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Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome

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KEY WORDS

Cow's milk allergy; food allergy; food protein-induced enterocolitis syndrome

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SUMMARY

Food protein-induced enterocolitis syndrome (FPIES) is a potentially severe non-IgE-mediated food allergy usually caused by cow's milk or soy, and more rarely by solid foods such as rice, oats, barley, chicken, turkey, egg white, green peas and peanuts. In children with FPIES, the presence of specific IgE antibodies to the causative food, either at presentation or during follow-up, defines an "atypical form" of FPIES characterized by a lesser probability of developing tolerance and a potential progression to typical IgE-mediated hypersensitivity. Although it is uncommon, the shift from non-IgE-mediated milk-protein induced enterocolitis syndrome to IgE-mediated milk allergy has recently been described. We report the first case, to our knowledge, of a shift from IgE-mediated cow's milk allergy to pure non-IgE-mediated FPIES, in a 4-month-old male infant.

Abbreviations:

CM : cow's milk

CMA : cow's milk allergy

SPT : skin prick test

FPIES : food protein-induced enterocolitis syndrome

Case report

At 15 days of age a male infant, exclusively breastfed from birth, developed generalized urticaria and localized edema to hands and feet just a few minutes after his first ingestion of cow's milk (CM) formula. A complete allergological work-up was performed, which came out positive for the skin prick test (SPT) and for serum-specific IgE antibodies (ImmunoCAP, Phadia, Uppsala, Sweden) to CM

and all CM proteins (specific IgE to CM 13.7kUA/l, alfa-lattoalbumin 21.7 kUA/ml, beta-lattoglobulin 17.2 kUA/l, casein 9.51 kUA/l, total IgE 149 kU/l), indicating possible IgE-mediated cow's milk allergy (CMA). The infant's mother was instructed to avoid using both CM formula and dairy products and to start an elemental diet based on an amino-acid formula.

At 3 months of age, a follow-up examination showed negative SPT to CM. An open oral food challenge with CM formula was then carried out. Two hours after the challenge, the baby presented paleness, hypotonia, lethargy, diarrhea and started to vomit, with no respiratory and/or cutaneous symptoms, confirming the diagnosis of CMA. Therefore, the infant was admitted to our Paediatric Clinic, where a rapid intravenous saline rehydration solution and a single dose of methyl prednisone

improved the situation within few hours. Blood tests showed slightly higher levels of lactic acid with no acidemia, significant neutrophilia and a very high level of procalcitonin (25ng/ml), even though no clinical signs of sepsis or infection were detected.

Three weeks later, SPT and serum-specific IgE antibodies to CM and all CM proteins were reassessed, and both tests were negative. The infant's mother was instructed to continue with the amino acidic formula milk with permission to begin weaning, though with strict avoidance of CM and dairy products. One month later, the infant became lethargic and started to vomit few hours after the first ingestion of veal, requiring hospital admission, intravenous rehydration and systemic steroids. A diagnosis of food protein-induced enterocolitis syndrome (FPIES) was made.

Discussion

CMA is the most common food allergy in childhood, affecting around 2–6% of children, with the highest prevalence during the first year of life (1). CMA tends to remit spontaneously within the first few years of life in about 50% of affected children, but it is often replaced by other allergic manifestations (the so-called “allergic march”) (2). CMA may affect several organs, predominantly the skin and gastrointestinal tract. The pathogenic mechanisms involved include both immunoglobulin-E (IgE)-mediated and non-IgE-mediated reactions (3).

FPIES is an uncommon and potentially severe non-IgE-mediated food allergy usually caused by CM or soy and more rarely by solid foods such as rice, oats, barley, chicken, turkey, egg white, green peas and peanuts (4,5). Common clinical features include recurring gastrointestinal symptoms such as emesis and diarrhea (varying from mild to severe), that usually manifest two to six hours after ingestion of the same offending food. Symptoms typically begin in the first month of life in association with failure to thrive and may progress to acidemia, dehydration, hypotension and even shock in 15–20% of patients (6,7). The diagnosis of FPIES can be made on the basis of a convincing clinical history, the absence of symptoms after eliminating the causative food and a positive delayed response to oral challenge with the incriminated food (8). Though FPIES is now recognized as a distinct clinical disorder, its pathophysiology has yet to be clearly defined. A T-cell-mediated inflammatory response of the intestinal mucosa induced by food allergens has been proposed as the

main mechanism, leading to an increase in gut permeability which might facilitate fluid shift and passage of proteins into the submucosa, activating antigen-specific lymphocytes (7,9). A possible role of humoral immune response in the pathophysiology of FPIES has also been postulated (9). Serum specific IgEs against the causative food are typically not detected in over 90% of cases of FPIES. However, in a few cases of FPIES, specific IgEs of the triggering food are detectable in serum, either at presentation or during follow-up, defining an “atypical form” of FPIES. These patients have a lesser probability of developing tolerance, a more prolonged course of FPIES and could progress to typical IgE-mediated hypersensitivity (10,11). Several reports of children with non IgE-mediated FPIES who developed IgE-mediated CMA have been published recently (12–14). This evolution suggests that testing specific IgEs to the causative food is mandatory before performing oral food challenge in FPIES (13).

We describe the case of a 4-month-old male infant with IgE-mediated CMA that turned into pure non-IgE-mediated FPIES. To the best of our knowledge, no previous reports of a shift from IgE-mediated hypersensitivity to a pure non-IgE-mediated reaction like FPIES have been published to date. We speculate that several factors – perhaps genetic, immunological and/or dietetic – could have a role in the mechanisms of food hypersensitivity, influencing the pathophysiology and clinical patterns in these patients. Further studies are required to define the mechanisms underlying FPIES in order to improve the diagnosis and management of the disease. Meanwhile, we suggest always considering the possibility of an inverse course of an IgE-mediated food allergy, which could show different clinical features from those expected, particularly in small infants whose immune-response is still modifiable.

Acknowledgements

The Authors are grateful to Ms Judyth Dillon for editing the English version of the manuscript.

Competing interests statement

The Authors have no competing interests with the subject matter or materials discussed in this manuscript.

Data sharing statement

There is no additional unpublished data from the study.

Contributorship statement

All the Authors made a substantial contribution to the intellectual content of the study.

Dr. Banzato and Dr. Mazzei conceived the study, collected the data, analyzed the data and wrote the initial draft.

Prof. Piacentini, Prof. Boner and Dr. Comberiati designed the study, ensured the accuracy of the data and analysis, wrote the initial draft and critically revised the manuscript for important intellectual content.

Prof. Peroni conceived and designed the study, collected the data, ensured the accuracy of the data analysis, and critically revised the manuscript for important intellectual content.

All the Authors have read and approved the version of the paper being submitted. Neither the manuscript nor any parts of it are under consideration by another journal or for electronic publication and have not been previously published.

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