

# Clinical manifestations of food allergy: the old and the new

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Food allergies are increasing in incidence, and the variety of triggering antigens is widening. There is also an increased recognition of the breadth of immunologically mediated responses to dietary antigens; the area of non-IgE-mediated food allergy is belatedly acquiring scientific respectability, aided by improved clinical recognition and basic scientific studies. The role of mucosal mast cells and eosinophils in intestinal allergic responses is now better recognized, and conditions such as eosinophilic oesophagitis are more prevalent than previously thought. However, the diagnostic difficulties of non-IgE-mediated allergies remain challenging. *Eur J Gastroenterol Hepatol* 17:1287–1291 © 2005 Lippincott Williams & Wilkins.

*European Journal of Gastroenterology & Hepatology* 2005, 17:1287–1291

**Keywords:** cytokines, food allergy, IgE, irritable bowel syndrome, oral allergy syndrome

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Received 27 July 2005 Accepted 31 August 2005

## Changing patterns of allergenic foods and potential mechanisms

Food-induced anaphylaxis appears to be unchanged from the initial descriptions a century ago. However, both the prevalence of food allergy and the pattern of triggering antigens have changed. Of the studies showing increasing incidence, a population-based questionnaire study from Toulouse [1] identified a cumulative prevalence of 6.7% and a point prevalence of 4.7%. Cow's milk, egg and peanuts were the most common triggering antigens, but there was a high incidence of allergies to relatively new antigens, including kiwi, shellfish and tree nuts. Similar changes have been reported from many centres, with the emerging allergens varying between countries.

Immediate food allergic responses result from a T helper type 2 deviated antigen-specific response, as has now been confirmed by labelling T cells with carboxyfluorescein succinimidyl ester before antigen stimulation [2]. Responses to peanut, milk or egg in allergic children are dominated by IL-4, IL-5 and IL-13, in contrast to IFN- $\gamma$  and TNF- $\alpha$  in non-allergic children or those who have outgrown the allergy [2]. Although these results imply that host immune responses, rather than antigenic properties, determine whether allergy is outgrown, other work has suggested that IgE reactivity to specific sequences of  $\alpha_{s1}$ -casein,  $\alpha_{s2}$ -casein and  $\kappa$ -casein is associated with long-term sensitization [3]. Either or both factors may be relevant for an individual child, and may be genetically determined by cytokine-response polymorphisms or the major histocompatibility complex type, respectively.

Other factors may contribute to the changing patterns of food allergy. Children are now exposed to multiple

antigens at low doses in manufactured foods. Sensitization may potentially occur percutaneously [4]. A reduction in early-life infectious exposures may provide insufficient innate immune responses for the induction of oral tolerance. The impaired generation of mucosal transforming growth factor beta-producing T cells has been reported in children with multiple food allergies [5], and reduced stimulated transforming growth factor beta production has been noted in both peripheral blood mononuclear cells and T-cell lines from milk-allergic patients [6,7]. Strong evidence that regulatory T cells are important in preventing dietary sensitization is provided by evidence that children outgrew milk allergy when milk-reactive CD4+CD25+ cells increased [8]. Conversely, in a study of over 150 adults, gain-of-function polymorphism in the promoter region of the CD14 (lipopolysaccharide receptor) gene, causing increased CD14 production and theoretically augmenting regulatory responses and decreasing IgE, was strongly associated with food allergy and intrinsic (but not atopic) asthma [9]. The role of infectious exposures in food allergy is thus probably complex.

## Recognition of different forms of dietary hypersensitivity

The broad concept of allergy initially proposed by von Pirquet was followed by the restriction of its definition to reactions in which IgE responses were clear. Recent evidence suggests that non-IgE-mediated food allergies are more common than previously suspected, particularly in children. In addition to an increased range of sensitizing antigens, different routes of sensitization have been reported, notably to maternally ingested antigen in breast-fed infants, who frequently sensitize to multiple antigens, and present with a

complex array of gastrointestinal, pulmonary and cutaneous symptoms [10,11].

Non-IgE-mediated responses to cow's milk in infants include vomiting or diarrhoea up to 24 h and eczema or wheezing up to 5 days after challenge [10]. Large volumes of milk may be needed to elicit delayed symptoms, which would have been missed on short-term challenge, and specific IgE and skin prick tests (SPT) are frequently negative. Many children with non-IgE-mediated allergies show evidence of multiple sensitizations, and management may thus be complex [10]. A large British cohort with multiple food allergies (77 with delayed reactions and 41 with immediate plus delayed reactions) showed clinical and immunological similarities between both groups [11]. Vomiting, irritability and eczema were common in infancy, and 80% of exclusively breast-fed infants sensitized before weaning. Although IgE was increased overall in immediate responders, both groups shared an otherwise identical pattern of delayed immune maturation (low IgA, IgG2, IgG4, CD8 and natural killer cells). Endoscopy frequently identified lymphocytic or eosinophilic oesophagitis and subtle enteropathy [11].

The importance of endoscopy is underlined by findings of intestinal lymphonodular hyperplasia, in both children with IgE and non-IgE-mediated food allergies [12]. Formal study of this lesion, in a single-centre cohort, showed increased mucosal  $\gamma\delta$  cell density in children reacting to open food challenge and in those responding to food elimination but not relapsing on short-term challenge. Remarkably, parental assessment of likely food allergy strongly predicted mucosal abnormalities; of 24 children whose parents reported a suspicion of food allergy, but whose conventional challenges were negative, eight showed duodenal lymphoid hyperplasia, whereas mucosal T-cell and  $\gamma\delta$  cell densities were indistinguishable from those with confirmed food allergy (and distinct from controls) [12]. Significant residual food-sensitive enteropathy also occurs in older children thought to have outgrown milk allergy [13], supporting the concept that many cases of non-IgE-mediated food allergies go unrecognized.

Further evidence for genuine mucosal responses in some adults with self-diagnosed food allergies, but negative to conventional allergy testing, was provided by transabdominal ultrasound assessment after duodenal allergen challenge. Abnormal findings occurred in 14 out of 32 patients, notably wall swelling and fluid exudation [14]. All patients with positive double-blind, placebo-controlled food challenge had these changes, as did eight out of 10 with positive SPT. However, identical findings were seen in five out of 15 patients with negative double-blind, placebo-controlled food challenge and

six out of 22 with negative SPT. This response mirrors that identified by the more invasive technique of luminal perfusion during allergen challenge. In patients with documented food allergies, mast cell (but not eosinophil) activation products were liberated into the lumen together with a marked water secretory response [15]. Taken together, these findings suggest that genuine mast cell-mediated allergic responses may occur in patients apparently negative upon food challenge, as the symptoms evoked are viewed as subjective and not diagnostic of allergy. Such a reaction, visibly occurring within the skin after food challenge, would not be dismissed so readily.

### Enhancing investigation of food allergies

A better selection for food challenge tests may now be possible. The prediction of a likely outcome may be based on a SPT response and specific IgE titres, whereas incorporation of the clinical history into decision-making may further reduce the numbers of patients requiring formal challenge [16,17]. The determination of appropriate cut-offs for SPT ( $>8$  mm) and specific IgE ( $\geq 15$  kU<sub>A</sub>/l) was found to give a 95% probability of clinical IgE-mediated reactions, in both tertiary and community settings [17]. By contrast, the diagnosis of non-IgE-mediated food allergies remains problematical. Skin patch testing may identify a proportion of food-sensitized children, particularly if they have eczema [18]. In addition to overall reduced IgG subclasses [11], distinct patterns of specific antibody response may be seen in children with non-IgE-mediated allergy; those with milk protein-induced enterocolitis showed reduced milk-specific IgG4 compared with those with immediate allergy [19]. No fundamental differences in lymphocyte responsiveness to milk were detected between the IgE-mediated and non-IgE-mediated groups.

### Emerging allergic disorders

#### Oral allergy syndrome

A localized oral/pharyngeal response to food antigens is often associated with pollens or plant-derived foods, and is dependent upon intact antigens (food processing may variably degrade these). Reactivity to birch pollen Bet v 1 antigen may induce cross-sensitization to Bet v 1-related antigens in other foods such as carrot, celery and soy, and other birch pollen antigens have similar homology to a variety of foods [20]. Common triggering antigens include Rosaceae fruits (e.g. peach, apple), and lipid transfer proteins have been implicated in oral allergy syndrome responses to a variety of foods. There is significant geographical variation in lipid transfer proteins responsiveness, with northern European individuals predominantly reacting to pollens, and southern European individuals reacting to fruits but not pollens. There is intriguing recent evidence that allergic reaction to pollen lipids may be mediated by

lipid antigen presentation via the non-classic MHC molecules CD1a and CD1d to CD4 T cells and CD4-CD8-negative  $\gamma\delta$  T cells [21]. These findings have yet to be extrapolated to food allergies, but suggest that greater attention should be paid to potentially antigenic lipids in foodstuffs.

Standard specific IgE tests to food extracts may be negative in oral allergy syndrome: most birch-pollen allergic patients reacting to soybean had negative specific IgE to soy extract but positive specific IgE to the Bet v 1-related antigen Gly m 4 [22]. Similar false-negative testing has been reported for other antigens, including peanut and tree nuts [20]. The importance of oral allergy syndrome is that it may presage the development of life-threatening anaphylaxis, but symptoms may be sufficiently mild or attenuated by antihistamines to induce sufferers to continue the intake of the causative antigens. Emerging therapeutic responses include subcutaneous or sublingual immunotherapy, which have shown promise in small controlled trials [23], inducing an IgG4 response.

#### **Food protein-induced enterocolitis**

Food protein-induced enterocolitis predominantly affects young infants, and overlaps with the more benign disorder of allergic colitis, in which infants present with bloody stools without systemic upset. This usually responds to the exclusion of cow's milk or soy proteins from the mother's diet, as most cases occur in exclusively breast-fed infants. The more serious food protein-induced enterocolitis is induced by a wider variety of antigens, including some solids [24]. The inflammatory changes are more severe than classic allergic colitis, with marked histological abnormality including crypt abscesses. The systemic symptoms may be severe, including protein-losing enteropathy and shock, with the clinical appearance sometimes mimicking severe sepsis [24].

#### **Allergic dysmotility**

Allergic dysmotility is an area of significant interest, because of the widespread belief among patients that dietary exclusions benefit a variety of functional gastrointestinal disorders. However, as delayed subjective gastrointestinal symptoms are not considered diagnostic in oral challenges, these are often dismissed as non-allergic. There has been much advance in this area, underpinned by an important animal model that confirms that dietary allergens can indeed induce dysmotility; mucosal eosinophil recruitment, mediated by the cytokine IL-5 and the chemokine eotaxin, occurs after allergen ingestion or inhalation, and causes antigen-induced enteric neural dysfunction [25].

#### **Irritable bowel syndrome**

Symptoms of apparent food hypersensitivity have been commonly reported in irritable bowel syndrome

(IBS); up to half of patients implicate foods in their symptoms. Exclusion diets are often helpful, although such an improvement has been attributed to food intolerance rather than allergy. Recent findings suggest a genuine immune response (non-IgE-mediated) to food antigens in at least some IBS patients. The association of IBS with specific IL-10 genotypes supports the role of mucosal immunity in its pathogenesis [26]. A study of dietary eliminations in established IBS found a significant reduction in symptom severity (in comparison with a sham diet based on irrelevant antigens), in patients whose exclusions were based upon IgG antibodies to dietary antigens [27]. A further study identified increased IgG4 titres to wheat, beef, pork and lamb in 108 IBS patients compared with controls [28]. No significant differences were found for 12 other antigens, or for IgE levels. However, the role of IgG and IgG4 antibodies in food allergies still remains poorly characterized.

#### **Constipation**

Constipation is another disorder in which allergic children with treatment-resistant disease may respond to antigen exclusion. A histologically based study of 52 children, treated by the exclusion of milk alone, or by oligoallergenic diet if responding poorly, identified 30 who responded to exclusion diet by the resolution of symptoms [29]. Mucosal findings in the diet-responsive group, of whom six had multiple food allergy, included erosions, increased intraepithelial lymphocyte mucosal eosinophils, together with a reduction in rectal mucus production, all improving on exclusion.

#### **Gastro-oesophageal reflux and eosinophilic oesophagitis**

Evidence that foregut dysmotility and gastro-oesophageal reflux (GOR) could be induced by food antigens came indirectly from the improvement of infants with colic upon milk exclusion, and directly by the description of milk-induced GOR [10,30]. As in allergy-induced constipation, mucosal eosinophilia appears to be common. Overlapping with milk-induced GOR is the important and increasingly recognized disorder of eosinophilic oesophagitis. In young children this disorder responds well to dietary exclusion, whereas in older children and adults there may be a role for inhaled aeroantigens, and therapy including corticosteroids may be required [31]. Although sharing some symptoms with GOR, the response to antacid therapy is poor, and pH testing is unhelpful. Endoscopic features include linear ridging and white surface plaques caused by eosinophilic microabscesses. A population-based study from Ohio [32] provided evidence of the increasing incidence of paediatric eosinophilic oesophagitis, which is now locally as common as Crohn's disease. Cases were identified from pathology records, using the criteria

of epithelial hyperproliferation and oesophageal eosinophilia. Of 315 cases identified since 1991, 306 were diagnosed after 2000. The local incidence has increased annually from 2000 to 2003, from 0.91 to 1.28 per 10 000 population, and prevalence has increased from 0.99 to 4.3 per 10 000. Associated clinical symptoms included positive SPT or food-specific IgE in 46%, and a family history of atopy in 73.5%. Eosinophilic oesophagitis is also increasing in adult populations, although underdiagnosis is common [33]. Among 31 adult patients from one centre, 26 (84%) had a history of allergic disease, raised IgE or allergen-specific IgE. Specific IgE to food allergens or inhaled aeroallergens was seen in 24 out of 31 (80%) and positive SPT was seen in 26 (84%) [33].

One finding of potential importance, in view of the increasing incidence of eosinophilic upper gut disorders and the widespread availability and massive use of acid-reducing therapies such as proton pump inhibitors, is that the reduction of gastric acid production by these drugs significantly augments allergic sensitization in both mice and humans [34,35]. The degradation of antigens by gastric acid appears to be important in minimizing the sensitization potential [35], and thus a vicious circle may be established, whereby apparently appropriate therapy for allergen-induced upper gastrointestinal symptoms worsens the underlying allergic disease. Developing diagnostic awareness of non-IgE-mediated allergy, and effective clinical testing has become an increasingly important challenge.

#### Conflict of interest

The author has presented lectures at meetings sponsored by several manufacturers of oligoallergenic formulae and has contributed to technical advisory panels.

#### Authors' contributions

All references were selected and reviewed by the author alone.

#### References

- Rancé F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy* 2005; **35**:167–172.
- Turcanu V, Maleki SJ, Lack G. Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. *J Clin Invest* 2003; **111**:1065–1072.
- Järvinen KM, Beyer K, Vila L, Chatchate P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2002; **110**:293–297.
- Lack G, Fox D, Northstone K, Golding J, for the Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348**:977–985.
- Pérez-Machado MA, Ashwood P, Thomson MA, Latcham F, Sim R, Walker-Smith JA, Murch SH. Reduced transforming growth factor- $\beta$ 1 producing T cells in the duodenal mucosa of children with food allergy. *Eur J Immunol* 2003; **33**:2307–2315.
- Rautava S, Isolauri E. Cow's milk allergy in infants with atopic eczema is associated with aberrant production of interleukin-4 during oral cow's milk challenge. *J Pediatr Gastroenterol Nutr* 2004; **39**:529–535.
- Beyer K, Castro R, Birnbaum A, Benkov K, Pittman N, Sampson HA. Human milk-specific mucosal lymphocytes of the gastrointestinal tract display a  $T_H2$  cytokine profile. *J Allergy Clin Immunol* 2002; **109**:707–713.
- Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive CD4+CD25+ regulatory T cells in children who have outgrown cow's milk allergy. *J Exp Med* 2004; **199**:1679–1688.
- Woo JG, Assa'ad A, Heizer AB, Bernstein JA, Hershey GK. The -159 C→T polymorphism of CD14 is associated with nonatopic asthma and food allergy. *J Allergy Clin Immunol* 2003; **112**:438–444.
- Hill DJ, Heine RG, Cameron DJ, Francis DE, Bines JE. The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. *J Pediatr* 1999; **135**:118–121.
- Latcham F, Merino F, Winter C, Lang A, Garvey J, Thomson MA, et al. A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. *J Pediatr* 2003; **143**:39–47.
- Kokkonen J, Holm K, Karttunen TJ, Maki M. Enhanced local immune response in children with prolonged gastrointestinal symptoms. *Acta Paediatr* 2004; **93**:1601–1607.
- Kokkonen J, Tikkanen S, Savilahti E. Residual intestinal disease after milk allergy in infancy. *J Pediatr Gastroenterol Nutr* 2001; **32**:156–161.
- Arslan G, Gilja OH, Lind R, Florvaag E, Berstad A. Response to intestinal provocation monitored by transabdominal ultrasound in patients with food hypersensitivity. *Scand J Gastroenterol* 2005; **40**:386–394.
- Santos J, Bayarri C, Saperas E, Nogueiras C, Antolin M, Mourelle M, et al. Characterisation of immune mediator release during the immediate response to segmental mucosal challenge in the jejunum of patients with food allergy. *Gut* 1999; **45**:553–558.
- Niggemann B, Rolinck-Werninghaus C, Mehl A, Binder C, Ziegert M, Beyer K. Controlled food challenges in children – when indicated, when superfluous? *Allergy* 2005; **60**:865–870.
- Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005; **115**:1291–1296.
- Stromberg L. Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002; **91**:1044–1049.
- Shek LPC, Bardina L, Castro R, Sampson HA, Beyer K. Humoral and cellular responses to cow milk protein in patients with milk-induced IgE-mediated and non-IgE-mediated disorders. *Allergy* 2005; **60**:912–919.
- Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. *Curr Opin Allergy Clin Immunol* 2005; **5**:267–273.
- Agea E, Russano A, Bistoni O, Mannucci R, Nicoletti I, Corazzi L, et al. Human CD1-restricted T cell recognition of lipids from pollens. *J Exp Med* 2005; **202**:295–308.
- Mittag D, Vieths S, Vogel L, Becker WM, Rihs HP, Helbling A, et al. Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of antigens. *J Allergy Clin Immunol* 2004; **113**:148–154.
- Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CAFM, et al. Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. *Clin Exp Allergy* 2004; **34**:761–769.
- Nowak-Węgrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; **111**:829–835.
- Hogan SP, Mishra A, Brandt EB, Royalty MP, Pope SM, Zimmermann N, et al. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001; **2**:353–360.
- Gonsalkorale WM, Perrey C, Pravica V, Whorwell PH, Hutchinson IV. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003; **52**:91–93.
- Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004; **53**:1459–1464.
- Zar S, Benson MJ, Kumar D. Food-specific serum IgG4 and IgE titers to common food antigens in irritable bowel syndrome. *Am J Gastroenterol* 2005; **100**:1550–1557.
- Carroccio A, Scalici C, Maresi E, Di Prima L, Cavataio F, Noto D, et al. Chronic constipation and food intolerance: a model of proctitis causing constipation. *Scand J Gastroenterol* 2005; **40**:33–42.
- Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S, Husby S. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. *J Pediatr Gastroenterol Nutr* 2004; **39**:383–391.

- 31 Furuta GT. Eosinophilic esophagitis: an emerging clinicopathologic entity. *Curr Allergy Asthma Rep* 2002; **2**:67–72.
- 32 Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004; **351**:940–941.
- 33 Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005; **115**:1090–1092.
- 34 Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K, *et al*. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005; **19**:656–658.
- 35 Untersmayr E, Poulsen LK, Platzer MH, Pedersen MH, Boltz-Nitulescu G, Skov PS, Jensen-Jarolim E. The effects of gastric digestion on codfish allergenicity. *J Allergy Clin Immunol* 2005; **115**:377–382.