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REVIEW PAPER

Food protein-induced enterocolitis syndrome – a little-known form of non-IgE-mediated food hypersensitivity

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ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is a presentation of non-IgE-mediated food allergy and is probably more common than is currently diagnosed. Epidemiological data that estimate the prevalence of this disease are limited. In infancy it is usually induced by cow's milk protein, rice, and soybean; in older children and adults fish and seashell may be the triggering factors. It is characterised by the presence of vomiting and diarrhoea that can lead to dehydration, lethargy, pallor, and metabolic acidosis. Chronic FPIES usually presents as failure to thrive. The diagnosis is based on clinical criteria. Potential cases can be misdiagnosed as more common paediatric illnesses, such as gastroenteritis or sepsis. Treatment consists of education and avoidance of the offending foods. In 2017 international guidelines for the diagnosis and management of FPIES were published [1]. This article contains current information on food protein-induced enterocolitis syndrome.

KEY WORDS:

food allergy, infants, food protein-induced enterocolitis syndrome, milk allergy.

INTRODUCTION

Food protein-induced enterocolitis (FPIES) is a specific non-IgE cell-mediated food allergy. It can be severe and lead to hypovolaemic shock. It usually occurs in young infants and manifests as chronic emesis, diarrhoea, and failure to thrive [2].

EPIDEMIOLOGY

In the past two to three decades hypersensitivity reactions to food have become more common, especially among children, in whom there are extensive data suggesting that food allergy affects up to 10% [3]. Non-IgE-mediated type of food allergy plays an important role. FPIES is a relatively rare disease and epidemiological data are lacking [4]. A study conducted in Israel on a cohort of 13,000 infants showed an incidence of FPIES triggered by cow's milk protein of 0.34%, compared to 0.5% for IgE-mediated allergy to cow's milk protein [5]. Studies report a male predominance (as it is with IgE-mediated food allergy); there is an increased incidence of FPIES and atopic diseases in children and their families [4]. There is no strong familial association in both parents and siblings, in contrast to eosinophilic oesophagitis [6]. The incidence of FPIES in Australian infants (< 24 months) was 15.4/100,000/year (which was higher than the incidence of eosinophilic oesophagitis or Crohn's disease), but the authors suggested that these numbers were underestimated due to methodological issues [7]. The average age of diagnosis was seven months. Although the majority of the patients experience resolution of FPIES usually by three to five years of age, a subset has persistent FPIES into adolescence and adulthood [8].

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PATHOPHYSIOLOGY

The exact pathophysiology mechanisms of FPIES have still not been well characterised. More studies providing insight into the pathophysiology are needed.

FPIES is a non-IgE-mediated food allergic disease. Based on the reports of cases, FPIES is presumed to be caused by protein component of foods [9]. By means of endoscopy and biopsy, it is presumed that FPIES is a T-cell-mediated disorder. The role of neutrophils, monocytes, mastocytes, and eosinophils has been suggested in the pathophysiology of FPIES [1]. Elevation of C-reactive protein at the onset of FPIES (that supports systemic inflammatory mechanisms) may be a poor prognostic factor for FPIES [10].

It has been observed that infants with cow's milk-triggered FPIES were more often delivered by c-section, suggesting a role for intestinal microbiota in the development of FPIES [6]. The role of exclusive breastfeeding in FPIES avoidance is not clear, but it has been hypothesised that IgA in breast milk could play a protective role [11].

Although FPIES is categorised as a non-IgE mediated allergic disorder, some patients may have positive specific IgE to the causal protein either at onset or during follow-up, this is referred to as "atypical FPIES" [6]. In such cases immediate allergic reactions after food intake are more likely to occur [9].

THE DIAGNOSIS

CLINICAL MANIFESTATION

FPIES usually presents between two and seven months of age as formulas and solid foods are introduced into the infant's diet. The most common causes in European countries and in the United States are milk, soy, wheat, barley, and oats [4]. Several studies also report reactions to other foods, including those considered as hypoallergenic, such as chicken meat, potatoes, rice, mushrooms, fruits, and vegetables. There are some geographical differences related to country-specific food habits and the timing of food-introduction in infancy. It is suggested that early introduction of soya and cow's milk can be a risk factor for the development of FPIES (for instance, in the USA, where formulas and especially soy formulas are more common). Most children react to a single food, but FPIES from multiple foods is not uncommon [6]. There are children who react to casein in hydrolysed formula and to cow's milk that passes through breast milk, although it is rare [9].

Acute FPIES and a chronic form have been described. The acute form is usually characterised by repetitive vomiting and lethargy that typically occur within one to four hours of ingesting the suspected food. When continuously exposed to the incriminated food, a chronic form develops with persistent vomiting, diarrhoea, and/or failure to thrive [6].

Acute FPIES manifestation

FPIES usually presents in infancy in one to four hours after ingestion of the triggering food as profuse, repetitive (15-20 times) emesis with or without diarrhoea. Loose stools may contain blood or mucus. Diarrhoea may be delayed and may occur within 2 to 10 hours. Secondary to vomiting pallor, lethargy, hypothermia, and, in the case of severe dehydration, hypovolaemic shock may be present. Laboratory tests show metabolic acidosis, increases neutrophil count of at least 1500 neutrophils above baseline (which peaks in six hours), thrombocytosis [4]. Diarrhoeic stool samples for occult blood may be positive [1].

Chronic FPIES manifestation

Chronic FPIES clinical presentation can vary and is not as well defined as acute FPIES. Chronic FPIES usually presents in neonates fed with cow's milk-based or soy-based formula from a young age. Such patients usually develop progressive diarrhoea with intermittent emesis over time. Affected children are characterised by poor weight gain and failure to thrive. Laboratory aberrancies include anaemia, hypoalbuminaemia, elevated white blood count with left shift, eosinophilia, and methemoglobinemia because of metabolic shifts. Infants with chronic FPIES will improve once the offending food or foods are eliminated from their diet [4].

DIAGNOSTIC CRITERIA

The diagnosis may be difficult because no specific confirmatory or exclusionary laboratory or diagnostic tests exist [6]. In 2017 international guidelines for the diagnosis and management of FPIES were published [1]. The document presents an executive summary of the first international consensus based on available evidence and aims to assist practitioners in their care of patients with FPIES. FPIES is a clinical diagnosis, mainly based on typical clinical manifestations, after exclusion of other causes of observed symptoms (Table 1, Table 2) [6]. The symptoms should completely resolve after avoidance of the incriminated food [9]. A careful history is the most important diagnostic tool in the evaluation of FPIES. The clinician must obtain details of all possible reactions, specific symptoms, timing of symptoms in relation to food intake, all suspected food triggers, and reproducibility of reactions with repeated exposure to the suspect food or foods [1].

In the vast majority of cases, history alone is sufficient to make a diagnosis; in certain cases, oral food challenge is the gold standard to confirm it (Table 3). Oral food challenge requires close supervision with immediate access to intravenous fluids (intravenous access should be secured). There are a variety of protocols for oral challenge food. The guidelines' authors [1] suggest admin-

TABLE 1. Cri Diagnostic criteria for patients presenting with possible acute FPIES – the diagnosis of FPIES requires that a patient meets the major criterion and ≥ 3 minor criteria [1]

Major criterion: • Vomiting in the 1- to 4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria: • A second (or more) episode of repetitive vomiting after eating the same suspect food • Repetitive vomiting episode 1-4 h after eating a different food • Extreme lethargy with any suspected reaction • Marked pallor with any suspected reaction • Need for emergency department visit with any suspected reaction • Need for intravenous fluid support with any suspected reaction • Diarrhoea in 24 h (usually 5-10 h) • Hypotension • Hypothermia
If only a single episode has occurred, a diagnostic OFC should be seriously considered, to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group. Furthermore, although not a criterion for diagnosis, it is important to recognise that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis

TABLE 2. Criteria for the diagnosis of chronic FPIES

Severe presentation: When the offending food is ingested on a regular basis (e.g. infant formula); intermittent but progressive vomiting and diarrhoea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis
Milder presentation: Lower doses of the problem food (e.g. solid foods or food allergens in breast milk) lead to intermittent vomiting and/or diarrhoea, usually with poor weight gain/FTT but without dehydration or metabolic acidosis
The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhoea in 24 h (usually 5-10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

TABLE 3. Diagnostic criteria for the interpretation of oral food challenge in patients with a history of possible or confirmed FPIES – the test will be considered diagnostic of FPIES (positive) if the major criterion is met with ≥ 2 minor criteria [1]

Major criterion: • Vomiting in the 1- to 4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria: • Lethargy • Pallor • Diarrhoea 5-10 h after food ingestion • Hypotension • Hypothermia • Increased neutrophil count of ≥ 1500 neutrophils above the baseline count

istration of the challenge food at a dose of 0.06-0.6 g, (usually 0.3 g) of the food protein per kilogram of body weight, in three equal doses over 30 minutes, and to observe the patient for four to six hours. They recommend not exceeding a total of 3 g of protein or 10 g of total food (100 ml of liquid) for an initial feeding. Lower starting doses and longer observation periods between doses should be considered in patients with a history of severe reactions. Testing for food-specific IgE may be beneficial for patients with atypical FPIES, but there is no need to perform it routinely [9].

In most cases there is no need to obtain radiographic or endoscopic testing; however, in certain cases endoscopy and biopsy may be necessary to exclude other causes [1].

DIFFERENTIAL DIAGNOSIS

According to the guidelines' authors [1], a number of conditions should be taken into consideration in differential diagnosis: gastroenteritis, sepsis, bowel obstruction and other causes of acute abdominal pain, celiac disease, inborn errors of metabolism, necrotising enterocolitis, epilepsy, and even anaphylaxis (in the case of hypotonia) can mimic the acute form of FPIES. The chronic form must be distinguished from celiac disease, FPE (food protein-induced enteropathy), FPIAP (food protein-induced allergic proctocolitis), oeosinophilic gastroenteritis, reflux disease, Hirschsprung disease, parasites, intoxication, and α-1-antitrypsin deficiency [4, 6, 9].

Nowadays scientists try to classify food allergy into phenotypes (based on clinical manifestation) and endotypes (based on molecular characteristics – engagement of different immune cells and pro-inflammatory mole-

cules) [12]. Some clinical manifestations can be distinguished among non-IgE-mediated food allergy type with predominance of gastrointestinal symptoms [10] described below.

FPIAP – food protein-induced allergic proctocolitis

FPIAP is thought to be the most common and benign form of non-IgE-mediated food allergy. The typical clinical manifestation of this disorder is isolated rectal bleeding (blood-streaked stools) appearing usually in the first few weeks-months of life in otherwise healthy infants fed with breast milk or infant formula. Resolution of symptoms 1-10 days after withdrawal of the trigger food is suspected. Elimination of the incriminated food from the maternal diet in exclusively breastfed infants is usually sufficient to resolve symptoms; an extensively hydrolysed or amino acid-based formula might be necessary in a minority of patients. Rectal bleeding resolves spontaneously in about 20% of breastfed infants, without any changes in the diet [10].

FPE – food protein-induced enteropathy

FPE is a rare condition. It is characterised by chronic diarrhoea that typically occurs between two and nine months of age, which may lead to failure to thrive. The most common triggering foods are cow milk, soybean, egg, and wheat. Endoscopy with biopsies is usually needed to confirm the diagnosis. Removal of the offending food is usually required, followed by reintroduction at home 4-8 weeks later to confirm the recurrence of symptoms [1].

MANAGEMENT OF ACUTE FPIES

Acute FPIES should be treated as a medical emergency. Approximately 15% of affected children can have hypovolaemic shock, and so one should be prepared to provide aggressive fluid resuscitation (bolus of 10-20 ml/kg of isotonic fluids should be administered intravenously followed by continuous intravenous maintenance infusion to correct metabolic disorders). According to the guidelines [1], acute FPIES should be managed individually. A single dose of intravenous methylprednisolone (1 mg/kg; maximum, 60-80 mg) can decrease presumed cell-mediated inflammation. The patient may require oxygen or mechanical ventilation. If anaphylaxis is suspected ("atypical FPIES"), epinephrine should be administered. ondansetron 0.15mg/kg intramuscularly for children > 6 months should be considered for management of emesis (this drug has the potential to prolong the QT interval). Mild-to-moderate acute FPIES can be treated with oral rehydration, including continuation of breast-feeding or administration of clear fluids. The patient should be observed and vital functions should be monitored for at least four to six hours.

NUTRITIONAL MANAGEMENT

The guidelines [1] precise dietary management of FPIES. Elimination of the offending food protein is necessary. Infants with acute FPIES usually return to their usual state of health within 4 to 12 hours and in chronic FPIES within 3 to 10 days of avoidance of the triggering food [9]. Children with FPIES to cow's milk or soya should continue to be breastfed. Children who are not breastfed (or when parents decide to stop breastfeeding) should use an extensively hydrolysed formula. 10-20% of FPIES patients will require an amino-acid formula. This position is in line with the World Allergy Organisation approach [13]. According to the British guidelines [14], in the case of severe FPIES amino-acid formula is suitable as a first-choice milk. Because of the risk of co-reactivity (as in IgE-mediated allergy) goat and sheep milk are not recommended in patients with cow's milk and soy FPIES. Milk from donkeys or camels may be an alternative for children living in different countries. Although most infants do not react to food allergens present in maternal breast milk, in the case of symptomatic FPIES occurring in an exclusively breast-fed infant, the mother should eliminate the trigger food from her diet.

Eliminated foods triggering FPIES should be reintroduced during oral challenge test or supervised feeding or at home in patients with milder reactions. The timing of such reintroduction is not strict. Oral challenge test may be performed after 12 to 18 months without symptoms [1].

Infants with FPIES might be at increased risk of developing symptoms to other foods, so introduction of complementary foods is a big challenge for caregivers. Guidance to parents should be provided during weaning [1].

LONG-TERM MANAGEMENT OF CHILDREN WITH FPIES

Growth (weight and height/length) of children with FPIES should be monitored regularly [1]. Children with FPIES, who have successfully eliminated the implicated food and remain asymptomatic, usually develop normally. As multiple food elimination can be associated with significant nutritional deficiencies, special attention should be paid to ensure nutritional adequacy.

Breastfeeding should be encouraged, and routine avoidance of allergenic food is not recommended in nursing mothers unless a reaction after breastfeeding has been documented [6].

The long-term prognosis is usually favourable. FPIES resolves in different ages. Soy FPIES resolves at the average age of 12 months, and for grains – 35 months. Sixty per cent of children with FPIES to cow's milk develop tolerance by the age of 12 months, 75% by two years and 85% by three years [1].

DISCLOSURE

The authors declare no conflict of interest.

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