

Clinical Communications

Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults

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Clinical Implications

- A distinct syndrome of acute non-IgE-mediated food hypersensitivity, which manifests with isolated gastrointestinal symptoms, has been observed to occur in the adult population. This has some features in common with infantile food protein-induced enterocolitis syndrome, but in adults, it is an acquired condition.
- Features include predominant sensitivity to seafood or egg and a female preponderance.

TO THE EDITOR:

We report a series of adult patients who presented with reproducible acute food-specific reactions manifested purely by gastrointestinal symptoms. Tests for food-specific IgE were negative. These reactions have some features in common with infantile food protein-induced enterocolitis syndrome (FPIES), a non-IgE-mediated gastrointestinal food hypersensitivity syndrome that is well described in the pediatric literature.^{1,2} One similar case has been reported in an adult.³ We report here our observations on the clinical phenotype and demographics of non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adult patients.

We identified consecutive patients who presented to an outpatient private practice between 2006 and 2013 with the following features of food hypersensitivity:

- Acute severe abdominal pain, repetitive vomiting, and/or diarrhea
- Reproducible on ingestion of specific foods on at least 2 separate occasions
- Symptoms isolated to the gastrointestinal tract with the absence of cutaneous, respiratory, or cardiovascular signs or symptoms of allergy
- Symptom resolution with avoidance of incriminated food
- Absence of food-specific IgE on skin prick tests and/or serology
- No other cause for symptoms identified
- Age $\geq$ 18 years

Data on demographics and clinical features were extracted from review of clinical records. This study was approved by our human research ethics committee. Thirty-one patients were identified. A female predominance was noted (24 women vs 7 men; ratio, 3.4:1). The median age of symptom onset was 29 years (interquartile range, 22-45.8 years), and presentation to our clinic for assessment was delayed by a median of 3 years (interquartile range, 1-19.3 years) (Table I). The median number of episodes was 2 (interquartile range, 2-2); 83.9% reported hypersensitivity to single food items with seafood the most

TABLE I. Patient demographics and summary of clinical presentation of adult non-IgE-mediated gastrointestinal food hypersensitivity (n = 31)

Sex, no. (%)	
Women	24 (77.4)
Men	7 (22.6)
Age, median (interquartile range) (y)	
Age of symptom onset	29 (22-45.8)
Age at presentation	47 (30.5-57.5)
Delay to presentation	3 (1-19.3)
Implicated food, no. (%)	
Single food item	26 (83.9)
Two food items	4 (12.9)
Three food items	1 (3.2)
Symptoms, no. (%)	
Abdominal pain	24 (77.4)
Vomiting	22 (71.0)
Diarrhea	18 (58.1)
Timing, median (interquartile range) (min)	
Onset time of symptoms	60 (52.5-120)
Duration of symptoms	120 (60-225)
Atopy (positive SPT), no. (%)	
Incriminated food	
Yes	0
No	28 (90.3)
Not done	3 (9.7)
Aeroallergens	
Yes	11 (35.5)
No	8 (25.8)
Not done	12 (38.7)
Atopy (clinical), no. (%)	
Allergic rhinitis	12 (38.7)
Asthma	6 (19.4)
Eczema	1 (3.2)
No atopic disease	15 (48.4)

SPT, Skin prick test.

commonly implicated (crustaceans, mollusks, or fish) followed by egg (Figure 1). Abdominal pain was the most common symptom, which occurred in 77.4% of our patients; 71.0% and 58.1% had vomiting and diarrhea, respectively. The median time to symptom onset after food ingestion was 60 minutes (interquartile range, 52.5-120 minutes) with variable duration of symptoms, median 120 minutes (interquartile range, 60-225 minutes). More than half of the patients had concomitant allergic diseases, with 38.7% who reported allergic rhinitis, 19.4% asthma, and 3.2% eczema. Individual case details are available in the Online Repository (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In 2 cases, symptoms were severe and led to emergency department attendance where treatment with opioid analgesics and/or fluid resuscitation was necessary. Patients frequently attributed their symptoms to food poisoning initially, but dining companions did not have reactions, and subsequent recurrent

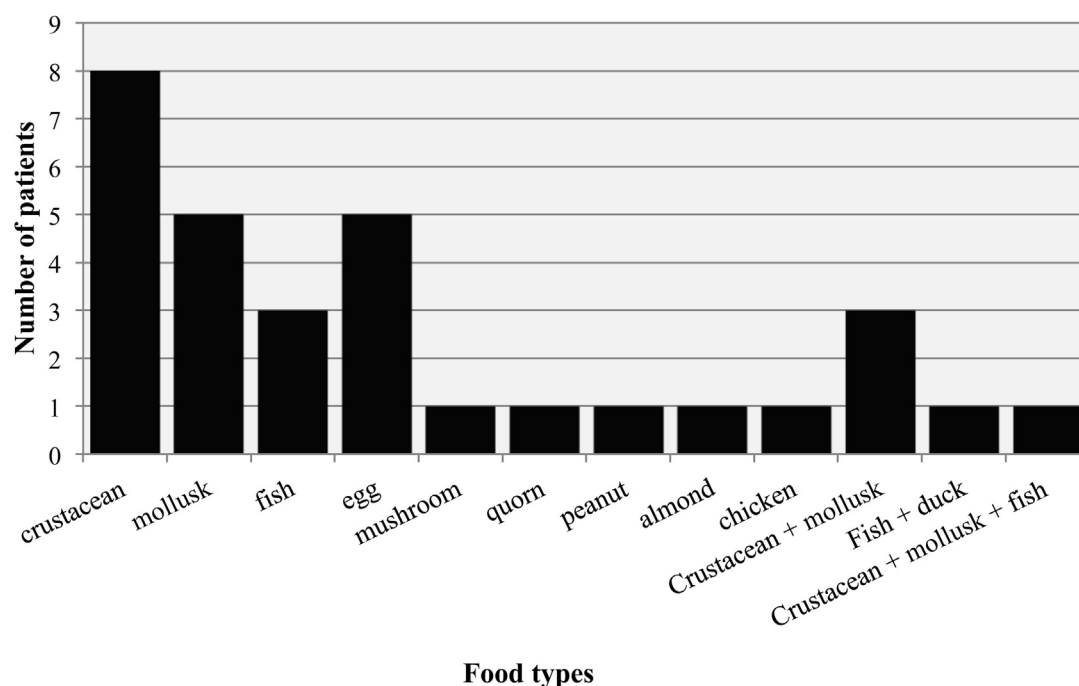


FIGURE 1. Foods reported to cause symptoms of non-IgE-mediated gastrointestinal food hypersensitivity in adults.

episodes confirmed linkage to specific foods. Many patients were referred for suspicion of IgE-mediated food allergy because severe acute reactions led to fear of anaphylaxis. Although gastrointestinal symptoms can occur in anaphylaxis, none of our patients progressed from pure gastrointestinal reactions to systemic allergy. We did not observe resolution of food-specific gastrointestinal hypersensitivity because patients continued to avoid the responsible foods. However, several patients had long histories, with reactions that occurred at up to 30-year intervals, some through accidental self-challenge.

Infantile FPIES is characterized by acute vomiting, diarrhea, and/or abdominal colic in the absence of other systemic manifestations of allergy, within 24 hours of food ingestion.^{1,2} It usually occurs in early infancy (1-3 months) but may have a delayed onset up to 9 months of age with introduction of solid food or when introduction of cow's milk or soy protein is delayed. Acute presentation may be accompanied by neutrophilia and thrombocytosis, blood in stools, and, in severe cases, metabolic acidosis and hypotension (15%-20% of cases). Chronic cases may present with bloody diarrhea and failure to thrive.

Although the clinical presentation of gastrointestinal food hypersensitivity syndrome in the adult patients we describe is similar (symptom type, time of onset, duration), based on our observations, there are differences between pediatric FPIES and adult gastrointestinal food hypersensitivity. With infants, there is a male preponderance.^{1,2} Unlike infants with FPIES, none of our adult patients presented in a chronic manner; in infants, there is often a delay in recognition,⁴ whereas adults usually recognize triggers promptly and cease ingestion. Cow's milk protein and soy protein is the most common cause of infant FPIES of children younger than 6 months old, but rice is the most common cause of solid food FPIES in children.⁵ In contrast, seafood and egg were more frequently implicated in our patients. The natural history is different; adult gastrointestinal food hypersensitivity is

acquired after previous tolerance and seems to be persistent (in some cases over many years), whereas infantile FPIES usually occurs on food introduction and tends to resolve by 3 years of age. Notably, these differences in natural history patterns are analogous to those which occur in IgE-mediated food allergy.

It has been postulated that the underlying mechanism of FPIES involves T-cell-mediated release of inflammatory cytokines such as TNF- α and an attenuated TGF- β 1 response, which results in increased intestinal permeability, malabsorption, and dysmotility.^{6,7} Indirect evidence from a previously published study on the histopathology of gut biopsy specimens in adults with gastrointestinal food allergy (food-specific IgE was not present in 11/14 patients in this study) suggests that a localized gut IgE-mediated mechanism (gut entopy) may be responsible.⁸

Our study is limited by its retrospective nature, which leads to potential recall bias when recording disease onset, number and frequency of episodes, symptom latency, severity, and duration. Importantly, we have not yet been able to carry out the criterion standard, double-blind placebo-controlled food challenge because the history was considered sufficient for a diagnosis, and most patients declined challenge due to fear of reactions. Practical aspects of designing challenges in the outpatient setting, including double blinding, dose grading, and period and closeness of observation are problematic. One patient underwent open challenge with almond (because, although skin prick tests were negative, there was concern about the risk of anaphylaxis), and gastrointestinal symptoms were reproduced. In children, clinical diagnosis is acceptable, and oral food challenges are recommended only in ambiguous cases or to assess for food reintroduction. We contend that, even in the absence of double-blind placebo-controlled food challenge, the clinical presentation of our patients (acute severe symptoms, food specificity and reproducibility, symptom-free with specific food avoidance) is distinct from other entities such as food toxin poisoning; irritable

bowel syndrome; gluten, lactose, or fructose intolerance; or inflammatory bowel disease.

In summary, non-IgE-mediated acute gastrointestinal food hypersensitivity with similarities to infantile FPIES may occur in the adult population. Further studies, including food challenge, are required to confirm these observations and delineate the epidemiology, mechanism, and natural history of this condition.

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REFERENCES

1. Jarvinen KM, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. *J Allergy Clin Immunol Pract* 2013;1:317-22.
2. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013;1:343-9.
3. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. *J Allergy Clin Immunol* 2012;130:1199-200.
4. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol* 2011;127:647-53.
5. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics* 2009;123:459-64.
6. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor β 1, transforming growth factor type I and II receptors, and TNF α in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2002;109:150-4.
7. Caubet JC, Nowak-Węgrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Expert Rev Clin Immunol* 2011;7:317-27.
8. Lin XP, Magnusson J, Ahlstedt S, Dahlman-Hoglund A, Lanson LA, Magnusson O, et al. Local allergic reaction in food-hypersensitive adults despite a lack of systemic food-specific IgE. *J Allergy Clin Immunol* 2002;109:879-87.

TABLE E1. Details of adult patients with non-IgE mediated gastrointestinal food hypersensitivities

No.	Age of presentation (yrs)	Sex	Age of symptom onset (yrs)	Implicated food	Time of symptom onset (mins)	Duration of symptoms (mins)	Number of episodes	Symptoms during event	Previously tolerated food	Other food allergies	SPT to implicated food	Other atopic conditions
1	21	F	19	Crustacean (prawn)	30	NR	2	AP, D, V	Yes	No	Negative	AR
2	21	M	20	Egg	30	NR	2	AP, D	Yes	No	Negative	AR
3	21	F	21	Mollusk (abalone)	60	360	2	AP, D, V	Yes	No	Abalone extract NA; negative to oyster and squid	None
4	24	F	NR	Crustacean	NR	NR	2	AP, D, V	Yes	No	Negative	AR
5	26	F	12	Chicken	60	2880	3	AP, D, V	Yes	No	Negative	None
6	28	F	NR	Egg	120-180 (estimated)	15	2	AP, D	Yes	No	Negative	None
7	29	F	27	Mollusk (oyster)	120	120	3	D, V	Yes	No	Negative	AR
8	30	M	28	Fish	15-30 (estimated)	120	2	A, V	Yes	No	Negative	AR
9	31	F	NR	Mollusk (oyster)	NR	NR	4	AP	Yes	No	Negative	AR, A
10	31	F	30	Egg	60	60	2	AP, D, V	Yes	No	Negative	A
11	39	F	18	Crustacean (prawn)	NR	Unwell 1 week	2	V	Yes	No	Negative	A
12	40	F	40	Crustacean (prawn)	60	60	2	AP, V	Yes	No	Negative	None
13	40	F	39	Mollusk (calamari)	90	10	2	V	Yes	No	Negative	AR
14	42	F	NR	Crustacean, Mollusk (oyster, mussel)	10	60	2	AP, D	Yes	No	Not done	A
15	46	F	46	Almond	20	120	2	AP, D	Yes	No	Negative	None
16	47	F	NR	Crustacean (prawn), Mollusk (mussel)	120	180	2	AP, V	Yes	No	Negative	AR
17	48	M	28	Fish	NR	120	3	AP, V	Yes	No	Negative	E
18	49	F	NR	Crustacean (prawn)	NR	NR	2	AP, V	Yes	No	Negative	None
19	53	M	33	Crustacean (prawn), Mollusk (scallop)	240	1440	2	AP, V	Yes	No	Negative	AR, A
20	53	F	53	Mollusk (calamari)	60	360	2	AP, D	Yes	No	Negative	AR
21	54	F	25	Egg	120	NR	2	AP, D	Yes	No	Negative	None
22	55	M	53	Quorn	10	NR	2	AP, D	Yes	No	Negative	None
23	57	M	53	Mushroom	180	120	2	D, V	Yes	No	Negative	None
24	58	F	NR	Egg	NR	NR	2	AP, D	Yes	Yes (crab)	Negative	AR, A
25	59	F	NR	Peanut	180	NR	2	D, V	Yes	No	Negative	None
26	60	F	45	Fish (salmon)	60	NR	4	AP, V	Yes	No	Negative	AR
27	62	F	25	Crustacean (prawn)	120-180 (estimated)	NR	2	AP, D, V	Yes	No	Negative	None
28	65	F	50	Crustacean (prawn), Mollusk (oyster), Fish (anchovy)	NR	NR	4	V	Yes	No	Negative	None
29	66	M	16	Crustacean (prawn)	120	120	6	AP, D, V	Yes	No	Negative	None
30	73	F	56	Fish, Duck	120	NR	2	AP, V	Yes	No	Negative	None
31	79	F	NR	Crustacean (crab)	NR	NR	2	V	Yes	No	Not done	None

NR, Not recorded; NA, not available; AP, abdominal pain; D, diarrhea; V, vomiting; AR, allergic rhinitis; A, asthma; E, eczema.