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POINT OF VIEW

Is food protein induced enterocolitis syndrome only a non IgE-mediated food allergy?

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Abstract Food protein induced enterocolitis syndrome (FPIES) is classified as non-IgE-mediated or cell-mediated food allergy, although there is an atypical phenotype so defined for the presence of specific IgEs. All diagnostic criteria for FPIES include the absence of skin or respiratory symptoms of IgE-mediated type. We present four cases that suggest that specific IgEs may have a pathogenic role, resulting in the existence of different FPIES phenotypes. This could be important from a diagnostic and therapeutic point of view.

Food protein induced enterocolitis syndrome (FPIES) is a food-related hypersensitivity disorder characterized by repetitive and projectile vomiting, often accompanied by pallor, lethargy, and diarrhea. Symptoms usually occur between 1 and 4 hours from the ingestion of the causal food.[1] It is believed that FPIES is a non IgE-mediated food allergy (FA), although details of the underlying pathogenic mechanism are not known.[2,3] The diagnostic criteria proposed over the years for identifying FPIES agree that children must not present classic IgE-mediated allergic symptoms.[4–10]

However, we have some doubt that the classification and diagnostic criteria of FPIES must be so rigid. For example, the condition of atypical FPIES is known, in which specific IgE against the causative food is detectable.[1] Moreover, cases have been described in the literature about children who turned from FPIES to IgE-mediated FA[11] and vice versa.[12] We previously published about a child with unusual clinical features of egg allergy,[13] presenting simultaneously both FPIES symptoms and immediate urticaria.

Here we describe other cases we collected, presenting a coexistence of FPIES symptoms and immediate urticaria. We therefore propose our opinion about the nosographic, diagnostic and therapeutic consequences of our observation.

Abbreviations: CM, cow milk; FA, food allergy; FPIES, food protein induced enterocolitis syndrome; OFC, oral food challenge; PtP, prick-to-prick; SPT, skin prick test.

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Case 1

A three-month-old child was brought to our allergy clinic because of, at the age of two months and three hours after his first ingestion of infant formula (80 ml), he had a very abundant vomiting episode. Neither pallor nor lethargy were noted. One week after this episode, he ingested another 80 ml of formula milk; in the areas of the neck and upper chest, where milk touched the skin, rash and wheals appeared in a few minutes. Then, after 30–45 minutes, he presented one abundant vomiting and, after another hour, also a second vomiting. He also appeared sleepy but not lethargic. These symptoms resolved after about 90 minutes. He had no diarrhea in both episodes. Prick-to-prick (PtP) with pasteurized cow milk (CM) and skin prick test (SPT) with alpha-lactalbumin commercial extract (Lofarma, Milan, Italy) resulted positive (mean wheal = 5 mm and 3 mm respectively), while SPT with casein and beta-lactoglobulin commercial extracts resulted negative. When the baby was four months old, we performed an oral food challenge (OFC) with formula milk. The child ingested 40 ml and in a few minutes we observed urticaria on his neck, in the areas where the bib was wet with CM. After two hours he started to be less lively and responsive, and at three hours from the ingestion of the milk he presented an abundant vomiting. Later, his general condition improved and he appeared more responsive. Then, we performed a rub test with CM on his abdomen and after 10 minutes smaller wheals of urticaria surrounded by erythematous halos appeared. Two weeks later, we also performed PtP and OFC with 20 grams of parmesan cheese; they both resulted negative.

Case 2

A three-month-old boy twice ate 60 ml of infant formula without any problem. The third time, 75 minutes after the ingestion his mother noted wheals in his face, that spread to the body in a few minutes. The baby appeared less reactive and he was conducted to the emergency room and hospitalized. Serum specific IgE were positive for CM (32 kU), α-lactalbumin (5 kU) and β-lactoglobulin (35 kU). The child and his nursing mother were suggested to a CM-free diet. When the baby was seven months old, we performed an OFC with formula milk in hospital setting. At this time, SPT positivity was detected for pasteurized CM (mean wheal = 7 mm), α-lactalbumin (5 mm) and β-lactoglobulin (4 mm). He started OFC with 0.5 ml of CM and doubled the dose every 20 minutes. After two hours from the beginning of the OFC (and 15 minutes after the last dose of 20 ml), he had a vomiting. After 45 minutes, the baby again drank 20 ml of CM and then 40 ml (last CM dose). The baby had a second vomiting after two hours and 15 minutes after the first vomiting and after one hour and 10 minutes after the last CM dose. For another two hours the baby had episodes of vomiting (one every 20–30 minutes), he had six episodes of vomiting overall and was pale and lethargic. Furthermore, wheals appeared on his neck during vomiting. Rub test with CM on his abdomen evocated wheals and erythema.

Case 3

A six-month-old boy was brought to our allergy clinic because at the age of two months, he ate 30 ml of formula milk (it was his second ingestion) and after five hours his parents noted erythema all over his body and angioedema of his right ear. After other 10 minutes, the child had two projectile vomiting and he appeared deeply lethargic. He returned to normal after another five hours. Since then, he ate only breast milk and fruit, and the nursing mother had a free diet, CM proteins included. When the baby was seven months old, we performed PtP with pasteurized CM (mean wheal = 7 mm) and SPT for casein (3 mm), β-lactoglobulin (6 mm) and α-lactalbumin (8 mm) commercial extracts. We performed an OFC with 50 ml of pasteurized CM administered in a single dose. After about 10 minutes from the ingestion, he presented erythema and 5–6 wheals on perioral skin. After two hours and 40 minutes from the ingestion of the CM, he had an abundant and projectile vomiting and numerous large wheals appeared on the abdomen, on the back, in the anterior and posterior region of the neck, and on legs. After about a half an hour the baby fell asleep and when he woke up he did not complain of symptoms.

Case 4

A previously always bottle-fed baby, at the age of 28 days had repetitive vomiting two hours after a meal of formula milk, associated with pallor and then diarrhea. It was suggested to use an extensively hydrolyzed formula as substitute. After two weeks, formula milk was reintroduced at home and the baby had repetitive vomiting, pallor, lethargy and diarrhea two hours after the ingestion. She started again a CM-free diet. At the age of one year, she tasted an ice cream that contained CM; after one hour the baby had urticaria all over the body and after two hours repetitive vomiting, lethargy and diarrhea. PtP with pasteurized CM performed at the age of 18 months resulted positive (mean wheal = 5 mm). OFC with CM at the age of 30 months evocated urticarial rash all over the body after 30 minutes; she did not present vomiting nor diarrhea on this occasion. After a month, OFC with muffin, that contained baked CM, was passed. A third OFC performed at the age of 36 months with pasteurized CM demonstrated the acquisition of tolerance.

FPIES is classified as non-IgE-mediated or cell-mediated FA respectively in the US[14] and European[15] guidelines of 2014. Instead, the Japanese guidelines[16] write that the mechanism is ''mainly'' non-IgE mediated type, leaving the door open to alternatives. Caubet at al.[17] wrote that a role for IgE in the pathophysiology of the FPIES has not been completely excluded.

The four cases we have described here, along with those already published,[11–13] support, in our opinion, the hypothesis of a pathogenic role of specific IgEs in some FPIES phenotypes. They lie between pure FPIES and classic IgE-mediated FA. Observation of this particular phenotype of FPIES could have practical and theoretical consequences.

From the nosographic point of view, we believe that FPIES is more appropriately classified between mixed, IgE- and non-IgE-mediated, FA, such as eosinophilic gastroenteritis.[14]

From the point of view of the diagnosis, we think that the elimination of the need for the absence IgE-mediated symptoms from the diagnostic criteria of FPIES can be considered. Vomiting at a time of 1–4 hours after the ingestion of the guilty food is, in our opinion, the most characteristic element of FPIES. It is different from that of gastrointestinal anaphylaxis, an IgE-mediated FA in which vomiting occurs within few minutes after the ingestion of the guilty food.[18] We believe that the diagnosis of ''classical'' IgE-mediated FA is unsuitable for the cases we have observed. We believe that they are much closer to the diagnosis of FPIES, just for the onset time of the symptoms and their duration. The lack of pallor and lethargy in case n. 1 does not rule out the diagnosis of FPIES. In fact, the mild form of FPIES provides for 1–2 episodes of emesis and no lethargy.[10]

From the point of view of diet therapy, in children with stories similar to those described may be reasonably tried the OFC with processed food if it is cow's milk or hen's egg. It has been reported, although in a small number of cases,[19] that the processed food forms can be tolerated in some children with FPIES. Also in our case 1, reported here, this has occurred.

Evolution, for the very few cases we have observed, is variable. The case that we have already published[13] maintained, at the last follow up made a year after publication, coexistence between typical symptoms of FPIES and typical cutaneous symptoms of IgE-mediated FA: the child had repeated vomiting at two hours after ingestion of raw egg and positivity of rub test indicating a contact hives, as well as the PtP positivity with raw egg. Three cases of the four described herein have also maintained the same coexistence of FPIES and IgE-mediated symptoms until the last follow up. Instead, case 4 has only shown generalized hives and no longer vomiting at 30 months of age.

In conclusion, the cases presented here induce us to hypothesize the existence of a FPIES phenotype in which specific IgEs have a pathogenic role. This could have practical and diagnostic and therapeutic implications, as well as more theoretical as the nosographic ones.

Ethic statement

We declared that the authorship of the paper ''Is food protein induced enterocolitis syndrome only a non IgE-mediated allergy?'' is limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study.

We ensure that we wrote entirely original works, and if we used the work and/or words of others, this has been appropriately cited or quoted.

We declare that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

We declare we did not undertake studies on patients. We simply reported what happened during normal clinical activity without carrying out experimental studies.

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Author contributions

SMS and CF designed the study and wrote the manuscript. GB and AR contributed to data collection. LL and SM performed the interpretation of the results. All authors read and approved the final manuscript.

Conflict of interest statement

The authors have no conflict of interest to declare.

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