

Shift from IgE-mediated cow's milk allergy to food protein-induced enterocolitis syndrome in 2 infants

To the Editor,

A 1-month-old male infant, only breastfed from birth, developed a localized edema of the hands and feet a few minutes after his first ingestion of a cow's milk (CM) formula. A complete allergy workup showed positive skin prick test (SPT) to CM (7-mm wheal) and serum-specific IgE (s-IgE) (ImmunoCAP, Phadia, Uppsala, Sweden) to CM and CM proteins (s-IgE to CM 62.3 kUA/L, alpha-lactalbumin 79.1 kUA/mL, beta-lactoglobulin 34.7 kUA/L, casein 98.7 kUA/L, total serum IgE 501 kU/L), allowing for a reliable diagnosis of IgE-mediated cow's milk allergy (CMA). The infant started a diet based on an extensive hydrolysate formula (eHF). At 4 months of age, a follow-up examination showed negative SPT to CM and s-IgE to CM and CM proteins (s-IgE to CM 0.27 kUA/L, alpha-lactalbumin 0.03 kUA/mL, beta-lactoglobulin 0.03 kUA/L, casein 0.24 kUA/L, total IgE 8 kU/L). An open oral food challenge (OFC) with CM was then carried out. Two hours after the ingestion of 100 mL of CM, the infant started vomiting (5 episodes) and presented paleness, hypotonia, and lethargy, with no respiratory and/or cutaneous symptoms. An intravenous line was applied with a prompt saline rehydration solution (160 mL) plus a single dose (0.8 mg) of ondansetron which improved the clinical condition within a few hours. A diagnosis of food protein-induced enterocolitis syndrome (FPIES) to CM was made according to the criteria of International Consensus guidelines.¹ The infant's mother was instructed to continue with eHF with permission to begin weaning, though with strict avoidance of CM and dairy products.

A 3-month-old male infant was admitted for an allergic evaluation because of suspected IgE-mediated CMA. He was born after an uneventful pregnancy and delivery and was breastfed together with intermittent bottle supplements from birth. At 2 months, he presented with generalized urticaria and one episode of vomiting within a few minutes after bottle-feeding. He was evaluated for CMA: SPT to CM was positive (5 mm of wheal) as well as s-IgE to CM, beta-lactoglobulin, and casein (13.5, 14.7, 1.9 KU/L, respectively) with negative s-IgE to alpha-lactalbumin, indicating an IgE-mediated CMA. The infant started a diet based on an eHF. At 3 months, he was reassessed: SPT to CM was negative as well as s-IgE to CM (0.03 KU/L), beta-lactoglobulin (0.01 KU/L), and casein (0.13 KU/L). For this reason, the infant underwent an open CM-OFC, which resulted in recurrent vomiting and lethargy 4 hours after the consumption of 100 mL of CM. He was treated with intravenous saline solution and a single dose of ondansetron with complete recovery within 2 hours. A diagnosis of FPIES to CM was confirmed.

IgE-mediated CMA is the most common food allergy in early childhood, affecting up to 2% of children under 2 years of age.²

The overall prognosis of IgE-mediated CMA in infancy is good with a remission rate of approximately 70%-80% by 3 years of age.² IgE-mediated CMA is characterized by rapid (within 2 hours of exposure) development of symptoms, variable in severity, including urticaria, angioedema, respiratory symptoms, gastrointestinal symptoms, cardiovascular collapse, and, in the more severe cases, even death.³

The clinical manifestations of IgE-mediated CMA differ significantly from FPIES, which is a non-IgE-mediated gastrointestinal food hypersensitivity presenting with profuse, repetitive vomiting, at sometimes with diarrhea, leading to dehydration and lethargy in the acute form.¹ It is most commonly caused by cow's milk or soy protein, although other foods can be triggers.⁴ Contrary to IgE-mediated CMA, FPIES typically occurs more than 2 hours after consuming the offending food.¹

The pathogenic mechanism underlying this syndrome is still little understood. It has been suggested that the disorder may be caused by the activation of intestinal T cells by food protein allergens with the release of pro-inflammatory cytokines, resulting in an increased intestinal permeability and fluid passage into the lumen.⁵

It has been reported that parenteral ondansetron controls symptoms of acute FPIES.⁶ Ondansetron acts on serotonin receptors both peripherally and centrally, and its benefit in chemotherapy-induced vomiting is thought to be through the inhibition of the serotonin receptors on the vagal nerve afferents in the gut that initiate the vomiting reflex.⁶ Whether the effects of ondansetron are mediated centrally or peripherally, the apparent efficacy of ondansetron raises questions as to whether inflammation is really the central mechanism underlying FPIES or whether the neuroendocrine-immune mechanism is possibly involved.⁶

The shift from IgE-mediated CMA to the IgE-mediated CM protein-induced enterocolitis syndrome has recently been described,⁷ and to the best of our knowledge, it is the only report published so far. The authors speculate that several factors (genetic, immunologic, and/or dietetic) could play a role in the mechanisms of food hypersensitivity, influencing the pathophysiology and clinical patterns in small infants whose immune response is still modifiable.

Furthermore, the conversion from FPIES to IgE-mediated food allergy to the same allergen is already been described and it is up to 30%.^{8,9}

There is the possibility of a bidirectional shift between IgE-mediated and non-IgE-mediated allergy, and therefore, IgE-mediated CMA and FPIES could be considered as the spectrum of the same disease.

We describe 2 cases of male infants with IgE-mediated CMA that turned into non-IgE-mediated CMA. Three cases (a previous report⁷ and our 2 cases) had similar characteristics: male sex, very precocious allergic reaction to CM, and very rapid negativization to CM proteins, and in one of these cases, we report an initial very high s-IgE level. It is known that the development of tolerance to CM, in IgE-mediated allergy, is easier to reach, greater is the decrease in s-IgE levels during a short period of time,¹⁰ but in our cases, the rapid negativization of s-IgE was surprising associated with the shift from IgE-mediated CMA to FPIES.

In conclusion, we suggest considering the possibility of a shift to FPIES in managing infants with IgE-mediated CMA and a rapid negativization of SPT and s-IgE to CM in order to implement a proper protocol of milk reintroduction.

ORCID

Simona Barni  <http://orcid.org/0000-0001-5598-2740>

Simona Barni¹ 

Francesca Mori¹

Annamaria Bianchi²

Neri Pucci¹

Elio Novembre¹

¹Allergy Unit, Department of Pediatrics, Anna Meyer Children's University Hospital, Florence, Italy

²Pediatric Unit, San Camillo Forlanini Hospital, Rome, Italy
Email: simonabarni@hotmail.com

REFERENCES

1. Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive

- Summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139:1111-1126.
2. Høst A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy*. 1990;45:587.
3. Fiocchi A, Brozek J, Schünemann H, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *Pediatr Allergy Immunol*. 2010;21(Suppl. 21):1-125.
4. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015;135:1114.
5. Berin MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2015;135:1108-1113.
6. Holbrook T, Keet CA, Frischmeyer-Guerrero PA, Wood RA. Use of ondansetron for food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2013;132:1219-1220.
7. Banzato C, Piacentini GL, Comberiati P, et al. Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome. *Eur Ann Allergy Clin Immunol*. 2013;45:209-211.
8. Onesimo R, Dello Iacono I, Giorgio V, et al. Can food protein induced enterocolitis syndrome shift to immediate gastrointestinal hypersensitivity? A report of two cases. *Eur Ann Allergy Clin Immunol*. 2011;43:61-63.
9. Kessel A, Danal I. The pendulum between food protein induced enterocolitis syndrome and IgE-mediated milk allergy. *Acta Paediatr*. 2011;127:685-688.
10. Shek L, Soderstrom L, Ahlstedt S, Beyer K, Sampson H. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol*. 2004;114:387-391.

DOI: 10.1111/pai.12882

A quality improvement initiative to increase access to food challenges

To the Editor,

Food challenges are critical to determine whether an individual has food allergy when history and testing are inconclusive or the allergy may have been outgrown.¹ Passing a challenge may have nutritional, psychological, and financial benefits.¹⁻³ We and others have shown that challenges can be safely carried out in a clinic setting.⁴⁻⁹

Challenges are underutilized, however, which can lead to unnecessary food avoidance, increased stress, and increased costs.³ One recent study estimated that delay in a food challenge resulted in an

annual increased cost to the patient/family of more than \$4000 and an overall cost of more than \$12 000.³

Due to high demand and limited access, patients in our clinic faced a delay of 6 months between a food challenge being scheduled and carried out. The primary limiting factor in offering challenges was availability of rooms for challenges which precluded us from meeting demand with weekday challenges. We therefore undertook a quality improvement initiative to improve access and decrease wait times. We focused both on increasing utilization (the fraction