

R. ONESIMO¹, I. DELLO IACONO², V. GIORGIO¹, M.G. LIMONGELLI², S. MICELI SOPO¹

Can food protein induced enterocolitis syndrome shift to immediate gastrointestinal hypersensitivity? A report of two cases

¹Department of Pediatrics, Catholic University - Rome - E-mail: smicelisopo@rm.unicatt.it

²Department of Pediatrics, Fatebenefratelli Hospital - Benevento

KEY WORDS

Food protein induced enterocolitis syndrome, immediate gastrointestinal hypersensitivity

Corresponding author

Dr. Stefano Miceli Sopo
Department of Pediatrics -
Catholic University of Sacred Heart
L.go Gemelli 8, 00168 Roma, ITALY
Tel. +39 (0)6-3015 4348,
FAX . +39 (0)6-3383211
E-mail: smicelisopo@rm.unicatt.it

SUMMARY

Food protein induced enterocolitis syndrome (FPIES) is a food-related non-IgE-mediated gastrointestinal hypersensitivity disorder. Atypical FPIES is characterized by the presence of specific IgE for the causative food. The guidelines suggested for diagnostic Oral Food Challenge in pediatric patients affected by suspected FPIES are different from the ones for children with IgE-mediated food allergy. We describe two cases of atypical FPIES that turned into IgE-mediated gastrointestinal anaphylaxis. Our experience suggests to adapt OFC according to the outcome of specific IgE for the causative food. When causative food-related IgE were positive, we suggest to follow the guidelines for IgE mediated food allergy.

Introduction

Food protein induced enterocolitis syndrome (FPIES) is a food-related non-IgE-mediated gastrointestinal hypersensitivity disorder. In acute symptoms it typically includes incoercible vomiting, diarrhea, dehydration, low-blood pressure and even lethargy and shock. They usually occur between two and six hours from ingestion of the causative food (1, 2). Moreover, the gastrointestinal tract is also a common target organ for IgE-mediated food allergy (immediate gastrointestinal hypersensitivity) (3). Symptoms of immediate gastrointestinal hypersensitivity occur minutes or even seconds after the ingestion of the incriminated food and include vomiting, abdominal pain and diarrhea that can be associated to allergic manifestations in other target organs (gastrointestinal anaphylaxis) (4).

We describe two cases of FPIES that turned into IgE-mediated gastrointestinal anaphylaxis.

Case 1

A 3-month-old boy, with no family history for allergic diseases, came to our observation for an allergy work up. When he was 40 days old he tasted formula milk (FM) for the first time (60 ml) presenting jet vomiting after two hours without compromise of the general conditions. After a few days he received FM again and presented jet vomiting and lethargy after three hours. His pediatrician suspected cow milk (CM) protein allergy. At two and at three months of life, detection of seric CM specific IgE (ImmunoCAP, Phadia, Uppsala, Sweden) and skin prick test with lactalbumin, beta-lactoglobulin, casein and fresh cow milk were performed and resulted negative. We made an oral food challenge (OFC) administering 0.3 g CM proteins/kg body weight into 3 doses over a 60 minutes period (2). After one hour and 20 minutes from the start of OFC, the child presented profuse vomiting and mild hypotension,

that quickly were resolved with saline solution infusion. In the subsequent days he had diarrhea streaked with blood. We confirmed the diagnosis of CM FPIES and prescribed an elimination diet with an extensively hydrolysed casein formula (HF) as substitute. After 18 months skin prick test (SPT) with lactalbumin and casein were performed and resulted negative, while SPT with beta-lactoglobulin and fresh cow milk tested positive (mean diameter respectively 5 mm and 7 mm). The outcome of ImmunoCAP test for serum CM IgEs was positive too (10 KUA/l). We performed a second OFC, according to the guidelines suggested for IgE-mediated food allergy (5): we started with 0,1 ml of CM and continued in a graded fashion. After 150 minutes from the start, at the time of the bolus dose of 100 ml, he presented profuse vomiting, edema of the glottis, lethargy and shock (blood pressure 50/20 mmHg). Adrenaline, steroids and massive saline rehydration were administered successfully. When he was 3 ½ years old atopy patch test for CM, skin prick tests for CM proteins and determination of CM-specific IgE levels were performed and resulted negative. OFC was repeated for the third time, according to the guidelines suggested for IgE-mediated food allergy. After two hours from the start, at the bolus of 40 ml, he developed pallor and severe hypotension (blood pressure 60/20 mmHg). The boy is still on a CM protein free diet.

Case 2

An 8-month-old girl was admitted to our attention with a history of continuous vomiting, diarrhea, pallor and hypotension 3 hours after she assumed FM. Before our evaluation, the symptoms recurred 4 times and were attributable to the ingestion of 30-40 ml of FM. She was breastfed and didn't have any atopic disease; her family history was positive for asthma in mother's infancy. She assumed FM for the first time when she was 10 days old, after a few hours she had an episode of vomiting. She assumed FM three times again, the last time at the age of 7 months. Each time after three hours from the ingestion she had continuous vomiting, diarrhea, pallor and only the last time also hypotension too (blood pressure 60/40 mmHg). Every time the symptoms resolved completely in a few hours. SPT were performed and resulted negative for casein, lactalbumin and lactoglobulin, while SPT with fresh cow milk resulted positive (4 mm). We diagnosed atypical FPIES without performing the OFC because of the clinical features and the high rate of the episodes. An elimination diet and extensively hydrolysed casein formula as substitute

were prescribed. When she was 16 months old, one year after the last reaction, OFC was performed to verify the possible acquisition of tolerance. We administered 0.3 g CM proteins/kg body weight in 3 doses over a 60 minutes period (2). After 4 hours from the start 200 ml of CM were administered, the patient had no symptoms; three hours after that OFC was considered negative. Unfortunately this time SPT were not repeated. The girl was then discharged with no elimination diet, because she overcame FPIES. Within five days after discharge she received CM without restrictions or adverse reactions except for small wheals of urticaria only where the lips had contact with cow milk. On the 6th and 7th day, after 20 minutes from CM ingestion, the girl developed cough, vomiting and urticaria on those areas touched by the vomited milk. The ingestion of little doses of parmesan cheese was not associated to adverse reactions. SPT were performed and resulted positive for lactalbumin, betalactoglobulin and fresh cow milk (respectively 4 mm, 3 mm and 5 mm), SPT for casein was negative.

On the 8th day, another OFC was performed, administering a bolus of 220 ml of CM, the same dose that the girl had previously taken at home. Immediately, a few small wheals of urticaria compared on the skin areas of the face where some milk fell and after 20 minutes from the ingestion the child coughed and vomited, and many urticaria lesions developed on the skin of the trunk and limbs touched by the milk. The general clinical conditions kept on being normal. We then concluded that FPIES was turned into IgE-mediated gastrointestinal anaphylaxis. The girl didn't assume CM proteins until 2 years of age, when she took it at home after parents' own decision. No clinical problems were observed and the child is now having a free diet.

Discussion

The diagnosis of FPIES remains a clinical one and relies on history, clinical features, exclusion of other causes and OFC. The guidelines suggested for diagnostic OFC in pediatric patients affected by suspected FPIES are different from the ones for children with IgE-mediated food allergy (6). There are many reasons for this choice:

- the adverse reaction develops 2 to 6 hours from the ingestion of the causative food;
- the minimum dose that can trigger the onset of symptoms is unknown;
- there is evidence to suggest an allergic basis for this disorder but our knowledge of the pathophysiology of FPIES is not complete.

Some sporadic observations led us to assume that in FPIES, food allergen ingestion-induced inflammation increase intestinal permeability and fluid shift (6). Some authors (7) postulated a T cell-mediated response, in which proinflammatory cytokine (TNF α) release would alter tissue permeability. Increased passage of the antigen into the submucosa would be favoured this way, followed by the activation of antigen-specific lymphocytes. Moreover, it is known that the regulatory cytokine TGF β 1 protects the epithelial barrier of the gastrointestinal tract against the penetration of foreign antigens. In duodenal biopsies of patients with enterocolitis a reduction of the type 1 TGF β 1 receptor population has been also reported (8). In conclusion, a deficient TGF β 1 response and an excessive TNF α response should be taken into account for pathogenesis of FPIES. It is not demonstrated that food related IgE had a relevant action in FPIES pathogenesis. Over 90% of patients have negative skin prick tests and undetectable serum food-specific IgE (1). Some children, despite showing all the clinical features of FPIES, have IgE vs the causative food and therefore are considered to be affected by an atypical form of the syndrome. Some authors have reported that (9) virtually each child affected by CM FPIES became tolerant within 20 months of life. On the other hand, it has been observed that the subsequent development of detectable IgE to the causative food may represent a poor prognostic sign for tolerance and it may be important to repeat the tests before diagnostic oral challenges (1).

Our cases demonstrated that when food-related IgE were positive, FPIES can persist over the average period of 20 months and can shift to IgE mediated food allergy of different clinical relevance.

In case 1 the clinical manifestations were particularly severe, with edema of the glottis and hypotension, and tolerance has not yet been reached, at the age of 3 ½ years. In case 2 IgE-mediated clinical manifestation was mild to moderate (contact urticaria and vomiting) and was clinically resolved relatively quickly, tolerance being achieved at the age of 24 months, instead.

Some aspects of the cases we described are not easy to understand. For example, in case 1 CM related IgE and IgE-

mediated symptoms were evident only for a period of time, around 2 years of age. The situation at the time of the third OFC has been less clear. Case 2 is interesting for the latency between the apparent achievement of tolerance at the first OFC and the development of IgE-mediated symptoms. Seven days were required to show the switch from atypical FPIES to gastrointestinal anaphylaxis.

In our view, in atypical FPIES with positive specific IgE it would be more prudent begin the OFC with doses of food lower than expected from the typical protocols for FPIES (2).

In conclusion, our experience suggests to adapt OFC according to the outcome of specific IgE for the causative food. When causative food-related IgE were positive, we suggest to follow the guidelines for IgE mediated food allergy.

References

1. Nowak-Węgrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; 111: 829-35.
2. Nowak-Węgrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2009; 9: 371-7.
3. Boné J, Claver A, Guallar I, Plaza AM. Allergic proctocolitis, food-induced enterocolitis: immune mechanisms, diagnosis and treatment. *Allergol Immunopathol* 2009; 3: 36-42.
4. Sampson HA. Food allergy. *J Allergy Clin Immunol* 2003; 111: S540-7.
5. Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009; 123 (6 Suppl): S365-83.
6. Powell GK, McDonald PJ, VanSickle GJ, Goldblum RM. Absorption of food protein antigen in infants with food protein-induced enterocolitis. *Dig Dis Sci* 1989; 34: 781-8.
7. Heyman M, Darmon N, Dupont C, et al. Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function. *Gastroenterology* 1994; 106: 1514-23.
8. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alfa in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2002; 109: 150-4.
9. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. *Arch Dis Child* 2009; 94(6): 425-8. Epub 2008 Oct 1.