

Food allergy and eosinophilic gastroenteropathy: a pediatric gastroenterologist's perspective

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SUMMARY

Food allergy or hypersensitivity is defined as an adverse reaction to food protein which is immune mediated. These disorders are most prevalent in infancy and early childhood. Immediate IgE mediated reactions after ingestion of the offending food are frequently evident by the history of exposure, corroborated by positive skin prick-tests or specific IgE antibodies in serum demonstrating the immunologic abnormality. Immediate reactions can be confirmed by double-blind food challenges. However, patients with food hypersensitivity may present with a variety of symptoms and signs including growth delay, diarrhea, vomiting, protein-losing enteropathy, hematochezia or a shock-like picture, without evidence of IgE mediated immune mechanisms. The immunologic abnormality is more likely cell-mediated and depends on demonstration of inflammation in tissue, often characterized by increased eosinophils. Signs, symptoms and inflammation will improve when the offending antigen is removed, and will return upon subsequent re-introduction, often after several hours or days. As part of the spectrum of gastrointestinal disease related to food allergy there exists eosinophilic gastroenteropathy (EGE) where tissue eosinophilia exists without any demonstrable food hypersensitivity. These «idiopathic» EGE represent a distinct group of disorders of unknown etiology with activation of eosinophils in the gastrointestinal tract leading to signs and symptoms. Dietary manipulation is frequently unsuccessful, therefore pharmacologic treatment is indicated. This review will outline the clinical spectrum and approach to diagnosis and management of food hypersensitivity disorders and EGE.

KEY-WORDS: Food allergy. – Eosinophilic gastroenteropathy (EGE). – Allergic bowel disease.

RÉSUMÉ

Allergie alimentaire et gastro-entéropathie éosinophilique. Point de vue d'un pédiatre gastro-entérologue. – On définit l'allergie (ou intolérance) alimentaire comme une réaction nocive à une protéine alimentaire, de mécanisme immunologique. Ces réactions sont surtout fréquentes chez le nourrisson et le jeune enfant. Ces réactions immédiates, médiées, par IgE, à la suite de l'ingestion de l'aliment responsable sont fréquemment de reconnaissance facile du fait de l'histoire, confirmée par des prick-tests cutanés positifs ou des IgE spécifiques démontrant l'anomalie immunologique. On peut confirmer les réactions immédiates par un test d'ingestion en double insu. Toutefois, les patients souffrant d'hypersensibilité alimentaire peuvent se plaindre de troubles fonctionnels variés comme un retard de croissance, de la diarrhée, des vomissements, d'une entéropathie entraînant une fuite protéique, de selles sanglantes en un tableau de chocs peu suggestifs d'un mécanisme immunitaire à IgE. L'anomalie immunologique consiste plus volontiers en une médiation cellulaire et relève de la démonstration d'une inflammation tissulaire souvent caractérisée par une hyper-éosinophilie. Les signes fonctionnels et physiques sont améliorés par la suppression de l'aliment responsable et se reproduisent lors d'une réintroduction ultérieure après, souvent, plusieurs heures ou jours. À côté de ces maladies gastro-intestinales dues à l'allergie alimentaire, il existe une gastro-entéropathie éosinophilique avec éosinophilie tissulaire sans hypersensibilité alimentaire démontrable. Ces gastro-entéropathies «idiopathiques» constituent une pathologie distincte, d'étiologie inconnue, avec activation des éosinophiles dans le tractus digestif provoquant des manifestations physiques et fonctionnelles. Les manipulations de régime sont souvent infructueuses, ce qui rend nécessaire un traitement pharmacologique. Cette revue se propose d'esquisser le tableau clinique ainsi que l'approche diagnostique et la prise en charge des troubles due à l'hypersensibilité alimentaire et des gastro-entéropathies éosinophiliques.

MOTS-CLÉS: Allergie alimentaire. – Gastro-entéropathie éosinophilique. – Colopathie allergique.

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The child with presumed food allergy continues to present a challenge for the clinician. Food allergies are common, affecting up to 6-8% of children (Bock). In certain instances, for example, IgE mediated anaphylactic reactions, it is clear that ingestion of food protein causes the reaction, and this can be demonstrated by re-exposure (Walker-Smith). However, gastrointestinal disorders characterized by predominantly eosinophilic inflammation in tissue may or may not be associated with known sensitization to identifiable food antigens. There is considerable overlap in what is observed in food allergy and idiopathic eosinophilic gastroenteropathy (EGE), since eosinophilic inflammation of tissue occurs in either condition. The following is an overview of gastrointestinal food hypersensitivity and EGE from the perspective of a pediatric gastroenterologist. Gluten-induced enteropathy is unique in its presentation, diagnosis and natural history and will not be discussed.

Any adverse reaction to the ingestion of food can be termed intolerance or sensitivity. True food allergy or food hypersensitivity is defined as a reproducible adverse reaction to a food protein antigen which is immune mediated. The classic example is an IgE mediated immediate reaction, although cell-mediated reactions occur (McDonald). Eosinophilic gastroenteropathy is defined as gastrointestinal disease characterized by abnormal numbers of eosinophils in the GI tract without an underlying cause (e.g. parasitic, collagen vascular disease). This distinction is somewhat arbitrary, as both entities may be characterized by tissue eosinophilia, and what is considered idiopathic may respond to the elimination of food protein antigens even though our ability to document a defined immune mechanism may be lacking.

TYPE I (IGE MEDIATED) IMMEDIATE HYPERSENSITIVITY REACTIONS TO FOOD

Immediate hypersensitivity reactions to foods are most common in young children, with 50% of these reactions occurring in the first year of life. The majority are due to cow's milk and soy protein from infant formulas. Twenty percent of these reactions occur in the second year of life, and 10% thereafter. Other foods begin to predominate in older children, including egg, fish, peanut and wheat. Symptoms referable to the gastrointestinal tract in IgE mediated allergy typically begin within minutes of the ingestion,

and are short-lived, although occasionally may be delayed for up to two hours. Symptoms include nausea, vomiting, abdominal pain and diarrhea, but may also include oral symptoms, skin manifestations, wheezing or airway edema. The rapid onset of symptoms correlates highly with positive skin prick or IgE-RAST tests to the offending antigen. Caution must be used since positive skin prick and RAST tests do not always predict clinically relevant reactions in blinded food challenges (Bengtsson). If the clinical history is equivocal then double blind food challenges in a controlled environment are needed to prove or disprove a reaction.

NON-IGE MEDIATED FOOD ALLERGY

Much of the study of this area involves infants with milk protein intolerance (Hill, Katz), however the following discussion could be applied to any dietary antigen. The clinical spectrum of cow's milk protein allergy is quite varied, and the presenting features often parallel the site of involvement, as it does for idiopathic EGE (Table I). Avoidance of cow's milk will resolve symptoms and histologic findings; re-challenge will reproduce the findings.

Eosinophilic colitis in infants is the most common manifestation of cow's milk protein allergy (Goldman, Machida). It is characterized by diarrhea with blood and mucous. It has been described in exclusively breast-fed infants from maternal dietary antigens transmitted into breast milk. Sigmoidoscopy is helpful to exclude other causes of bleeding and to document eosinophilic colitis by mucosal biopsy. Intraepithelial and degranulating eosinophils are usually present. Removal of milk protein from infants or breast-feeding mothers usually leads to resolution in symptoms, although microscopic or gross blood may persist for several weeks.

Table I. – Clinical presentation of cow's milk protein allergy.

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| <ul style="list-style-type: none"> • Acute hypersensitivity (urticaria, wheezing, anaphylaxis, vomiting, pain, acute diarrhea) • Failure to thrive • Protein losing enteropathy, edema, chronic diarrhea • Iron deficiency anemia • Eosinophilic colitis • Milk-induced enterocolitis syndrome • Atopic dermatitis • ? Infantile colic |
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Cow's milk allergy can also cause a **small bowel enteropathy** leading to chronic inflammation with villous atrophy. Patients present with diarrhea and failure to thrive, peripheral blood eosinophilia, iron deficiency anemia and hypoalbuminemia from protein-losing enteropathy. At times, patients may present without overt gastrointestinal symptoms, but profound anemia or hypoalbuminemia. Treatment with a milk free diet leads to a rapid resolution of symptoms, and the return of normal villi.

Allergic gastritis is a common feature of cow's milk protein allergy. Symptoms include pain and vomiting, especially if the gastric outlet is narrowed by muscle wall involvement. Mucosal biopsies may demonstrate eosinophilia, but muscle eosinophilia may be isolated. This condition may mimic hypertrophic pyloric stenosis in infants.

Allergic esophagitis is characterized by dysphagia, pain and symptoms mimicking gastroesophageal reflux. Intense eosinophilia is seen on esophageal biopsy, with esophageal pH probe studies showing no acid reflux. This has been seen in association with cow's milk allergy in infants, with elemental formula leading to resolution of symptoms and histologic findings (Kelly). We have found increased mucosal mast cells in allergic esophagitis, distinguishing these patients from those with inflammation from gastroesophageal reflux.

Food-protein induced enterocolitis syndrome is characterized by a severe reaction to ingestion of the offending food occurring 4-6 hours after ingestion. It is characterized by vomiting, diarrhea, frequently hematochezia, lethargy and a shock-like picture. IgE mediated mechanisms cannot be demonstrated (Sicherer).

NATURAL HISTORY OF FOOD ALLERGY

The natural history of both IgE and non-IgE mediated food allergies in young children, suggests tolerance develops with time. In a cohort of 100 children followed prospectively for immediate and delayed sensitivity to foods, 28% developed clinical tolerance by two years, 56% by 4 years and 78% by six years (Bishop). It is recommended that the initial re-exposure to the offending antigen be done in a step-wise fashion in a setting where acute allergic reactions can be treated.

IDIOPATHIC EOSINOPHILIC GASTROENTEROPATHY (EGE)

Idiopathic eosinophilic gastroenteropathy is an inflammatory condition of the gastrointestinal tract characterized by eosinophilic inflammation in tissue. Frequently it is accompanied by peripheral blood eosinophilia. As described by Katz *et al*, the clinical presentation and pathologic features of this disease closely resemble the enteropathy caused by allergy to milk, therefore food hypersensitivity must be excluded.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of eosinophilia of the gastrointestinal tract includes food allergy, parasitic infection, connective tissue diseases including vasculitis and Menetrier's disease. Eosinophilia of the antral mucosa can be associated with *H. pylori* infection, so appropriate studies for *H. pylori* should be performed. Increased numbers and activation of eosinophils in tissue can be seen in ulcerative colitis and Crohn's disease, therefore early inflammatory bowel disease may mimic eosinophilic gastroenteropathy. Hypersensitivity to medications should always be considered if appropriate. Hypereosinophilic syndrome may affect the gastrointestinal tract, but extreme eosinophilia with involvement of multiple organ systems will point to this diagnosis. When the muscular form of EGE affects the gastric outlet, it may resemble hypertrophic pyloric stenosis and outlet obstruction from chronic granulomatous disease. Upper gastrointestinal involvement with muscle layer thickening may be difficult to distinguish from Crohn's disease or small bowel malignancy.

CLINICAL PRESENTATION OF EGE (Table II)

The presenting symptoms and signs of eosinophilic gastroenteropathy depend on the distribution of the involved areas of the gastrointestinal tract and to what extent the depth of the bowel wall is affected (Talley). The clinical presentation helps distinguish mucosal, muscle layer and serosal disease. Each of these forms of the disease are associated with peripheral blood eosinophilia, or increased eosinophil precursors in bone marrow, but it is uncertain why only some areas of the bowel are affected. There is no consistent response to eliminating foods, therefore by definition this is not a food hypersensitivity.

Table II. – Common presenting features of eosinophilic gastroenteropathy.

Common symptoms	
Vomiting	40/80 (50%)
Diarrhea	39/79 (49%)
Growth Delay	36/78 (46%)
Abdominal Pain	26/79 (33%)
Rectal Bleeding	14/73 (19%)
Laboratory features	
Peripheral blood eosinophilia	62/80 (78%)
Hypoalbuminemia	15/23 (65%)
Increased serum IgE	42/61 (69%)
Positive IgE RAST to foods	16/35 (46%)
Skin prick positive to foods	9/26 (35%)

Mucosal disease is the most common form of EGE typically presenting with abdominal pain, vomiting and/or diarrhea, and rectal bleeding. The diarrhea may arise from small bowel mucosal disease leading to malabsorption and growth delay, or may arise from colonic disease. Protein-losing enteropathy with hypoalbuminemia is a common finding. The diagnosis is best made by multiple endoscopic biopsies at multiple sites, as the characteristic mucosal eosinophilia may be patchy. The disease may affect the GI tract diffusely, with obvious thickening of intestinal mucosa or may affect only specific sites. Eosinophilic esophagitis presents with dysphagia, pain and even stricture formation. Rare manifestations include perforation, hepatobiliary disease and pancreatitis.

Muscle layer disease presents with obstruction, and may affect any area of the bowel. However, the classic site of involvement in childhood is at the gastric outlet and may mimic other causes of gastric outlet obstruction.

Serosal eosinophilic gastroenteropathy is rare, and typically presents with abdominal pain and ascites. Abdominal paracentesis will show marked eosinophilia.

PATHOLOGIC FINDINGS

EGE is characterized by increased eosinophils in tissue, although there is no widely accepted criteria for the pathologic diagnosis (Goldman). For mucosal biopsies, emphasis is placed on a minimum average number of eosinophils per high power field (*e.g.* > 15-20/hpf) or if eosinophils constitute more than 25 % of the inflam-

matory infiltrate. Some authors, attach greater significance to the finding of intraepithelial and degranulating eosinophils, as indicators of increased activity of eosinophils. A recent pediatric autopsy series from Texas (Lowick) calls into question what is considered «normal» for eosinophils in the GI tract, unless geographical differences are present. They found that 52 % of cases had at least one site with > 20 eosinophils per hpf, with mean mucosal eosinophil counts ranging from 35 in the cecum, 15 in the duodenum and 5 in the antrum.

Classical tests of allergy (IgE RAST and skin prick tests) will be negative (Bengtsson), unless the patient has both IgE and non IgE mediated disease, so investigators have looked for evidence of cell-mediated immunity such as lymphocyte proliferation assays (Eigenmann). Peripheral blood mononuclear cells are collected from patients, and incubated in the presence of food antigens. Some studies have demonstrated increased reactivity to food antigens in allergic patients, but other studies have not supported this finding. Until more data are available it is difficult to define a clinical role for these tests. Patch testing of the skin with food antigens to demonstrate delayed hypersensitivity is another modality which deserves further study, however, local skin reactions may not be representative of reactions in the gastrointestinal tract.

If commonly available ancillary testing is not helpful, then the diagnosis will rest on the resolution of symptoms on an elimination diet, with a return of symptoms on re-challenge. Unlike the rapid response characteristic of IgE mediated disease, a prolonged challenge may identify delayed reactions with predominantly gastrointestinal symptoms up to six days after exposure (Baehler). In infants, avoidance of food protein antigens using hypoallergenic casein or whey hydrolysate formulas are safe and effective in the majority of infants, however, amino acid-based products may be necessary (Sampson). Elemental diet can be used as a treatment or as a diagnostic tool to assess complex food allergies, by eliminating dietary protein antigens completely, then systematically rechallenging the patient with offending foods (Justinich). Avoidance of the food allergen remains the mainstay of therapy. Pharmacologic therapy has not been effective in preventing manifestations of food allergy. A recent report suggests that the immune response to antigens can be altered by altering gut flora with the addition of *Lactobacillus* in infants with atopic dermatitis and cow's milk allergy (Majamaa).

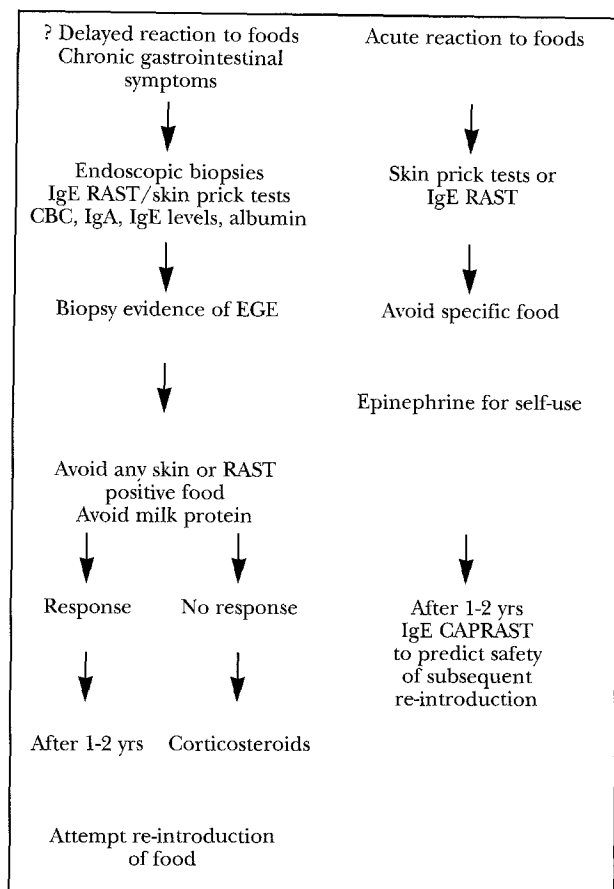


Fig. 1. – Approach to Investigation and Management of Food Allergy and EGE.

APPROACH TO INVESTIGATION AND MANAGEMENT OF FOOD ALLERGY AND EGE (fig. 1)

Patients with acute reactions to food should be investigated with either skin prick tests or IgE RAST tests to confirm an IgE mediated mechanism. Dietary instruction is given for avoidance, and patients should receive instruction on the use of epinephrine. IgE CAPRAST tests may indicate when the sensitivity is lost, and help with the planning of challenges. Double-blind food challenges

may be used to prove or disprove reactions in equivocal cases. In patients with biopsy evidence of eosinophilic gastroenteropathy an attempt should be made to identify potential food allergens and to eliminate these proteins first. Our practice is to perform a complete blood count and differential, serum albumin, serum IgA, IgE and either IgE CAPRAST or skin prick tests to common foods. If small intestinal inflammation or atrophy is seen, antibody serology for celiac disease is included. If these tests are unrevealing or there is no response to elimination of identified antigens, then a strict milk-protein-free diet is tried for four weeks. Even in the absence of objective evidence of milk sensitivity, we find this approach effective in over 50 % of patients. We have also used elimination diets to try to improve symptoms and then investigate which foods may be implicated as they are re-introduced. Ultimately, complete exclusion of intact food protein using exclusive elemental diet can be used to determine whether food antigens are implicated in disease. One report describes the reversal of growth delay, laboratory abnormalities and long-term dependence on corticosteroids in EGE on an exclusive elemental diet, although it is uncertain whether the improvement was due to removal of food antigens or some other mechanism (Justinich).

Corticosteroids are the mainstay of pharmacologic therapy for idiopathic eosinophilic gastroenteropathy. We start with prednisone or equivalent at 2mg/kg per day with tapering to low dose alternate day therapy within 6-8 weeks. Eosinophilic inflammation typically responds to treatment with corticosteroids, and symptoms will resolve quickly. A subgroup of patients will relapse when tapered, and may do well with low dose alternate day therapy. Agents which stabilize mast cells have been used including sodium cromoglycate without consistent response, and ketotifen, which has been shown to be effective in corticosteroid dependent patients (Melamed). Topically active corticosteroids (*e.g.* Budesonide) may be an alternative to systemic corticosteroids.

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