ARTICLE

Non-IgE-mediated food allergies

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Diagnosing mixed or non-IgE-mediated allergy is challenging. A clear cause-effect relationship between exposure to the suspected food and symptoms is not always possible, as symptoms develop over time and are more chronic in nature. Skin-prick tests and specific IgE to the allergen are usually negative. An elimination diet may be necessary to diagnose non-IgE-mediated type food allergy. The suspected allergen should be excluded from the diet for 2 - 6 weeks under dietetic guidance to assess for improvement of symptoms. After symptom improvement, a rechallenge is necessary to definitively prove causal relation.

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Non-imunoglobulin E (IgE)-mediated conditions include combined IgE and cell-mediated conditions such as atopic dermatitis (AD) and eosinophilic oesophagitis (EoE), and pure T-cell-mediated conditions such as food protein-induced enterocolitis syndrome (FPIES), allergic proctocolitis and enteropathy syndromes.

Diagnostic tests in non-IgE-mediated food allergy

Diagnosing mixed or non-IgE-mediated allergy is challenging. A clear cause-effect relationship between exposure to the suspected food and symptoms is not always possible, as symptoms develop over time and are more chronic in nature. Skin-prick tests (SPTs) and specific IgE (sIgE) to the allergen are usually negative. An elimination diet may be necessary to diagnose non-IgE-mediated type food allergy. The suspected allergen should be excluded from the diet for 2 - 6 weeks under dietetic guidance to assess for improvement of symptoms. After symptom improvement, a rechallenge is necessary to definitively prove causal relation.

Endoscopy with biopsies to show bowel inflammation is often helpful especially in EoE. Currently evidence for atopy patch testing (APT) is not convincing.[1-3]

Combined IgE- and cell-mediated food allergic conditions

Atopic dermatitis (AD)

AD is associated with food allergy in 35% of children with moderate-to-severe skin rash.[4] The majority of reactions are IgE-mediated and in those with reactions, approximately 10% (i.e. 3 - 4% of total) have isolated flares of eczema without any IgE-mediated symptoms. The prevalence is much lower in patients with less severe disease and in adults.

Investigations for food allergy are not routine in all cases of AD. Concomitant or causative food allergy should be considered in those patients with a convincing history of food allergy and those with moderate-to-severe eczema that does not respond to appropriate and adequate topical treatment.[5] The diagnostic workup for IgE-mediated food allergy in the setting of eczema is the same as for IgE-mediated food allergy without eczema. Patients being worked up for eczema flares alone should be referred for full allergy assessment prior to considering any dietary modification. Eczema patients are often multiply sensitised, but tolerant to those foods, so the diagnostic workup for food allergy triggering isolated flares of eczema centres primarily on elimination and rechallenge testing to prove causality.

Eosinophilic oesophagitis (EoE)

Multiple food allergens are implicated in this disorder manifested by feeding disorders, reflux symptoms, vomiting, dysphagia and food impaction.[1,6] The variety of symptoms is experienced mostly after eating. In children, the age of presentation influences the complex of symptoms. Very young children present with feeding difficulties and failure to thrive, older children present with vomiting and abdominal pain, and teenagers with dysphagia and food impaction.[7,8] Other allergic diseases are often present. Food allergens and aeroallergens may play a significant role in the pathophysiology. SPT, sIgE and APT may be used to help identify associated foods, but these tests alone are not sufficient to make the diagnosis.[3]

Upper endoscopy with multiple (2 - 4) biopsies from both the proximal and distal oesophagus (4 - 8 in total) is recommended.[9,10] Eosinophilia due to gastro-oesophageal reflux disease should be eliminated by prior treatment with proton-pump inhibitors for at least 6 weeks. The diagnosis is confirmed with oesophageal biopsy showing more than 15 eosinophils per high-powered field in the presence of typical symptoms. Other disorders with eosinophilia like Crohn's, coeliac disease or achalasia should be excluded.

Management of EoE

Dietary aspects[11]

Elimination diets may be an effective therapy for EoE.

There are 3 approaches for dietary elimination:

- total elimination of all food allergens with feeding exclusively on an elemental or amino-acid-based formula
- targeted elimination of specific foods as guided by allergy testing, usually SPT or patch testing
- an empirical six-food elimination diet removing the six most common food allergens that are triggers for EoE: soy, egg, milk, wheat, nuts and seafood.

The duration of the treatment is usually 4 - 8 weeks, followed by a stepwise re-introduction period once remission has been achieved. Foods are re-introduced every 5 - 7 days and the most allergenic foods in EoE (such as milk, egg, wheat, soy, beef and peanuts) are left until last. Repeat oesophagoscopy and biopsies are done if symptoms recur. Some centres recommend periodic endoscopy and biopsy after re-introduction of 3 - 4 foods to confirm histological remission.

Food manipulation is not successful in all patients and some require pharmacotherapy in addition to, or instead of, dietary manipulation.

Pharmacological therapy

Not all cases of EoE are suitable for dietary therapy. The patient may not be prepared to accept the dietary restrictions or may fail to respond to this approach. A subgroup of EoE cases appears to be sensitised to aeroallergens; these cases tend to have seasonal symptoms and may need medication to alleviate symptoms.

The mainstay of drug therapy is the topical administration of corticosteroids, although proton-pump inhibitors have a role to play:

Proton-pump inhibitor therapy. Because reflux may cause oesophageal eosinophilia and be mistaken for EoE, it is critical to treat reflux, even where not proven, prior to oesophageal biopsy. In addition, reflux may be a result of EoE, therefore proton-pump inhibitors also have a role in treating established EoE.

Corticosteroids. Corticosteroids are an effective therapy and improve the clinicopathological features of EoE; however, when discontinued, the disease often recurs.

- *Topical corticosteroids.* Topical corticosteroids have been shown to be effective in inducing clinical and histological response (and remission) in children and adults with EoE. Two preparations have been assessed, viz. swallowed fluticasone proprionate and oral viscous budesonide.[6,10] Topical therapy has relatively few side-effects although fungal infection (*Candida*) is a recognised potential complication.
- *Systemic corticosteroids.* Although highly effective, the side-effects of oral therapy limit its use to short courses in severely affected cases. Systemic (oral) steroids should only be used in emergency cases when rapid improvement of symptoms is needed, e.g. severe dysphagia, weight loss or oesophageal strictures, or when topical steroids have been ineffective.[6,10]

Other medical therapy

The following additional medications have not been shown to be of consistent benefit and none can therefore currently be recommended as routine treatment for children with EoE:[6,10]

- leukotriene antagonists
- cromolyn sodium
- omalizumab
- anti-interleukin-5 antibodies (mepolizumab, reslizumab)
- azathioprine, 6-mercaptopurine and antitumour necrosis factor.

Oesophageal dilation

Oesophageal strictures, which are a recognised complication of EoE, can be effectively managed with oesophageal dilation but this does not improve the underlying inflammatory process.

Eosinophilic gastroenteritis (EG)

Patients with EG may present at any age, and any portion of the gastrointestinal tract, from the oesophagus to the colon, may be involved,[12] with symptoms varying according to the site of significant eosinophilic inflammation. These may include ascites, nausea, diarrhoea, malabsorption, weight loss, oedema and obstruction.[1] Infants may present with projectile vomiting as a result of gastric outlet obstruction. Adolescents on the other hand may present with symptoms similar to irritable bowel syndrome. Like in EoE, 50% of patients with EG have other atopic diseases.[12] In some cases, especially in young patients, food allergens may be implicated.

Cell-mediated food allergic conditions

Food protein-induced enterocolitis syndrome (FPIES)

FPIES occurs primarily in infants younger than 9 months of age. It is a severe disease caused predominantly by cow's milk and soy. Any food may however be implicated, and cases caused by rice, oats, meat, chicken and some vegetables are described. In the classic form dietary exposure causes severe emesis, diarrhoea and hypotension (in 15%) approximately 2 hours after ingestion.[1] Patients often present to the emergency room with severe dehydration and hypotension. A milder, more chronic form may present with emesis, diarrhoea, poor growth, anaemia, hypoproteinaemia and lethargy. Contrary to food protein-induced allergic proctocolitis, FPIES rarely occurs in breastfed infants. Symptoms improve promptly on removal of the culprit food, but it may take weeks for the T-cell-mediated inflammation to resolve totally. The prognosis is good and tolerance to the allergens is usually attained by the age of 3 years. Oral food challenge should be performed at that time to confirm resolution and tolerance.[12] Such challenges must be considered high-risk challenges and be performed in a hospital setting with intravenous access and a modified protocol with lower doses and longer periods between introduction of foods.

Food protein-induced allergic proctocolitis

In food protein-induced allergic proctocolitis, healthy infants present with mucus-laden bloody stools within the first few weeks to months of life. Cow's milk protein is usually implicated, mostly in formula-fed infants and less commonly through transfer in breastmilk. Change of formula to an elemental formula or restriction of cow's milk from the maternal diet usually results in resolution of symptoms within 48 hours. The condition has a good prognosis and usually resolves at the end of the first year of life.[1,12]

References

1. Burks AW, Tang M, Sicherer S, et al. ICON: Food allergy. J Allergy Clin Immunol 2012;129(4):906-920. [http://dx.doi.org/10.1016/j.jaci.2012.02.001]
2. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and management of food allergy. 2014. http://www.eaaci.org/resources/food-allergy-and-anapyhlaxis-guidelines.html (accessed October 2014).
3. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States. J Allergy Clin Immunol 2010;126(suppl):S1-S58. [http://dx.doi.org/10.1016/j.jaci.2010.10.008]
4. Gray C. Allergies in eczema. Current Allergy & Clinical Immunology 2011;24(3):185-191.
5. Jordaan HF, Todd G, Sinclair W, Green RJ. Aetiopathogenesis of atopic dermatitis. S Afr Med J 2014;104(10):706-709. [http://dx.doi.org/10.7196/SAMJ.8840]
6. Levin ME. Eosinophilic oesophagitis. Current Allergy & Clinical Immunology 2010;23(1):22-27.
7. Levin M, Motala C. Eosinophilic oesophagitis in Cape Town, South Africa (abstract). Clinical and Translational Allergy 2011;1(suppl 1):26.
8. Fell JME. Recognition, assessment and management of eosinophilic oesophagitis, Arch Dis Child 2013;98:702-706. [http://dx.doi.org/10.1136/archdischild-2012-302838]
9. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128(1):3-20. [http://dx.doi.org/10.1016/j.jaci.2011.02.040]
10. Dellon E, Gonsalves N, Hirano I, Furuta G, Liacouras C, Katzka D. ACG Clinical Guideline: Evidence Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis. Am J Gastroenterology 2013;108:679-692. [http://dx.doi.org/10.1038/ajg.2013.71]
11. Papadopoulou A, Koletzko S, Heuschkel R, et al., ESPGHAN Eosinophilic Esophagitis Working Group and the Gastroenterology Committee. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr 2014;58(1):107-118. [http://dx.doi.org/10.1097/MPG.0b013e3182a80be1]
12. Mansoor DK, Sharma HP. Clinical presentations of food allergy. Pediatr Clin N Am 2011;58:315-326. [http://dx.doi.org/10.1016/j.pcl.2011.02.008]