

CHAPTER 6

Diagnostic criteria for gastrointestinal food allergy in childhood

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Cow's milk and cow's milk-based formulae are the major offenders in the first years of life. When soy formulae are used to treat cow's milk allergy, sensitization to soy may occur [1]. They may cause quick onset and slow onset symptoms.

Proteins in eggs, nuts, fish and cereals have all been described as eliciting IgE-mediated gastrointestinal food allergy, often accompanied with skin symptoms [2] but they can also cause small intestinal mucosal damage on occasion [3].

Clinical presentation

Children with gastrointestinal food allergy may present in three basic ways.

Quick onset

Acute symptoms which are historically clearly related to food ingestion, occur within an hour of eating food and are characteristically associated with IgE antibodies. Usually a single food only, e.g. egg may cause these quick onset symptoms.

Slow onset

Children with a variety of gastrointestinal symptoms including failure to thrive, chronic diarrhoea and rectal bleeding, which are not usually historically related to food ingestion; these children on gastrointestinal investigation prove to have definite pathology such as a small intestinal enteropathy or a colitis.

Analysis of the features of the gastrointestinal pathology suggest that gastrointestinal food allergy is its cause. Subsequently, it can be shown that food elimination relieves all the symptoms.

Quick and slow

There are a group of children who have a mixture of

quick and slow onset symptoms related to several foods but who respond only partially to elimination of these from the diet. They typically have an atopic background. Psychological features may be important.

Gastrointestinal food allergy includes a number of distinct clinical syndromes. As a consequence there can be no simple all embracing diagnostic criteria as for coeliac disease which is a single syndrome.

An absolute and essential first criterion for the diagnosis of gastrointestinal food allergy must be a response to a food elimination diet. This response will include clinical and laboratory observations.

A second criteria for diagnosis is a positive food challenge but this is not always essential for routine clinical practice. Food challenge is not required when the characteristic clinico-pathological diagnostic features are present at initial diagnosis. These include chronic diarrhoea with failure to thrive in association with the biopsy findings of partial villous atrophy accompanied by a thin mucosa often with patchy abnormality and a moderate rise in intraepithelial lymphocyte count [4,5]. The need for challenge in children with gastrointestinal food allergy will depend upon the individual clinical syndrome. ESPGAN has made recommendations for diagnostic criteria [6].

Clinical diagnosis

Response to an elimination diet

In each category a response to an elimination diet is essential. In children with multiple food allergies, however, this may be incomplete. Typically there should be relief of all symptoms, gain in weight and normal growth.

Responses to a food challenge

The diagnosis can only be definitely established in each category at present by a food challenge. In the past when there was much scepticism about the very existence of gastrointestinal food allergy, very strictly diagnostic criteria such as the Goldman criteria [7] using three

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challenges under strict clinical control were demanded. This is no longer necessary or practical in the 1990s for routine diagnosis especially in small infants when there may be a risk of acute anaphylaxis.

In older children with multiple food allergy 'blinded' food challenges may be necessary, but these should not be done in infancy.

Current practical diagnosis in each category depends upon clinical analysis in relation to laboratory diagnosis.

Diagnosis of quick onset allergy

There is usually a clear history of relief of symptoms on withdrawal of the offending food with a rapid return on challenge. Symptoms include acute vomiting, facial urticaria, lip swelling and sometimes wheezing and acute diarrhoea.

Laboratory diagnosis

In early infancy and especially in breastfed babies who develop acute cow's milk allergy, the presence of a specific elevation of IgE antibodies to cow's milk and a specifically positive radioallergosorbent test (RAST) or skin-prick test to cow's milk may be diagnostically valuable. Similarly a positive skin-prick test for egg in children with egg allergy is diagnostically useful. Its persistence usually means continuing intolerance to egg, although antigen-specific IgE antibodies may persist when the child has lost all evidence of clinical sensitivity.

In older children such investigations may reveal the presence of several positive results not only to foods but also to inhaled antigens and so indicate an atopic tendency.

Diagnosis of food allergy associated with gastrointestinal pathology

Initial diagnosis concerns investigation of infants with chronic diarrhoea, usually with failure to thrive. Sometimes infants with failure to thrive, and other children with gastrointestinal symptoms including rectal bleeding, have been investigated either by a small bowel biopsy or colonoscopy with multiple biopsies. The pathological features revealed by these biopsies demonstrate pathology which has the features of gastrointestinal food allergy.

There are two main groups: food sensitive small intestinal enteropathy and food sensitive colitis. Both groups may clinically overlap on occasion.

Food sensitive enteropathies

These are transient disorders of infancy and early childhood. As with coeliac disease, analysis of the initial biopsy features, taking into account the clinical context, permits a clinical diagnosis to be made, followed by a second and vital diagnostic feature, which is a clear and usually rapid clinical response to food elimination.

The most frequent diagnosis is cow's milk-sensitive enteropathy which is a model for other food-sensitive enteropathies such as soy-sensitive enteropathy.

Diagnosis of cow's milk-sensitive enteropathy

Children with this disorder nearly always have failure to thrive and chronic diarrhoea. Vomiting and abdominal distension may also occur [8].

Diagnostic biopsy

The initial diagnostic small intestinal biopsy is of particular importance and it has the following characteristic features morphologically.

- 1 There is a villous atrophy of variable degree, usually with some hyperplasia of the crypts. A flat mucosa is unusual and the lesion is typically less severe than that found in coeliac disease.
- 2 The mucosa is often thin and the abnormality is frequently patchy. Therefore, two or more biopsy specimens are helpful for initial diagnosis [4].
- 3 There may be some elevation of the intraepithelial lymphocyte count but not usually to the levels found in coeliac disease [5]. Typically, but with occasional exceptions, gamma-delta expression of the intraepithelial lymphocytes is not increased [9]. This is by contrast to coeliac disease where there is an increased level of these lymphocytes.

Response to elimination diet

Once a child is seen with these clinical and biopsy features, a cow's milk protein-free diet should be commenced. This should be a protein hydrolysate. A soy formula is not recommended as children may become intolerant to soy, developing a soy-sensitive enteropathy in between 15 and 60% of cases of cows' milk-sensitive enteropathy [10,11]. In order to verify the diagnosis there should be a rapid symptomatic response to a cows' milk free diet, i.e. relief of diarrhoea and gain in weight, with histological evidence (at some point) of morphological improvement of the small intestinal mucosa on the elimination diet.

Need for challenge

An early cows' milk challenge is not diagnostically essential in a child with chronic diarrhoea and failure to thrive, who has both the typical small intestinal enteropathy and a rapid clinical response to an elimination diet. An early (i.e. less than 1 year) challenge carries the risk of anaphylaxis [12]. Thus, in practice, the timing of milk challenge is best delayed to the age of 1 year or more. By then, in fact, most children with cows' milk-sensitive enteropathy will have recovered and cows' milk challenge decides the safety of cow's milk re-introduction. In view of the risk, albeit small, of acute anaphylaxis, food challenges should ideally be done in hospital. For children with previous enteropathy it is best to precede challenge with a small bowel biopsy to demonstrate healing or at least improvement in morphology.

Diagnosis of cow's milk colitis

These infants typically have bloody diarrhoea or rectal bleeding [12] but are well nourished and not failing to thrive. There may be an association with atopic disease [14]. It occurs in early infancy in bottlefed infants and breastfed infants whose mother is drinking cows' milk.

Infection with *Campylobacter* and *Shigella* must be excluded. The definitive diagnostic investigation is endoscopy and biopsy. The major differential diagnosis is chronic inflammatory bowel disease (usually ulcerative colitis). Characteristically there is a dense infiltration of eosinophils in an otherwise normal mucosa, although non-specific inflammatory changes have also been described.

The second step in diagnosis is to demonstrate a complete relief of symptoms on an elimination diet (which should include the mother when the child is breastfed), i.e. cessation of rectal bleeding.

With recognition of this syndrome an early diagnostic milk challenge is not essential routinely.

Some clinicians will elect to do a follow-up endoscopy and biopsy, others will not. Usually an early cow's milk challenge is best avoided and delayed until the age of 9–12 months. Follow-up is essential to exclude chronic inflammatory bowel disease.

Multiple food allergy

This is the most difficult and sometimes controversial area for diagnosis. It is in this group, which usually occurs in older children, that 'blinded' food challenges are necessary. The small intestinal mucosa is typically normal. There is often an atopic background. Response

to food elimination may be partial. Some children have been reported to respond to disodium cromoglycate [15]. However, an appropriately blinded, placebo-controlled trial has not yet established its role in these patients.

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