

Food protein-induced enterocolitis syndrome – not only due to cow's milk and soy

Levy Y, Danon YL. Food protein-induced enterocolitis syndrome – not only due to cow's milk and soy.

Pediatr Allergy Immunol 2003; 14: 325–329. © 2003 Blackwell Munksgaard

Over a of 7-year period, six patients (four males, two females aged 3–12 months) were diagnosed with food protein-induced enterocolitis syndrome (FPIES) triggered by foods other than cow's milk and soy: chicken in four, turkey in two, peas in one, and lentils in one (five patients reacted to more than one food type). All reactions developed within 2 h of ingestion of the allergenic food. To exclude other conditions with similar clinical symptoms, three infants underwent work-up for sepsis, one infant underwent work-up to exclude metabolic defects, and one underwent a barium enema to rule out intussusception. All were negative. Pediatricians should be aware that FPIES may be caused by foods other than cow's milk and soy, mainly chicken, turkey and foods from the legume family, and that it may present also in infants older than 6 months.

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Key words: food allergy; enterocolitis; cow's milk; soy; chicken; turkey; peas; lentils

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Accepted 18 December 2002

Food protein-induced enterocolitis syndrome (FPIES) is a symptom complex of severe vomiting and diarrhea caused by non-IgE-mediated food allergy. Symptoms typically begin in early infancy and, when severe, may lead to lethargy, dehydration, hypotension, and metabolic acidosis (1, 2). The main allergenic foods are cow's milk and soybean (3–5). Very rarely have other foods, such as chicken, turkey, peas or rice, been described as allergens in this syndrome (1, 2, 6, 7).

In the present study, we describe our experience with patients in whom FPIES was caused by foods other than cow's milk and soy; their relatively older age is stressed as well.

Patients and methods

The files of the Allergy Clinic at Schneider Children's Medical Center of Israel from 1995 to 2001 were reviewed for all patients with a diagnosis of enterocolitis syndrome caused by foods other than cow's milk and soy. Six patients (four males and two females) aged 3–12 months were identified.

The patients were referred initially by their primary physician, a pediatric gastroenterologist, or the hospital's inpatient departments. The medical files of the inpatient departments and emergency departments were reviewed. The patients underwent a detailed clinical and nutritional history, physical examination, and commercial skin prick tests for food allergens (cow's milk, soy, egg, wheat, sesame, fish, peanuts, and any other food suspected by the clinical history), with saline and histamine 1 mg/ml as the negative and positive controls, respectively (Center Laboratories Inc., ALK-Abelló Company, Port Washington, NY, USA). The skin test results were considered positive if the wheal diameter was 3 mm greater than the negative control. Specific IgE antibodies against food allergens were measured using the AlaSTAT method (DPC, Los Angeles, CA, USA). An oral food challenge was performed in one patient according to the protocol described in the literature (1, 3): an intravenous (i.v.) line was inserted, and the food was given in an open challenge in increasing amounts over 2 h, to a total of 0.6 g/kg body weight of protein.

Table 1. Clinical features of patients with food protein-induced enterocolitis syndrome

Patient no.	Sex	Allergenic food	Age at reaction	Symptoms	Time to onset (h)	Skin tests	Specific IgE antibodies	Follow-up
1	M	Soy	4 weeks	Vomiting, diarrhea lethargy, dehydration, metabolic acidosis, methemoglobinemia	2	All negative	All negative	7.5 years old, still reacts to accidentally ingested soy. Does not eat peas, turkey.
		Soy	5 weeks*	Vomiting, pallor, lethargy	2			
		Pea	8 months	Vomiting, pallor, lethargy, diarrhea	2			
		Turkey	11 months	Vomiting, pallor, lethargy	2			
2	M	Chicken	3 months†	Vomiting, diarrhea, hypotension	2	All negative	All negative	5 years old, eats chicken since age 3 years.
3	F	Milk	3 weeks	Vomiting	2	Positive only to milk	Negative to soy and chicken	2 years old, does not eat soy, milk or chicken.
		Soy	2 months	Vomiting	2			
		Chicken	4.5 months	Vomiting, pallor, lethargy	2			
		Chicken	12 months‡	Vomiting, lethargy, dehydration, bloody diarrhea	2			
4	M	Milk	7 months	Vomiting, pallor, lethargy, bloody diarrhea, dehydration	4	All negative	ND	18 months old, eats soy.
		Lentils	8 months	Vomiting, pallor, lethargy	2			
5	M	Turkey	6 months	Vomiting	2	All negative	ND	3 years old, does not eat chicken and turkey.
		Chicken	12 months	Vomiting, pallor, dehydration	2			
6	F	Milk	3 months	Vomiting, pallor, lethargy	2	Positive only to milk	ND	2 years old, eats soy, does not eat milk or chicken.
		Chicken	7 months	Vomiting, pallor, lethargy	2			
		Chicken	8 months§	Vomiting, pallor, lethargy	2			
		Chicken	12 months§	Vomiting, pallor, lethargy	2			

*Accidental ingestion; †re-exposure during i.v. hyperalimentation due to protracted diarrhea; ‡oral challenge at hospital; §home trials. ND = not done.

Patients were followed on a yearly basis or as necessary.

Results

The clinical features of the patients are summarized in Table 1. The clinical histories are presented in detail to illustrate several important points.

Patient 1

This male infant was admitted to the pediatric intensive care unit at age 4 weeks because of an acute episode of vomiting, diarrhea, hypernatremic dehydration, metabolic acidosis and methemoglobinemia, starting 2 h after soy formula ingestion. Past medical history showed an uneventful pregnancy and delivery; birth weight was 3530 g, and there were no perinatal complications. The child was initially fed humanized milk formula, which was changed to soy-based formula at age 1 week because of constipation. On admission, sepsis work-up was negative. Treatment consisted of full-fluid resuscitation. The patient was discharged in good condition

after 3 days, with the recommendation to continue feeding with humanized milk formula.

Thereafter the patient was readmitted several times for a similar clinical picture: at age 5 weeks, accidental ingestion of soy-based formula caused recurrent vomiting and apathy, and at age 8 months, the first-time ingestion of soup containing peas, water and salt caused recurrent vomiting, pallor, apathy and later diarrhea. Both episodes were treated using i.v. fluids. On follow-up, growth and development were normal, and he was able to eat cereals, eggs, other vegetables and chicken without any adverse effects. However, at age 11 months, ingestion of turkey meat induced the same clinical picture of recurrent vomiting, apathy and pallor. The patient was admitted for i.v. fluids and a work-up to exclude metabolic defects such as hyperammonemia and urea cycle enzyme defects, which are associated with similar symptoms. The results were negative.

Oral challenge with a peanut snack performed at age 2 years was negative.

Currently, at age 7.5 years, the patient still reacts to soy-containing foods, such as vegetarian

sausages (accidental ingestion) with recurrent vomiting, pallor and apathy, for which he must receive i.v. fluids for several hours. Repeated skin prick tests and blood tests for specific IgE antibodies to soy were negative. He has not been exposed again to peas or turkey.

Patient 2

This male infant was admitted at age 3 weeks because of diarrhea. Past medical history showed an uneventful pregnancy and delivery; birth weight was 3180 g, and there were no perinatal complications. He was breast-fed with humanized milk formula supplement. Sepsis work-up was negative. The diarrhea continued despite Nutramigen nutrition and persisted over the following 6 months, during which time the patient received hyperalimentation through a central line. Infectious, immunological and metabolic work-ups were all negative, and a gastroscopy and a colonoscopy revealed no abnormalities.

Several attempts at oral nutrition besides Nutramigen, including mashed chicken meat, were unsuccessful. At age 3 months, re-exposure to 50 g mashed chicken meat led to recurrent vomiting, diarrhea and hypotension, and the patient had to be resuscitated with oxygen and i.v. fluids.

At 1 year of age, the condition improved, and the patient was able to eat Nutramigen with cereals and gradually, vegetables and fruits. Since age 2 years, he has ingested cow's milk, eggs and peanut butter. Oral challenge with chicken performed at age 3 years in another hospital was negative. Currently, at age 5 years, he is able to ingest a varied diet, including chicken, without any adverse events.

Patient 3

This female infant presented at age 3 weeks with recurrent vomiting after ingesting humanized milk formula for the first time. Before that she had been exclusively breast-fed. Past medical history revealed an uneventful pregnancy and delivery by cesarean section due to breech position; birth weight was 2800 g. Sepsis work-up performed at age 3 days because of fever was negative. A switch to soy-based formula at age 2 months also induced vomiting, so the child continued to be breast-fed with Nutramigen supplementation. At age 4.5 months, exposure to chicken and vegetable soup led to recurrent vomiting with pallor and apathy, but the patient recovered without i.v. fluids. She was able to eat

vegetables and fruits without adverse events, but no attempt was made to give her cereals or bread owing to a paternal history of celiac disease.

Physical examination at 1 year revealed unsatisfactory growth. Therefore oral challenge with chicken was performed at the hospital. Recurrent vomiting, pallor, apathy and dehydration developed after ingestion of 5 g of cooked chicken breast, and i.v. fluid treatment was required for 12 h. Bloody diarrhea appeared after hospital discharge, but it quickly resolved. Stool cultures were negative. Currently, at age 2 years, she is eating Nutramigen, eggs, cereals, fruits and vegetables but has not been re-exposed to chicken, milk or soy.

Patient 4

This male infant was admitted at age 7 months because of vomiting, pallor, apathy and bloody diarrhea, which developed 4 h after re-exposure to humanized milk formula. He was born after an uneventful pregnancy and delivery by elective cesarean section; birth weight was 3000 g and there were no perinatal complications. He had been exclusively breast-fed for 6 months. Stool cultures taken on admission were negative. The patient was switched back to breast-feeding supplemented with soy-based formula. Consumption of fruits and vegetables, such as potatoes, carrots, celery and squash, was not associated with any adverse events. At age 8 months, ingestion of lentils for the second time led, after 2 h, to recurrent vomiting, apathy and pallor, necessitating in-hospital treatment with i.v. fluids. A barium enema, performed for suspected intussusception, revealed no abnormalities. Currently, at age 12 months, he consumes a varied diet, but without milk, milk products or lentils.

Patient 5

This male infant was born at term by cesarean section because of breech presentation; birth weight was 3450 g. He had meconium aspiration and respiratory distress syndrome and was discharged at age 16 days. He was breast fed with humanized milk formula and soy-based formula supplementation without adverse events. Since the age of 6 months, he has presented to the emergency department several times for episodes of vomiting after ingestion of turkey meat. At age 12 months, he developed recurrent vomiting, pallor and lethargy after ingestion of chicken meat and was hospitalized for i.v. fluid treatment.

Patient 6

This female infant was admitted at age 3 months because of recurrent vomiting and apathy after ingestion of humanized milk formula. She was born after an uneventful pregnancy and delivery without any perinatal complications. She tolerated soy, but developed vomiting, pallor and lethargy after ingestion of chicken meat at 7 months. She had two additional episodes, the most recent at age 12 months, on re-exposure to chicken at home. All episodes necessitated hospitalization for i.v. fluid treatment.

Discussion

Sicherer et al. (1) defined the criteria for FPIES as follows: (i) age less than 9 months at initial diagnosis; (ii) same symptoms on repeated exposure to the incriminated food within 24 h without any other cause; (iii) gastrointestinal symptoms only; and (iv) resolution of symptoms on removal of the offending protein from the diet and/or elicitation of the same symptoms by a standardized food challenge within 24 h of administration. In our series, only one patient (no. 3) underwent a controlled oral challenge to chicken at age 12 months to confirm the diagnosis. In the remainder, the diagnosis of FPIES was based on the typical clinical pattern of reactions to several foods, together with the reappearance of symptoms on inadvertent exposure to the allergenic foods in patients 1 and 6. Patient 1 continues to react to soy at age 7.5 years, with the same symptoms, though less severe. As in our series, three of the patients described by Sicherer et al. (1) were older at the time of the initial reaction; two were 2 years old, and one was 9 years old.

Two of our patients also reacted to milk, one patient to soy, and one patient to milk and soy. Of interest, however, are the foods other than milk and soy that elicited the FPIES: chicken in four, turkey in two, peas in one, and lentils in one. Two patients (nos. 1 and 5) reacted to more than one of these foods. Peas, turkey and chicken were mentioned as allergens in the series of Sicherer et al. (1), inducing a reaction in one patient at age 5 months (peas), and in one at age 2 years (both turkey and chicken). David (6) described a 2.5-year-old boy with severe atopic dermatitis who reacted to comminuted chicken during an elimination diet. Symptoms included drowsiness, limpness and shock, with poor peripheral circulation. In another report, one patient had recurrent episodes of chicken-induced enterocolitis syndrome starting at age 6 months (7).

To the best of our knowledge, there are no additional case descriptions of turkey-induced enterocolitis syndrome, although patients with an IgE-mediated allergy to chicken and turkey, without egg allergy, have been reported (8, 9). The allergens in avian meats have not been defined. Allergenic proteins of poultry meats were detected at molecular weights of 21, 23 and 50 kDa and at an additional band of 91 kDa for turkey (8). Immunoblots from patients allergic to several avian meats revealed IgE binding to several proteins of similar molecular weights in all of the avian meats (9).

Lentils and peas belong to the legume family. Although lentils have not been reported as a cause of FPIES, there are descriptions of IgE-mediated allergy and anaphylactic reactions to lentils in children, especially from the Mediterranean area (10,11). Immunoblotting patterns from children with lentil allergy showed IgE-binding ranging from 14 to 74 kDa (11).

The metabolic acidosis, hypernatremic dehydration and methemoglobinemia in patient 1 at age 4 weeks necessitated admission to the pediatric intensive care unit and full sepsis work-up. Transient methemoglobinemia has been reported as a result of protein intolerance in infants (12). The unusual culprit foods and somewhat older ages of our patients prompted the attending pediatricians to also perform other examinations and tests besides sepsis work-up. Patient 1 underwent a metabolic work-up to rule out ammonia cycle enzymatic defects, and patient 4 underwent a barium enema to rule out intussusception.

Skin prick tests were positive for milk in two of the three milk-reacting infants (patients 3, 6). However, their clinical presentation did not differ from that of the other infants, and they have not been rechallenged with milk. None of our patients had positive skin prick tests to lentils, peas, chicken or turkey. The skin prick tests were performed with commercial extracts. We did not perform prick-prick tests with the natural foods; these tests were found in some cases to be positive, while the commercial skin prick tests were negative (13). Nevertheless, the lack of skin and/or respiratory system involvement during the allergic reactions in all our patients, together with negative blood tests for specific IgE antibodies in the three patients who were tested, favor the possibility that these allergic reactions were not IgE mediated.

The fact that five of our patients reacted to more than one food and one patient reacted after a nutritional attempt during protracted diarrhea may indicate that there are infants who are more

prone to FPIES. Until a specific immunological marker is found, FPIES will be diagnosed clinically. Pediatricians should be aware that foods other than milk and soy may elicit symptoms, even in relatively older infants, i.e. towards the end of the first year of life.

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