



Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,
Alergología y Asma Pediátrica

www.elsevier.es/ai



EDITORIAL

Food Protein-Induced Proctocolitis. The shadow of allergic disorders



For over a hundred years, ever since allergic processes were first described, the scientific community has attempted to clarify the physiopathological mechanisms that can help us to explain why and how allergy occurs; to know the factors that influence the development of allergic processes in infants or adults; and to determine why different individuals respond differently to the same allergen.

The discovery of immunoglobulin E was an important advance, although over time it has been demonstrated that the immunological pathways implicated in allergy are multiple, and many remain to be discovered and identified.

Allergic responses to food have been known for a long time. The ancient Egyptians described how to feed sick people with abdominal pain, vomiting or blood in stools after eating certain foods. Over the years, some of these processes have been explained in terms of the role played by immunoglobulin E, although many remain unexplained.

For several decades we have been trying to find out what happens in the immune system of those patients in which no relevant role of immunoglobulin E in food allergic processes is observed. In this regard, the inflammatory processes induced by food proteins have been described, but what proteins are we talking about? Do other factors play a specific role?

Disorders of the gastrointestinal tract are one of the leading causes of paediatric consultation, and a large percentage of these disorders are due to immunological reactions to food.

In contrast to immunoglobulin E-mediated reactions, non-IgE-mediated allergic disorders are characterised by subacute and/or chronic symptoms, and have been traditionally classified as Food Protein-Induced Enterocolitis Syndrome (FPIES), Food Protein-Induced Allergic Proctocolitis (FPIAP), Food Protein-Induced Enteropathy (FPE), celiac disease and iron deficiency anaemia induced by cow's milk.¹ In addition, food allergens appear to have an influence on gastroesophageal reflux in children, and on abdominal cramps.²

A series of doubts arise in these processes:

- Are we facing new allergic processes?
- Are cases frequent in children?
- Have they been clinically characterised?
- Are they easy to diagnose?
- Do all cases have safe, fast and effective treatment?

The answers to all these questions remain unknown.

Although the true prevalence of these diseases is not clear, several studies show them to be less common than immunoglobulin E-mediated food allergies. Specifically, in the case of FPIAP, the estimated prevalence is 0.16%,³ although an increase has been observed in recent years.

Food Protein-Induced Allergic Proctocolitis (FPIAP) is very common in children, and is of a transient nature. It manifests in children with remnants of blood mixed with mucus in stools.⁴ Although as mentioned, FPIAP has a prevalence of 0.16% in healthy children, the figure reaches 64% in the case of patients with blood in stools.⁵

Several questions arise. Is FPIAP a current disease or did we simply not know how to identify it in the past? Can all foods cause FPIAP?

Many foods are involved as triggers of FPIAP, but cow's milk and soy have been the most commonly reported.⁶ Today, however, the most common causal foods are cow's milk and egg in infants, though we cannot rule out other foods such as legumes, fish, meats and nuts in adults. There are even cases in which reactions occur to several foods, making the diagnosis rather complicated.⁷

The clinical presentation is also diverse, with the presence of one or more symptoms. The most frequent manifestation is the presence of blood traces in stools, sometimes mixed with mucus, and with the possible association of vomiting and/or abdominal pain.⁸

Is there a safe, effective and efficient approach to the diagnosis? Here the answer is easy: No. Food Protein-Induced Allergic Proctocolitis is a clinical entity that was first described a few years ago. Consequently, if we have not yet been able to identify the causal agent, it will be even more difficult to establish a system capable of identifying

a ghost, a shadow. We can of course resort to the clinical manifestations – this being the most widespread approach at this time. In this regard, correlating the presence of clinical signs and symptoms to the intake of one or several foods in the patient's medical history can allow us to suspect the causal agent of FPIAP.

Different non-specific markers can be used, such as the disappearance of clinical symptoms when suppressing a given food, or even the reappearance of symptoms when the food is reintroduced. In short, however, the clinical manifestations prevail. In any case, oral food challenge (OFC) can be avoided when the clinical history is very clear or the symptoms are severe.

Laboratory tests such as blood count, blood gases and biochemistry may offer complementary information, or help predict the clinical course, especially in infants with vomiting and lethargy, facilitating the differential diagnosis with other diseases such as sepsis, infectious gastroenteritis, necrotising enterocolitis, intestinal obstruction, inborn errors of metabolism, inflammatory bowel disease, celiac disease, eosinophilic gastrointestinal disease and anaphylaxis.⁹

It is sometimes necessary to use invasive techniques such as endoscopy with biopsy.

Based on the above, we can gain an idea of the type of disease implicated in an infant with these symptoms and thus distinguish among FPIES, FPIAP, enteropathy and anaemia secondary to iron deficiency due to cow's milk. The first difference refers to patient age at onset, since FPIAP appears between 1 and 4 weeks of life, and FPIES between one day and one year of life. The manifestation of enteropathy in turn depends on the timing of food introduction, and anaemia develops between 2 and 20 months of life. In all cases cow's milk and sometimes soy are the most frequently involved foods, though only FPIES and FPIAP are commonly characterised by multiple hypersensitivity to food.

The clinical manifestations are helpful. In this regard, FPIES is characterised mainly by vomiting, diarrhoea and bloody stools - although the latter is more prominent in FPIAP.

With regard to the laboratory test findings, we can observe hypoalbuminaemia in FPIES, with possible acidemia and methemoglobinemia that are not seen in the other processes.

The biopsy shows FPIAP to be characterised by focal colitis and linear mucosal erosions, with nodular lymphoid hyperplasia.

In each of these processes, eliminating the causal food from the diet is the solution to all the problems.¹⁰

These data, which have already been published by investigators such as Anna Nowak-Węgrzyn, support the

findings of the study to be published in the current issue of *Allergologia et Immunopathologia*, entitled: "Tolerance Development in Food Protein-Induced Allergic Proctocolitis: Single Centre Experience".

In sum, these are eminently clinical diagnostic entities in which the medical history and the data obtained from the parents is important. So let us not forget that we are first and foremost physicians and not test interpreters, and that before us we have a sick child and not a report with laboratory test data. And, of course, we must not forget the words of Hippocrates, the father of medical science, which guide our work as physicians: "*Primum non nocere*".

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