

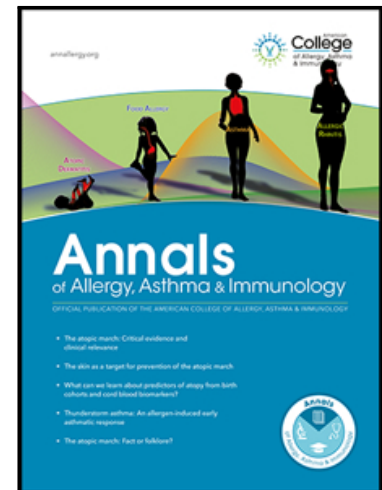
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Food Protein Induced Enterocolitis Syndrome: Not Just in Children

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Food protein induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergy that presents with isolated gastrointestinal symptoms after consumption of specific foods. FPIES is often underdiagnosed and the incidence of FPIES is higher than previously believed¹.

The mechanism of an FPIES reaction is not well understood. A T-cell mediated pathway resulting in enteric inflammation and increased intestinal permeability have been proposed¹ but involvement of innate immunity remains a mechanistic consideration¹. Since there are no reliable and validated diagnostic biomarkers for FPIES, diagnosis is reliant on history, physical exam and oral-food challenge (OFC)^{2,3}.

FPIES has been classically thought of as a childhood disease. Recently, however, this condition has been described in adults although specific food triggers, risk factors and symptoms at presentation appear to differ between the two populations².

Children with FPIES

Natural History

Both chronic and acute FPIES typically present in infancy, between 2–7 months of age, usually following several feedings with cow's milk or soy-formulas³. Chronic FPIES has been reported in infants under 4 weeks, typically following exposures to cow's milk or soy formulas³. Acute FPIES typically presents at a median age of 5–7 months, following introduction of solid foods³.

Age at resolution of cow's milk and soy-induced FPIES ranges from 10 months to 5 years¹. For solid foods, the median age of tolerance acquisition is 4–7 years of age¹. A small portion of children (2%–12%) with atypical FPIES may develop IgE-mediated allergy to culprit food, which is distinct from adult FPIES^{1,3}.

Demographic characteristics

FPIES in children has a slight male predominance and is frequently associated with atopic disease³.

Symptoms

The acute form typically presents with profuse, repetitive vomiting, lethargy and pallor, occurring 1–4 hours after food ingestion^{1,4}. Diarrhea appears a few hours later in some patients⁴. Acute symptoms most often resolve within 24 hours after food ingestion¹.

Severe cases may be complicated by hypothermia and hypotension and metabolic changes such as acidemia and methemoglobinemia mimicking sepsis⁴. Though patients with FPIES may require intensive care, there have been no reported deaths from FPIES⁴.

The chronic form is characterized by watery diarrhea, occasionally with blood or mucus, chronic intermittent emesis, and/or lethargy¹. Poor weight gain and failure to thrive are common¹. With continued feeding, chronic symptoms worsen progressively and in severe cases may culminate in dehydration, metabolic acidosis and methemoglobinemia^{3,4}. Symptoms typically resolve within a few days after withdrawal of the offending food³.

Food triggers

The food most commonly implicated in chronic FPIES is cow's milk-formula, followed by soy-formula¹. Grains such as rice and oat are the most common solid foods followed by eggs, meats, fish, vegetables, poultry and sweet potato. In Mediterranean countries including Italy and Spain, fish is the most common eliciting food indicating geographic variation in food triggers⁴.

Adult-onset FPIES

In recent years, adult onset FPIES has been increasingly recognized. Demographic characteristics and trigger foods differ between children and adults with FPIES, despite similarities in presentations of isolated gastrointestinal symptoms following consumption of a trigger food².

Demographics and natural history

The average age of onset of FPIES in adults is around 35 years old but may present from late teenage years to over 65 years of age^{2,5}. Progression to IgE sensitization or allergy has not been shown^{2,5}. A female predominance has been observed in adults with FPIES as opposed to males for childhood onset FPIES^{2,5}. While there is an abundance of research on childhood FPIES, natural history of adult-onset FPIES remains unknown.

Symptoms

Adults present with isolated gastrointestinal symptoms after consumption of a food trigger^{1,5}.

Patients frequently attribute their symptoms to food poisoning although other dining companions are devoid of symptoms⁵. Symptom typically begin about 2-3 hours following ingestion of the implicated food^{2,5} and generally last between 1–4 hours^{2,5}. Reported symptoms, in order of frequency, are abdominal pain followed by vomiting then diarrhea^{2,5}. 30% of patients experience all three symptoms². Time to resolution of adult-onset FPIES is not known since patients continue to avoid specific triggers. However, there have been reports of reactions occurring up to 30-years after initial onset of symptoms⁵.

Spectrum of severity

Symptoms of FPIES are reproducible upon consumption of the food trigger. There have been no reported cases of worsening symptoms or progression to anaphylaxis². Occasionally, severity of symptoms requires fluid resuscitation and treatment with opioid analgesics⁵.

Food Triggers

Fish and crustacean shellfish are the most common causes of adult FPIES^{1,2,5}. Other reported triggers include cow's milk, wheat, egg and mushroom^{1,2}. Another study reported quorn (a meat substitute), peanut, almond, and chicken being additional triggers⁵.

Diagnosis and Management

Diagnosis is usually made on history but the gold standard diagnostic test is an OFC¹. This is often not performed due to the significant patient discomfort incurred. As with FPIES in children, there are no reliable tests for diagnosis. However, significant neutrophilia is noted in

many instances¹. Serum IgE and skin prick tests are typically negative when assessing patients with FPIES^{1,2}.

It is important to rule out other conditions that might mimic FPIES, because the presenting symptoms are generally non-specific. Conditions such as celiac disease, lactose intolerance and IgE-mediated allergies must be ruled out with appropriate investigations before a diagnosis of FPIES in adults is confirmed.

Currently, management of FPIES in adults is identification of trigger foods and avoidance through the use of elimination diets^{1,2}.

Conclusion

A great deal about FPIES remains unknown, especially in adults. We have little understanding of the pathophysiology of the disease nor do we know the mediators giving rise to the dramatic symptoms. Currently, there are no accurate and simple diagnostic tests. OFCs are cumbersome and unpleasant for the patient. The only treatment available is an elimination diet which, without proper substitutions, could cause malnutrition, especially in children. Further research is urgently needed to better diagnose and treat patients with FPIES.

FPIES is more common than previously thought and needs to be properly diagnosed and managed in both adults and children. Symptoms can be debilitating and in some cases life threatening, so it is important to promptly recognize and diagnose patients with this condition.

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	Adults	Children
Typical age of onset	35 Years of age	2-7 Months of age
Sex distribution	More females	Slight male predominance
Frequency of specific symptoms	Abdominal pain > vomiting > diarrhea	Vomiting > pallor > lethargy > diarrhea > hypotension

Risk of hypotension	Not reported	5 – 15 %
Metabolic Acidosis	Not reported	More common in chronic FPIES
Major food triggers	Shellfish, fish, cow's milk, wheat, egg	Cow's milk, rice, soy, oat, egg, fish, vegetables
Natural History	Doesn't progress to anaphylaxis on rechallenge	Remission, usually resolves by school age.
Prick Skin Tests	Negative	5 to 25%, in cow's milk or rarely with other foods
Serum Specific IgE	Negative	2 – 12% in atypical FPIES
Specific Biomarkers	None	None

Table 1: Comparison of childhood-onset and adult-onset Food Protein Induced Enterocolitis Syndrome (FPIES)