5. Ballmer-Weber BK, Holzhauser T, Scibilia J, Mittag D, Zisa G, Ortolani C, et al. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 2007;119:1489-96.
6. Asaumi T, Yanagida N, Sato S, Shukuya A, Nishino M, Ebisawa M. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *Pediatr Allergy Immunol* 2016;27:44-9.
7. Motomura C, Matsuzaki H, Ono R, Iwata M, Okabe K, Akamine Y, et al. Aspirin is an enhancing factor for food-dependent exercise-induced anaphylaxis in children. *Clin Exp Allergy* 2017;47:1497-500.
8. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134:1016-1025.e43.
9. Oyefara BI, Bahna SL. Delayed food-dependent, exercise-induced anaphylaxis. *Allergy Asthma Proc* 2007;28:64-6.
10. Holzhauser T, Wackermann O, Ballmer-Weber BK, Bindslev-Jensen C, Scibilia J, Perono-Garoffo L, et al. Soybean (Glycine max) allergy in Europe: Gly m 5 (beta-conglycinin) and Gly m 6 (glycinin) are potential diagnostic markers for severe allergic reactions to soy. *J Allergy Clin Immunol* 2009;123:452-8.