

Food Allergy as Seen by an Allergist

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ABSTRACT

The clinical expression of allergic disease is the consequence of a series of complex gene–environment interactions that occur at the materno–fetal interface and throughout infancy, leading to persistence of the Th2 immune response. It has been proposed that atopic eczema is the cutaneous manifestation of a systemic disorder that also gives rise to asthma, food allergy, and allergic rhinitis. The recent emergence of genes regulating epidermal barrier function has raised the question of whether the skin barrier in atopic eczema is defective from the outset, rendering the epidermis “leaky,” thereby increasing the risk of allergen penetration and the succeeding inflammatory reaction that contributes to atopic eczema. Food allergic sensitisation and eczema frequently coexist during the first 2 years of life, and food allergy is more prevalent in infants and children with

moderate to severe eczematous inflammation. The majority of food allergic reactions are caused by 8 foods, with milk, egg, and peanut occurring with greatest frequency. The acquisition of food-specific tolerance occurs predominantly with foods in which the epitopes are grouped together in a conformational structure (milk, egg, wheat, soy), whilst it rarely occurs in patients allergic to foods in which the epitopes are arranged in a linear fashion (nuts, seeds, fish). Better tests and novel therapies, such as immunotherapy and oral tolerance induction, are required for the management of food allergy. *JPGN* 47:S45–S48, 2008. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

GENETICS PLUS ENVIRONMENT CONTRIBUTE TO ALLERGY

It is well established that there is a major genetic contribution to allergy and a number of candidate genes have been identified for both eczema and asthma (1). Recently, null mutations in the filaggrin gene, situated within the epidermal differentiation complex on chromosome 1q21, have been found to play an important role in the pathogenesis of eczema (2). The filaggrin gene mutations are found in 27% of patients with severe eczema and appear to confer risk factors for disease persistence, multiple allergic sensitisation, and asthma in the context of eczema. This discovery convincingly demonstrates the important role of the disrupted skin barrier in the pathogenesis of eczema and allergic sensitisation.

Genetics alone cannot account for the significant increase in the prevalence of allergic diseases during the past 2 decades. This increase is far more likely to be attributed to a series of complex gene–environment interactions occurring either during pregnancy or during

the first few months of life. Healthy infants typically adopt a type 1 T helper cell (Th1) cytokine profile at birth, whilst atopic infants maintain the type 2 T helper cell (Th2) skewed environment normally associated with pregnancy. Disruption of the skin barrier enhances the permeability of allergens, microbes, and detergents, which causes further skin barrier damage and differentiation of Th2 cells under the regulation of Th1 cells and regulatory T cells (Figure 1).

In children with atopic dermatitis, there is an increased number of immunoglobulin (Ig) E-bearing Langerhans cells, which play an important role in allergen presentation and in the recruitment of Th2 cells into acute eczematous lesions. In chronic eczema, however, the cellular infiltrate shifts to include eosinophils, macrophages, and inflammatory dendritic cells with the recruitment of predominantly Th1 cells. Interestingly, in chronic eczema circulating autoantibodies directed against cellular proteins can be found, leading to speculation that what initially began as an allergen-driven process may subsequently become an autoimmune process in patients with severe eczema. This may give us some insight into why allergen intervention

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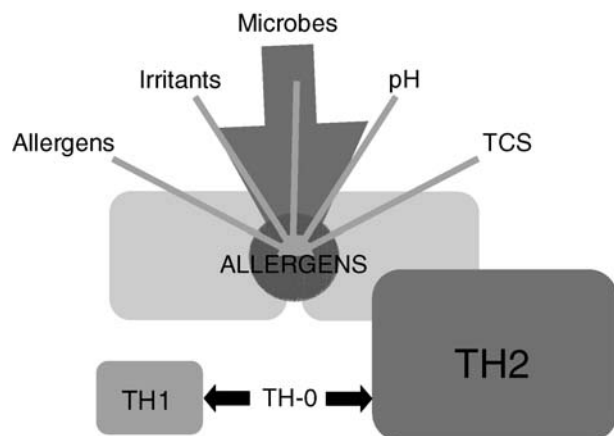


FIG. 1. Gene–environment interactions lead to Th1/Th2 switching. pH of the skin is normally 4.5, but can be raised by surfactant agents (eg, soaps, detergents). An increase in pH is damaging to the skin barrier. TCS, topical corticosteroids; TH1, type 1 T helper cell; TH2, type 2 T helper cell.

strategies are likely to be more effective when instituted early.

ALLERGIC VERSUS NONALLERGIC REACTIONS

Hypersensitivity reactions can be characterised as allergic or nonallergic (Figure 2). The latter is caused by toxic, pharmacological, or enzymatic triggers. The former is either IgE mediated (eg, food, drug, venom) or non-IgE mediated (eg, coeliac disease, contact dermatitis, gastroenteropathy, allergic alveolitis) between IgE- and non-IgE-mediated hypersensitivity reactions in conditions such as atopic eczema and allergic gastroenteropathy.

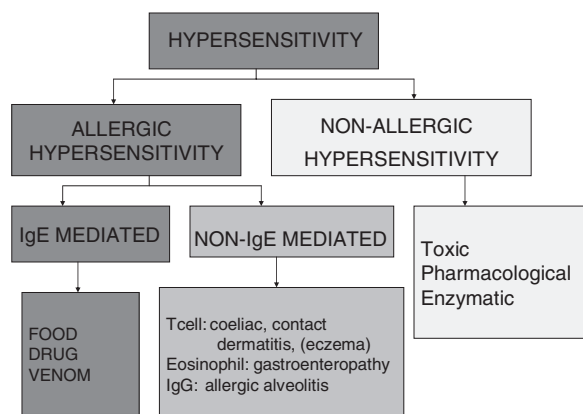


FIG. 2. Characterisation of hypersensitivity reactions. IgE, immunoglobulin E.

ALLERGIC MARCH IN HIGH-RISK INFANTS

The onset of eczema is frequently mirrored by the onset of food allergic sensitisation, with food-specific IgE and eczema rising and peaking within the first 2 years of life. This is followed by an increase in inhalant allergen sensitisation and a corresponding increase in asthma and allergic rhinitis. Atopic eczema is often the first manifestation of allergic disease, with up to half of all infants with eczema developing asthma and two thirds developing allergic rhinitis in subsequent years. This association of diseases is frequently referred to as the allergic march.

Food and inhalant allergen sensitisation in atopic eczema is common. There is compelling evidence to suggest that atopic sensitisation in infants with eczema is a marker of disease severity. Sensitisation to foods and inhalants is associated with more severe eczema, increased risk for disease persistence beyond 7 years, and an increased risk for developing allergic airways disease (3,4). Specific sensitisation to egg in infants with atopic eczema has a positive predictive value of 80% for the development of asthma and significantly increases the risk of aeroallergen sensitisation (5).

In the Early Prevention of Asthma in Atopic Children study ($n = 2184$), the frequency of sensitisations to foods and aeroallergens in infants ages 1 to 2 years with eczema was found to be 50%, with infants testing positive to milk (~40%), egg (~25%), peanut (~23%), grass (~7%), and dust mites (~20%) (6). Sensitisation does not, however, confirm the presence of allergic disease, although at higher levels, threshold values for reactivity have been defined for certain food allergens (eg, milk, egg, peanut, fish). Patients testing above these threshold values have a higher probability of being food allergic.

Studies utilising the double blind placebo controlled food challenge test demonstrate that 30–56% of children with moderate or severe eczema have an underlying food allergy (7). Removal of proven food allergens from the patient's diet can lead to significant clinical improvement in their eczema. It is important initially for patients to avoid the implicated foods completely, because even small amounts of food allergen can contribute to food-specific IgE synthesis and the spontaneous release of histamine from basophils. Regular follow up and re-assessment is important as the natural history is for the majority of patients to acquire tolerance over time to most allergens.

WHICH FOODS CAUSE ALLERGIC REACTIONS?

Despite the enormous diversity of the human diet, relatively few foods cause allergic reactions. In children

approximately 90% of all allergic reactions to foods are caused by 8 foods: milk, egg, peanuts, tree nuts, fish, soya, wheat, and shellfish (7). Peanut, egg, and milk allergy occur more frequently in children than in adults (8). There is considerable homology due to the existence of cross-reacting proteins (panallergens) between various plant and animal proteins. Whilst some cross-reacting proteins are clinically important, others are not. The homology between peanuts and tree nuts is relevant, with 30% to 50% of peanut allergics also reacting to tree nuts. Most children with cow's milk allergy will be unable to tolerate goat's milk. The cross-reactivity between peanuts and other legumes is clinically irrelevant, with 95% of peanut-allergic individuals being able to tolerate a variety of other legumes (9).

CONFIRMATION OF ALLERGY: RULE OF 3S

The evaluation of food allergy relies on a careful history and physical examination, which seeks to identify the culprit allergen and explores the differential diagnosis of an allergic reaction. The historical likelihood or probability of food allergy being present can be classified as high, equivocal, or low.

Skin prick tests and serum tests to detect specific IgE antibody are used to confirm an allergen-specific immediate allergic reaction. The tests have their limitations, being highly sensitive (generally >90%) but only moderately specific (~50%) in identifying a clinical reaction. Therefore, a negative test result, in the presence of a good response to a histamine-positive control, is good at ruling out an IgE-mediated reaction, whereas a positive test will overestimate IgE-mediated allergy 50% of the time, if used as a screening test. When the index of suspicion is high based on a good history, the tests are useful for confirming allergy; conversely when the index of suspicion is low, the tests are useful for ruling out a diagnosis of allergy. When there is a lack of correlation between the history and tests of specific IgE or when the history and tests are equivocal, confirmation by an open or blinded provocative challenge test is usually required to make the diagnosis. Thus, 3 possible conclusions can be drawn from the patient history and allergy testing: definitely food allergic (needs elimination diet), doubt about food allergy (needs food challenge), or definitely not food allergic (no dietary restriction required).

WHO OUTGROWS THEIR FOOD ALLERGIES?

Most children lose their sensitivity to most allergenic foods within the first 3 to 5 years of life, particularly

when binding epitopes are held together in a conformational structure (milk, egg, wheat, soya), rendering them less stable and more susceptible to heat degradation. Infants with non-IgE-mediated allergy to milk and soy typically achieve tolerance during the second year of life. In infants with IgE-mediated allergies to milk, egg, soya, and wheat, tolerance is achieved slightly later, with 85% of children outgrowing their allergies by age 5 years. Induction of tolerance is accompanied by a fall in food-specific IgE concentrations. Recent studies suggest that specific patterns of epitope diversity may be associated with persistence of milk allergy. In particular, binding to casein rather than to whey epitopes appears to predict persistence of milk allergy (10).

Other allergens (eg, nuts, seeds, fish) are more likely to persist into adult life due to the presence of linear binding epitopes. In the 20% of children with peanut allergy who acquire tolerance to nuts (ie, who outgrow their nut allergy), most are younger than 2 years at presentation, have few additional food allergies, have mild initial reactions, have declining specific IgE, and experience a long (>3 years) interval since their last reaction (11).

THE FUTURE

The future management of food allergies requires better tests that further explore the utility of epitope specificity in predicting disease outcomes. Studies looking into novel therapies aimed at suppressing the allergic response (eg, anti-IgE, traditional Chinese medicine [food allergy herbal formula-1 and -2]) are under way. Immunotherapy using peptides or mutated allergen proteins, DNA immunisation, and oral tolerance induction may be of benefit in the future, but at present these options require further investigation before they are accepted into clinical practice.

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