

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES) – A REVIEW

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ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES) is an under-recognised and frequently misdiagnosed syndrome – characterised by severe protracted diarrhoea and/or vomiting and frequently associated with additional symptoms such as pallor and/or lethargy – which has its onset soon after the ingestion of the particular food protein. FPIES represents a severe cell-mediated, gastrointestinal food hypersensitivity. Although typically ascribed to cow's milk and soy, FPIES has been described after the ingestion of a wide range of food proteins.

This brief review aims to summarise current knowledge of food protein-induced enterocolitis syndrome (FPIES).

PRESENTATION AND PREVALENCE

The presentation of FPIES varies from mild (e.g. non-dehydrating vomiting and/or diarrhoea) to severe and potentially life-threatening symptoms. Symptom progression may occur rapidly to a state of dehydration. Hypovolaemic shock is associated in up to 20% of cases.¹ A combination of vomiting, lethargy and resulting acidosis understandably – and necessarily – leads to a primary diagnosis of sepsis. In this clinical scenario, the dietary history may not receive prominence with the result that the syndrome recurs with each subsequent ingestion of the food protein. Failure to recognise the association with diet may lead to multiple intensive or high-care admissions due to supposed recurrent sepsis.²

It is unclear whether prior ingestion of the food protein is required in order to induce the FPIES 'sensitivity' or if symptoms can occur *de novo*. FPIES has only been described in childhood, and in particular, early childhood (at the time of introduction of complementary feeds, i.e. breast-milk alternatives and/or solid foods).

The prevalence and incidence of FPIES are not known. Attempts to determine them are hampered by the variable presentation, under-recognition of the syndrome, infrequently performed diagnostic challenges and, perhaps, the rarity of the condition.

DIAGNOSIS

The FPIES diagnosis is a clinical one; equivocal scenarios require resolution by modified oral food challenge (OFC) tests.³ Standard OFCs are modified in anticipation of rapid-onset vomiting and/or diarrhoea. Therefore, intravenous cannulation is necessary prior to

commencement, as are stepwise challenge increments. Lengthy intervals between incremental food doses are mandatory. It is also wise to prepare intravenous bolus replacements, anti-emetics and steroid medications.

The FPIES diagnostic criteria include the onset of predominantly gastrointestinal (GI) symptoms in young infants (usually before 9 months of age), which are consistently present on repeat ingestion of the trigger food. Recurrent vomiting usually occurs within 1-2 hours. Removal of the offending food protein from the diet leads to rapid – and complete – resolution of symptoms within 24-48 hours.^{1,4} Additional pathognomonic FPIES features include a raised white blood cell count with a predominance of neutrophils. This finding necessarily blurs the clinical picture, raising the clinician's suspicion of sepsis. The presence of bloody diarrhoea may also lead to suspicion of infectious diarrhoea, coagulation defects or intussusception in those who fail to appreciate the significance of the temporal association with a new food. The absence of fever, presence of eosinophilic debris in the stools and negative stool cultures can help differentiate these conditions. Characteristically, inflammatory markers are not raised. Biopsies show crypt abscesses, diffuse inflammatory cell infiltrates with plasma cells in the colon, and oedema with mild villous injury in the small intestine. FPIES may occasionally present with insidious chronic diarrhoea, vomiting and failure to thrive.¹

Patients with FPIES classically return negative allergy tests (specific-IgE and/or skin-prick testing). Endoscopy is often unhelpful as infants may remain well between challenges. Atypical cases have been described with detectable specific IgE to the causal protein and with a more prolonged course of allergy.¹ However, given the high population prevalence of IgE-mediated food allergy (between 4% and 6% in young children in developed countries), it is not surprising that a proportion of children with FPIES have concomitant IgE-mediated food allergy.

Studies suggest that atopy patch testing (APT) can aid prediction of tolerance and thus avoid unnecessary food challenges. Indeed, Fogg *et al.*⁶ demonstrate in 19 children with FPIES that APT returns a remarkably high sensitivity and specificity.

DIFFERENTIAL DIAGNOSIS

Acute infective conditions remain the primary differential diagnosis, e.g. sepsis and/or gastroenteritis. Conditions such as milk-protein-induced proctocolitis, enteropathy and eosinophilic gastroenteropathies may also present with similar, overlapping features. FPIES represents the severe end of the spectrum of food allergy that affects only the gut. Table 1 outlines the comparative features of FPIES, gastroenteritis and IgE-mediated food allergy.

ROUTE OF EXPOSURE AND TYPICAL FOOD PROTEIN TRIGGERS

The route of allergen exposure is usually by ingestion. There are no reports of FPIES in exclusively breastfed infants. This is in contrast to IgE-mediated food allergies where acute skin reactions and even non-IgE-

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Table I. Comparative features of FPIES, gastroenteritis and classic IgE-mediated food allergy

	FPIES	Gastroenteritis	IgE-mediated allergy
Presenting age	Weaning	Any	Predominant in early childhood
Atopy	No greater than population	No greater than population	Always
Allergy test positive*	No greater than population	No greater than population	Always
Profuse vomiting	Usual	Frequent	Frequent
Profuse diarrhoea	Usual	Usual	Infrequent
Hives & angio-oedema	No	No	Usual
WCC (with neutrophilia)	Usual	Usual	Eosinophilia not uncommon
Stool culture positive	No	Common	No
Stool eosinophilic debris	Usual	No	Infrequent
Inflammatory markers raised	No	Common	No
Clinical response to dietary avoidance	Characteristic	No	Characteristic

*Allergy test = skin-prick test and/or specific-IgE.

WCC – white cell count.

mediated conditions, such as dietary protein-induced proctocolitis, have been attributed to food protein passage through breast milk.²

Milk and soy are most frequently implicated; it is not uncommon for infants to react to both (50%).¹ Many solid food allergens have also been implicated in FPIES.² Cross-reactivity is high, e.g. when one fin-fish species is implicated, children may react to other fin-fish. Table II lists case reports which reflect the food proteins regarded as responsible for inducing FPIES.

MANAGEMENT

While the pathophysiological immune basis for FPIES is poorly understood, the cornerstone of management of children with FPIES is careful exclusion of the causal food protein (and cross-reactive proteins), preferably under the supervision of a paediatric dietitian. Most infants with FPIES will tolerate extensively hydrolysed casein formula; if not, an amino-acid based formula is appropriate. Breast milk is well-tolerated as infants tend not to react to maternally ingested proteins passed into breast milk as reported in some other food allergies.¹

The prognosis of FPIES is good – resolution will occur within 2 years in 60% of cow's-milk-sensitive and 25% of soy-sensitive patients.^{9,10} Confirmation of resolution

may require carefully supervised modified OFCs.

SUMMARY

FPIES is an under-recognised but not infrequent syndrome. It should always be considered in the differential diagnosis of young children who present with acute, severe, dehydrating diarrhoea, particularly if it is recurrent. Modified incremental OFCs will be necessary to verify the diagnosis if the presentation is equivocal, and to determine whether tolerance to the candidate food protein has developed. Symptoms resolve dramatically after avoidance of the causal food protein (and cross-reactive foods). The prognosis of the condition is favourable.

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Table II. Case reports involving food proteins associated with FPIES

Study	N	Diagnosis made by oral challenge test	Food allergens
Fogg <i>et al.</i> ⁵	19	Yes	Cow's milk, soy, rice, egg, wheat, oat
Vandenplas <i>et al.</i> ⁶	1	Yes	Chicken
Nowak-Wegrzyn <i>et al.</i> ²	14	Yes	Rice, sweet potato, squash, string beans, peas, oat, barley, chicken, turkey
Levy & Danon ⁷	6	Yes	Chicken (4), turkey (2), peas (1), lentils (1)
Zapatero Remón <i>et al.</i> ⁸	14	Yes, in 9/14. Others diagnosed on history, skin-prick test and IgE. Atopy patch test in 8.	Fish