Non-IgE-mediated food allergies

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All authors’ degrees, affiliations and conflict of interest statements can be found online at http://dx.doi.org/10.7196/SAMJ.9201

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Non-immunoglobulin 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 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.

Eosinophilic oesophagitis (EoE)

Multiple food allergens are implicated in this disorder manifested by feeding disorders, reflux symptoms, vomiting, dysphagia and food impaction.[1-3] 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.5-8 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.[9] 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

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 propionate and oral viscous budesonide.[11,10] 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.[11,10]

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:[9,10]

- 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,[11,12] with symptoms varying according to the site of significant eosinophilic inflammation. These may include ascites, nausea, diarrhoea, malabsorption, weight loss, oedema and obstruction.[12] 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.[11] 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.[11] 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.[11,12]

References