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Non-IgE Mediated Food Allergy Syndromes

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Abstract

In contrast to IgE-mediated food allergies, diagnosis of the various non-IgE mediated food allergy syndromes can be challenging due to the overall lack of noninvasive confirmatory testing for these disorders. Many of the non-IgE food allergy syndromes are diagnosed clinically, based on history and managed empirically with food avoidance. Therefore, it is essential for the practicing allergist to be familiar with the myriad presentations of non-IgE mediated food allergy. This review focuses on the presentation and management of the non-IgE mediated food allergy syndromes.

Keywords

food allergy; non-IgE mediated food allergy; food-protein induced enterocolitis syndrome (FPIES); allergic proctocolitis; eosinophilic esophagitis (EoE); eosinophilic gastrointestinal disorders (EGID); eosinophilic gastritis

Food Allergy: Definition

Reproducible adverse reactions which occur after eating a food but that are not mediated by immunologic mechanisms are classified as food intolerances and can occur by metabolic, pharmacologic, toxic or undefined mechanisms. Classic examples of food intolerance include lactose intolerance and scombroid fish poisoning. In contrast, a food allergy is a reproducible, adverse health event occurring after exposure to a specific food that is mediated by an immunologic mechanism.¹ Food allergy reactions can be mediated by IgE- or non-IgE-mediated mechanisms. Both mechanisms of allergy require an immunologic sensitization to the food antigen which results in a reproducible, immune-mediated reaction upon re-exposure to the food. We will now review various forms of non-IgE mediated food allergy.

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Clinical Trial Registration: None

Food Protein-Induced Proctocolitis

Food protein-induced proctocolitis is also known as allergic proctocolitis, allergic dietary proctitis, dietary protein proctitis, and colloquially by primary care providers as "milk protein allergy," and usually presents with blood and mucous in the stool in otherwise healthy infants.² A prospective birth cohort study performed in Israel identified the prevalence of food-protein induced proctocolitis at 0.16%, however this may be lower as many children did not undergo confirmatory food challenge testing.³ From a recent meta-analysis of 312 patients, at the time of presentation, 49% of infants were breastfed, 44% were on cow's milk formula, and 6.8% were on soy formula.² If the history is completely consistent with allergic proctocolitis then there is no further need for diagnostic workup. However, if studies are obtained then mild anemia, fecal-occult positive stool, and colon biopsy with >60 eosinophils per high powered field are the common findings.¹ When the infant is otherwise well appearing and gaining weight, the generally accepted therapy has been strict elimination of cow's milk or other trigger foods from the diet until 12 months of age.^{1, 4} Diet modification is accomplished by changing formula or maternal exclusion diet. If this is followed by resolution of visibly bloody stools within 48–72 hours, the presumptive diagnosis of food-protein associated proctocolitis is typically accepted. However, recent data suggests that elimination of cow's milk may not affect duration or severity of bleeding in the majority presenting with rectal bleeding, and that other transient etiologies such as viral and bacterial infections can be identified in some cases.^{3, 5, 6}

Food Protein-Induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome can be divided into two forms: acute and chronic. The acute form is the more common form and is characterized by profuse repetitive emesis and lethargy that begins 1–4 hours following ingestion of the causal food.¹ It is often accompanied by decreased activity, lethargy, pallor, diarrhea, and in 15% of cases may proceed to severe systemic symptoms which include hypothermia, methemoglobinemia, acidemia, and hypotension. These acute reactions are often accompanied by leukocytosis with neutrophilia and thrombocytosis, though these laboratory findings are not specific for FPIES. Alternatively, if a causal food is being ingested every day, children may develop chronic FPIES. Chronic FPIES is uncommon and difficult to diagnose with certainty. It occurs in children who have been ingesting the offending food on a daily basis and presents with chronic/intermittent emesis or reflux, watery diarrhea, and may progress to weight loss or failure to thrive. The diagnosis of FPIES is certain if the symptoms improve with withdrawal of offending food and acute symptoms of FPIES are present when it is reintroduced (vomiting 1–4 hours following food challenge). It is important to note that due to the nonspecific symptoms and lack of provider familiarity with the diagnosis, many patients with FPIES experience delay to diagnosis or misdiagnosis.^{7, 8}

The most common FPIES triggers in a geographic region may reflect the pattern of infant food introduction in that area. For example, in the US FPIES often presents in infancy with reaction to cow's milk and soy under 6 months of age, or slightly older children with reactions to grains like rice, wheat or oat.^{8, 9} However, in Italy, Australia, or in Israel FPIES to soy is less common, while in Italy FPIES to fish is seen more frequently.^{10–12} The

majority (65–80%) of children have FPIES to only one food, most commonly milk or soy.^{8, 9, 13} However, in US case series, 30–50% of patients reacting to milk also react to soy, but the proportion of dual-sensitized patients is much lower in non-US countries.^{9–11, 13} Reactions to grains such as rice, oat or wheat are the next most common group, but reactions to egg, meats, vegetables and fruits have also been described.^{9, 11, 13} Interestingly there have been a few described FPIES reactions in adults ingesting shellfish, fish or egg with no evidence of IgE-mediated sensitization.^{14, 15}

The exact prevalence of FPIES is unknown; although, there is a single Israeli prospective birth cohort study demonstrating cumulative incidence of cow milk FPIES at 0.35% over a 2 year period in a single Israeli hospital.¹² Although case series of several hundred patients have been published from tertiary care centers, it remains unclear exactly how widespread FPIES may be. These cohorts may reflect considerable referral bias and may fail to capture patients with less severe symptoms who do not present to a specialist for workup.

The diagnosis of FPIES relies heavily upon eliciting a careful dietary history. If a patient has had multiple characteristic, delayed reactions with a food then this can be considered diagnostic of FPIES. FPIES reactions may vary in severity based on the amount of the food trigger which has been ingested as well as patient-specific factor such as race, age, and co-morbid illness. If the patient's history is unclear after taking a careful history then oral food challenge can be used judiciously to confirm the history. Diagnostic food challenges for FPIES should be performed under physician supervision and careful consideration should be given to obtaining intravenous access prior to initiating the challenge in patients with difficult access or a history of severe reactions.

The mainstay of treatment for FPIES is avoidance of the offending food(s). Acute episodes of FPIES need to be recognized as potential emergencies, with up to 15% risk of hypotension.¹⁶ Two small studies have described successful use of intramuscular or intravenous ondansetron to abort acute FPIES episodes, with resolution of symptoms within one hour.^{16, 17} Oral dissolvable ondansetron has been demonstrated to be effective in large trials for gastroenteritis in children, and therefore although this has not been studied in FPIES it may potentially be a successful administration route as well.¹⁸

Data suggests that the majority of children will outgrow FPIES around 3 years of age.^{9, 12, 13} However, there is considerable variability in the literature regarding the age at which children outgrow each particular food, which may reflect the regional differences from which the study's cohorts are derived. For example, from a Korean cohort 75–90% of patients tolerated soy by 6–8 months, whereas in two separate US cohorts soy tolerance occurred at a mean of 2.8 years of median age of 6.62 years.^{9, 13, 19} In general, this data is derived from observational cohorts and therefore may be biased towards older ages as patients were not actively challenged to assess for FPIES resolution. Although there is not enough data to support routine clinical use, one putative predictive factor for milk FPIES resolution may be development of positive milk specific IgE or skin testing. Caubet et al. described that in their cohort, 24% of patients with milk FPIES (17 total patients) had either positive milk specific IgE or SPT, and none of these patients were tolerating milk at the end of the study period. The majority of patients in this group did not outgrow typical FPIES

symptoms at the study's end, but 41% (7 of 17) SPT positive patients had symptoms evolve into typical IgE mediated food allergy symptoms over time.¹³ The mechanism of this change is not clear, and additional work is needed to determine the prevalence of "atypical," IgE-positive variant of FPIES.

Food Protein-Induced Enteropathy

Food-protein induced enteropathy is a syndrome of recurrent abdominal pain and chronic malabsorptive diarrhea which may progress to weight loss and growth failure. Vomiting may or may not be a feature of this condition.^{1, 20, 21} Celiac Disease, or gluten-sensitive enteropathy is the most common of these conditions and is characterized by small intestinal villous blunting and lamina propria inflammatory infiltrate in conjunction with positive endomyesium and tissue transglutaminase antibodies and HLA DQA1*501 and B*201 alleles.¹

In the 1960's it was first described that children may present with enteropathy due to sensitivity to cow's milk or soy in infancy or during school age years. Sensitivity to more than one protein has also been described, in particular in celiac patients sensitized to a second food such as cow's milk.²¹ The exact prevalence of non-celiac food –protein induced enteropathy is unknown, but it is generally thought to be a rare condition. However, it should be considered in the differential diagnosis if a patient with celiac disease has removed wheat from the diet and has persistent symptoms. Transition to amino acid-based formula is recommended in cases of enteropathy due to cow's milk or soy. Symptoms should typically resolve within one or two weeks, although in severe cases patients may require additional time and IV nutritional support if weight loss and GI damage was extensive.²¹

Eosinophilic Gastrointestinal Disorders

Primary eosinophilic gastrointestinal disorders (EGID) are characterized by eosinophilic infiltrate into the gastrointestinal tissue in the absence of another demonstrable cause and include: eosinophilic esophagitis (EoE), eosinophilic gastritis, gastroenteritis, enteritis, and colitis.

Eosinophilic esophagitis (EoE) is the most common of the eosinophilic gastrointestinal disorders. It is estimated to have a prevalence of approximately 1/2000, which may be rising, and is most common in Caucasian males. Of all the non-IgE mediated food allergy syndromes, we have the greatest understanding of underlying genetics and mechanism in EoE. Recent data has implicated Th2 pathway cytokines IL-5, IL-4, IL-13, IL-15, TSLP and eotaxin-3 in EoE pathogenesis, these mechanisms have been recently reviewed elsewhere and therefore we will not review extensively here.²² In children, EoE is more likely to present with abdominal pain, nausea, emesis and failure to thrive. In adolescents and adult, symptoms of heartburn, dysphagia, food impaction and stricture are more common. The diagnostic gold standard for EoE is the presence of at least 15 eos/high power field (hpf) in esophageal biopsy taken from multiple sites obtained with esophagogastroduodenoscopy (EGD) after recommended 8 weeks of maximum proton pump inhibitor (PPI) dose.²³ EGID are unknown to clearly have a food-related pathogenesis in contrast to EoE, which can be

managed by dietary avoidance, topical corticosteroids and, if needed, interventions such as esophageal dilatation.

The other manifestations of EGID are less likely to be food-related than EoE. In general, the manifestations of EGID vary based on the anatomical location within the GI tract and upon which layer of the GI tissue is involved. Eosinophilic gastritis may present with epigastric abdominal pain, nausea and vomiting. The diagnostic criteria for EGID account for the occurrence of low levels of eosinophilic infiltrate in other areas of the intestinal track, which can be physiologic beyond the esophagus. On biopsy >30 eos/hpf in the gastric mucosa are considered diagnostic for eosinophilic gastritis.²⁴ Eosinophilic colitis may present with abdominal pain, diarrhea, tenesmus, and occasionally bloody stool. On biopsy >60 eos/hpf in the gastric mucosa are considered diagnostic.²⁴ Classification schemes based on the layer of GI tissue have also been proposed.^{24, 25} The differential diagnosis for EGID is broad, and includes parasitic infection, medication allergy, eosinophilic granulomatosis with polyangitis syndrome (Churg-Strauss), inflammatory bowel disease, and hypereosinophilic syndrome.^{25, 26} An eosinophilic infiltrate of the colon and rectum can also be seen in graft-versus-host-disease in bone marrow transplant patients, and may even be an early manifestation of inflammatory bowel disease.²⁶ The role of food allergens is not well defined for other eosinophilic GI disorders except EoE. Although there have been case reports of improvement in a few cases of eosinophilic gastritis and gastroenteritis with empiric elimination diets, this may be non-specific and there have been no large trials demonstrating a role for allergy testing or elimination diets with exception of EoE.^{25, 27}

Conclusions

The management of each of these disorders requires careful attention to nutrition, especially in growing children. Children should have height and weight plotted against appropriate growth charts at each visit, and adults' weights should be tracked over time as well. Liberalizing new foods into the diet when indicated can help to promote better nutrition, especially if the diet had been particularly limited. Of particular concern is the issue of ensuring appropriate formula substitution in infants under one year of age if milk and soy allergy are present. In cases where multiple food allergies are present, collaboration with a licensed nutritionist familiar with food allergy is highly recommended. For eosinophilic GI disorders, enteropathies, or if any additional co-morbid GI disorder is present then collaboration with a gastroenterologist is required as well. Therefore, maintaining good communication between all providers becomes central to patient safety and satisfaction.

The non-IgE food allergy syndromes can present from infancy through adulthood with a diverse set of symptoms, requiring careful history taking in order to arrive at the final diagnosis. The prognosis of non-IgE food allergy syndromes is highly variable, and although most will outgrow early onset forms (ie: FPIES, proctocolitis) others like the eosinophilic gastrointestinal disorders are thought to be more persistent.²⁸ Although there has been considerable progress in our knowledge of these disorders, many questions remain. In particular, the specific immunologic mechanisms driving the majority of non-IgE food allergies are largely unknown, and therefore the therapies for these conditions remain quite nonspecific.

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Abbreviations Used

IgE	immunoglobulin E
FPIES	food protein-induced enterocolitis syndrome
US	United States
EGID	eosinophilic gastrointestinal disorder
HPF	high powered field
PPI	proton pump inhibitor
EoE	eosinophilic esophagitis

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