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Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom

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ABSTRACT

Background: Food protein-induced enterocolitis syndrome (FPIES) is a pediatric non–IgE-mediated allergic reaction to foods. The diagnosis of FPIES is clinical, with children presenting typically 2 to 4 hours after ingestion of a food protein. The most striking symptoms are vomiting, lethargy, and pallor. Misdiagnosis and delay in presentation to an allergist or gastroenterologist are common.

Objectives: To investigate the pathway of patients with FPIES presenting to a specialist clinic in the United Kingdom to ascertain whether they experienced delays or misdiagnoses and to investigate their symptoms and triggers.

Methods: All patients with FPIES presenting over a 3-year period (2010–2013) in a tertiary pediatric allergy clinic in London were analyzed retrospectively. This was performed by searching electronically for all patients with a diagnosis of FPIES and manually reviewing paper notes. Presenting symptoms and management pathways were collated.

Results: Fifty-four patients were identified, with an average age of onset at 8 months. They initially presented to medical professionals other than an allergist or gastroenterologist. The most frequent presenting symptom was vomiting followed by signs suggesting shock or hypotension and diarrhea. Differential diagnoses included gastroenteritis, sepsis, and surgical abnormalities. The main eliciting foods were cow's milk, fish, egg, soy, and wheat.

Conclusion: In the United Kingdom, FPIES typically has its onset at 8 months. Patients experience a delay of 12 months in the diagnosis of FPIES and frequently have multiple episodes and interim diagnoses. A great need remains for enhanced education of medical practitioners dealing with children about the varied presentations of FPIES.

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a pediatric non–immunoglobulin E (IgE)-mediated allergic disorder triggered by the ingestion of food, whether solid or liquid. FPIES was initially described in 1967 to cow's milk.[1] Up to 65% of patients with FPIES react to cow's milk and soy; however, FPIES also can be caused by a wide variety of solid foods in up to 25% of these patients with soy and milk FPIES.[2] FPIES usually presents within the first 6 to 12 months of life with some nonspecific symptoms along a spectrum of severity: repeated debilitating vomiting is typical and often accompanied by diarrhea, and in more severe cases hypotension can develop,[3] manifesting as signs of shock. The symptoms resolve once the offending food protein has been removed from the diet and reoccur on re-exposure.

Unlike immediate-onset IgE-mediated allergies, FPIES typically presents 2 to 6 hours after ingestion of the culprit food ("acute" FPIES); this delay commonly leads to misdiagnosis and presentation to an acute medical setting, where a diagnosis of sepsis or gastrointestinal viral illness is typically entertained. Unlike sepsis, in FPIES the blood inflammatory markers are not increased, but the peripheral white cell count can be elevated, peaking at 6 hours, adding to the clinical confusion surrounding the diagnosis. The diagnosis of FPIES is made on clinical grounds; currently there are 2 accepted sets of diagnostic criteria (Table 1).[4,5] FPIES also can present with a subacute or chronic presentation ("chronic" FPIES) that manifests as intermittent vomiting, diarrhea, faltering growth, and sometimes dehydration.[6] This subacute or chronic presentation has been attributed to continuous exposure to the food trigger, such as

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Table 1
Diagnostic criteria of food protein-induced enterocolitis syndrome

Powell[4]	Leonard[5]
<9 mo old at initial reaction	<9 mo old at initial diagnosis
Exposure to incriminated food elicits repetitive vomiting and/or diarrhea within 4 h without any other cause for symptoms	Repeated exposure to causative food elicits typical symptoms without alternative cause
Symptoms limited to gastrointestinal tract	Absence of symptoms that suggest an IgE-mediated reaction
Avoidance of offending protein from the diet results in resolution	Removal of causative food results in resolution of symptoms
Re-exposure or food challenge elicits typical symptoms	Re-exposure or food challenge elicits symptoms within 4 h

cow's milk or soy formula. Chronic FPIES is less common, perhaps owing to the initiation of hypoallergenic formula (in patients in whom cow's milk protein or soy is the trigger).[7] The prevalence of FPIES is difficult to ascertain owing to its frequent misdiagnosis. One suggested incidence for cow's milk FPIES has been reported as 0.34% in the first year of life.[8] The increased reporting of FPIES in the past 2 years[9] may be due to an increased disease incidence (as is the case for other non-IgE gastrointestinal diseases, such as eosinophilic esophagitis) or to an increasing awareness of the disease entity.

In 1 cohort, the median age of achieving tolerance to the allergenic foods was 24 to 28 months, with most becoming tolerant by 3 years.[10] The exception to this was soy, which achieved only a 30% tolerance rate by that age.[10] A recent cohort has suggested that patients with soy FPIES grow out of it by 6.7 years of age.[11] Katz et al[8] supported this early resolution, with 94% of cow's milk FPIES being outgrown by 30 months. Mehr et al[12] found that most were tolerant by 3 years of age, but interestingly this included soy. Different ages in tolerance seem to be due to geographic differences in populations; differences in how patients are managed also may play a role.[11]

The pathophysiology of FPIES is unclear. Most patients have no evidence of specific IgE antibody response against food protein, but food-specific IgE has been detected in up to 20%.[8] A report by Van Sickle et al[4] suggested that the mechanism is driven by circulating lymphocytes sensitive to the food antigens. More recently, Caubet and Nowak-Węgrzyn[13] reiterated that FPIES is T-cell driven, although the exact role of T cells remains undefined. Adding to this is a recent abstract by Nowak-Wegrzyn et al[14] showing that children with FPIES exhibit a marked increase in interleukin-10 and interferon-γ–induced protein 10.

The authors investigated the presenting clinical features and referral pathways of children presenting with FPIES in the United Kingdom.

Methods

A large UK retrospective audit was performed of patients presenting to a tertiary London pediatric allergy service (Children's Allergy Service, St Thomas' hospital, London, United Kingdom); this service accepts referrals to allergy and combined allergy and gastroenterology clinics. All patient notes were accessed after an electronic clinical database and clinic letter search for *FPIES, food protein induced enterocolitis,* and *delayed gastro-intestinal food allergy.* Then, a retrospective paper and electronic case note review was performed of all patients with a diagnostic coding of FPIES over a 3-year period (2010–2013).

Acute was differentiated from chronic FPIES using the Powell criteria and the criterion of "protracted symptoms" or "faltering growth," which is a locally agreed inclusion criterion. Information was collated for patient demographics, age at first presentation to a health professional, symptoms at first presentation, to which health professional a patient presented initially, and the number of attendances to a health professional before referral to an allergy service. In addition, data were collected on allergy investigations performed and any precipitating allergens identified. These were transcribed onto an Excel spreadsheet and analysis was performed using Excel 2010 (Microsoft, Redmond, Washington).

Results

Seventy patients were initially identified as being diagnosed with FPIES through the database and electronic referral and outpatient letter search of 14,800 outpatient appointments. Sixteen patients were excluded on further investigation of the clinical and electronic notes owing to ambiguity in the diagnosis. A diagnosis of FPIES was made in 54 of 14,800 referrals (0.36%) to a specialist allergy service. Of the 54 diagnoses with clinical certainty, 32 (59%) concerned boys. The ethnicity of most patients was described as white or white British (15 of 54, 28%; Table 2). Thirty-two patients initially presented to their general practitioner and 9 to the emergency department; 13 patients did not have this recorded. Patients had presented to a medical professional a mean of 2 times (range 1–10 times) before an allergist or gastroenterologist specialist referral; initial health care providers included primary care physicians (59%), general pediatricians (20%), and emergency department physicians (17%; Table 3). Indeed, most patients were referred to at least 1 other hospital specialty before allergy referral (average number seen 1.5, range 0–3 specialists). The mean symptom duration before allergy referral was 20.2 months (range 2.75–144 months, median 13 months).

The most common presenting clinical signs, in order of frequency, were vomiting (44 of 54, 81%; increasing to 84% when considering acute FPIES alone); shock or hypotension, suggested by listlessness, loss of consciousness, appearing gray (pallor), clamminess, and hypotonia (32 of 54, 59%); and diarrhea (10 of 54, 19%); additional clinical signs included abdominal pain, other stool change, and weight loss (Table 4).

The list of differential diagnoses made, in order of decreasing frequency, included IgE-mediated food allergy (50%), surgical abnormalities (17%), gastroenteritis (13%), lactose intolerance (13%), gastrointestinal inflammation (8%), sepsis (4%), and eosinophilic esophagitis (4%). The surgical differential diagnoses included intussusception, malrotation, obstruction, and volvulus.

Most patients presented with symptoms of acute FPIES (50 of 54). The median age at initial presentation to a health professional

Table 2
Ethnicity of patients

Ethnicity	n	%
White (white British)	15	28
White other	2	4
Mixed	2	4
Asian	3	6
Bangladeshi	1	2
Latin American	1	2
Mixed Asian	1	2
Black	1	2
Other	4	11
Not stated	9	17