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EDITORIAL

FPIES: The dark side of food allergy



A long, long time ago ... in a known world of IgE mediated food allergies, a powerful force flowing from the dark side was becoming more prevalent.

So could read the beginning of a series of events and changes that are developing in the until now known world of food allergies. Although described years ago, food protein-induced enterocolitis syndrome (FPIES) comprises a range of clinical entities little known to date, but with an incidence that has increased in our setting over the last two decades.¹

Food allergic disorders of non-IgE-mediated and mixed physiopathology are estimated to account for 40% of all cases of allergy to cow's milk proteins, including FPIES syndrome, food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPIE) and gastrointestinal eosinophilic disorders.^{2,3}

Hippocrates described cow's milk as causing gastrointestinal symptoms and urticaria, and reported that some infants fed cows' milk suffered prolonged diarrhea, vomiting and failure to thrive that resolved after cow's milk was withdrawn from their diet. In 1940, Rubin reported intestinal bleeding due to the intake of cow's milk in newborn infants.⁴ Gribosky and Powell in turn described infants who experienced recurrent vomiting, bloody diarrhea and bloating in the first 6 weeks of life.^{5,6} In this regard, the first Consensus Guide for the Diagnosis and Management of FPIES will be published in 2017.⁷

The prevalence of FPIES is still unknown, though Katz in the Israeli population reported an incidence of 0.34% (44/13,019), very similar to the incidence of IgE-mediated allergy to cow's milk in this population (0.5%).⁸ It is likely that mild FPIES phenotypes referred to cow's milk and soy are not actually diagnosed as FPIES, and are treated empirically with formula changes in the first year of life, with resolution of the symptoms.

Risk factors for the development of FPIES include cesarean delivery, the male sex, and FPIES to other foods. In turn, FPIES is associated to atopy in 30% of the patients; 40–80% have a family history of atopic disease; and 20% have a family history of food allergy.⁸ Published data from different sources suggest that the introduction of cow's milk may be a risk factor for the development of FPIES.⁹ In addition, although egg is not a common cause of FPIES, when

introduced at 5.5 months as a control allergen, it was seen to cause symptoms of FPIES in 30% of the infants with FPIES to cow's milk or soy.

Wheat is likewise not a common triggering food. However, its true prevalence in FPIES is probably modified by the common practice of delaying the introduction of wheat, rice or oats in infants with FPIES after 12 months of life. These observations, and optimum timing of food introduction, must be validated by prospective studies in larger populations.

Breastfeeding seems to play a protective role against FPIES, since exclusively breastfed infants without formula supplementation prove asymptomatic until direct feeding with the causal food.

The physiopathology of FPIES involves mechanisms that have still not been well characterized. The syndrome is regarded as a T cell-mediated disorder. In fact, T cell activation by food allergens may mediate local intestinal inflammation through the release of proinflammatory cytokines such as TNF- α and IFN- γ , resulting in increased intestinal permeability and fluid movement, which is believed to constitute the basis of pallor, poor perfusion, hypothermia and methemoglobinemia. Local inflammation may be mediated by activated peripheral mononuclear cells, increased TNF- α , and decreased expression of TGF- β receptors in the intestinal mucosa. However, basal antigen absorption is normal in FPIES.¹⁰

Acute reactions in FPIES appear to be associated to Th2 orientation of the T cell cytokine profile, consistent with classical IgE-mediated allergic reactions to foods. After tolerance is achieved, both IFN- γ and IL-10 increase significantly.¹¹

Powell reported leukocytosis with left-shift as a common finding in patients with FPIES, including it as one of the diagnostic criteria.⁶ An increase in neutrophil count in peripheral blood, peaking after 6 h with an average increase of 9900 cells/ μ L, was reported. Thus, neutrophils also appear in the stools of patients with FPIES and in gastric juice aspirates.

Eosinophils reside in the gastrointestinal tract, with the exception of the squamous cell mucosa of the esophagus. Eosinophil accumulation is found in many disorders, such

as eosinophilic gastroenteropathies, food-induced proctocolitis, classical IgE-mediated food allergies, inflammatory bowel disease, and gastroesophageal reflux disease. In FPIES with chronic diarrhea, eosinophils and Charcot-Leyden crystals identified with the Hansel stain have been observed in stool samples.¹²

On the other hand, humoral responses are poorly characterized in FPIES. In this regard, the syndrome is a food allergy gastrointestinal disorder, and on considering the importance of IgA in mucosal immunity, deteriorated IgA production or secretion might play a role in the physiopathology of FPIES.¹³ It is unclear how exclusive breastfeeding avoids FPIES, though it has been hypothesized that IgA in breast milk, either alone or as a complex with secreted antigens, could play a protective role.

Finally, the efficacy of ondansetron suggests the potential role of a neuroendocrine pathogenic mechanism in FPIES.

The clinical manifestations of FPIES depend on the frequency and dose of the ingested food. It should be noted that there are no classical allergic symptoms of the skin (such as hives, pruritus or inflammation) or respiratory tract (wheezing, coughing, sneezing). The chronic form presents with symptoms of intermittent vomiting, watery or mucosal diarrhea, scant weight gain, and dehydration.¹⁴ The onset of the acute form is between 1 and 3 h after ingestion, with vomiting (in number of 10–20) and dehydration, lethargy, pallor, hypotension, hypothermia and methemoglobinemia.¹⁵

Cow's milk and soy and rice formulas are the most frequent triggering factors. Solid causal foods include cereals (rice, oats, barley, corn), meats and poultry, eggs, vegetables (potatoes, squash), fruits, vegetables (tomatoes) and legumes (peanuts, lentils) or even shellfish, mollusks and fish (more commonly in adults).

In relation to the diagnosis, the NIAID Food Allergy Guidelines recommend evaluation of the case history and oral food challenge (OFC). Powell established the original diagnostic criteria: 1. Exposure to food causing repetitive vomiting and/or diarrhea within 4 h after ingestion; 2. Limitation of the symptoms to the gastrointestinal tract; 3. Avoidance in the diet of the offending protein leads to symptoms resolution; and 4. Oral food challenge or isolated re-exposure restarts the typical symptoms. Modifications are introduced by the panel of experts in 2017, distinguishing between a major criterion (vomiting between 1 and 4 h after ingestion of the suspect food with the absence of IgE or cutaneous or respiratory symptoms) and minor criteria (other episodes of vomiting after intake of the food or of different foods, lethargy, pallor, reporting to emergency care due to some reaction, need for intravenous fluid therapy, diarrhea lasting under 24 h, hypotension and hypothermia). The diagnosis requires the presence of the major criterion and of at least three minor criteria.¹⁶

There are no FPIES-specific laboratory tests or radiographic findings. An increase in leukocyte count (up to 6 h after food intake) and the presence of methemoglobinemia support the diagnosis.

A differential diagnosis must be established with other processes such as anaphylaxis, infectious gastroenteritis, sepsis, necrotizing enterocolitis, metabolic defects (urea cycle defects, hereditary fructose intolerance, hyperammonemia, etc.), lactose intolerance, neurological disorders, Hirschsprung's disease, celiac disease, etc.

The response in all these processes is similar, in the same way as the triggering factors. In this regard, the mean age for tolerance varies from 4 years for oats to 6.7 years for soybeans, with an average of 5 years.¹⁷ These data are consistent to those presented in several studies. Thus, a series of 77 patients diagnosed with FPIAP reported an age at onset of the symptoms of 3.3–4.7 months, with a predominance of milk in 78% of the cases. However, these authors report that tolerance in FPIAP is achieved after one year of causal food suppression from the diet, as demonstrated in the article entitled: "Tolerance development in food protein-induced allergic proctocolitis: a single-center experience", to be published soon in this journal.

It therefore can be concluded that many infants and children diagnosed years ago with a clinical condition called food intolerance effectively present non-IgE mediated allergies in which the physiopathological basis comprises involvement of the immune system. What remains to be established is the specific mechanism of activation, as well as the factors intervening in the process, and this will be clarified by future clinical and laboratory research.

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