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An Update on Pediatric Atopic Dermatitis and Food Allergies

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An otherwise healthy 15-month-old female presented to Pediatric Dermatology for evaluation and management of moderate atopic dermatitis since 4 months of age. The patient had eczematous dermatitis with a waxing and waning course, with significant pruritus, sleep disturbance, and no symptom-free periods. The family had previously been instructed to use a combination of daily moisturizers with hydrocortisone 2.5% ointment during flares, but because of concerns about steroid side effects used only very small quantities of prescription medication.

At 8 months and while exclusively being breastfed, the patient was evaluated by an allergist. Mother had noticed that when she ingested large amounts of egg, the infant's eczema would flare. When she removed egg from her diet, the eczema improved but did not resolve. Skin testing was performed on the child and was positive to egg and negative to milk and peanut. Serum IgE food allergy (FA) testing at 14 months was positive to milk, wheat, and tree nuts; however, the child ingested wheat and tree nuts regularly without any noted symptoms. The family limited the patient's dairy intake because of concerns that it exacerbated the dermatitis but did not see significant improvement.

Physical examination was significant for diffuse eczematous plaques with lichenification and moderate thickening on the neck and upper and lower extremities favoring the antecubital and popliteal fossae. Scattered erythematous, edematous plaques, and excoriations were also present diffusely. Approximately 30% of the body surface area was involved.

The diagnosis of atopic dermatitis was reviewed in detail including clinical course, treatment options, and possible triggers and trigger avoidance. The role of FAs and potential false positive food-specific IgE testing were discussed in detail, and the patient was started on a treatment plan to control her atopic dermatitis using triamcinolone ointment 1%, 30-40 g per week for the first 2 weeks, with a tapered-dosing schedule. No change in diet was recommended except for continued avoidance of egg.

At her 1-month follow-up appointment, the patient's skin symptoms were significantly improved. Physical examination revealed mild hypopigmentation with small focal areas of erythema and mild lichenification in the antecubital fossae and neck, with no exudation or excoriation. Importantly, the patient's mother reported significantly improved quality of sleep and decreased pruritus. The mother was advised to continue the atopic dermatitis treatment as planned and continue to follow-up with her allergist to monitor for possible outgrowing of the egg allergy.

Atopic dermatitis is the most common chronic, relapsing inflammatory skin condition in children worldwide, affecting 5%-20% of pediatric patients.[1] It is a complex disease mediated by both genetic and environmental factors arising from dysregulation of the immune system, dysfunction of the epidermal barrier, and inflammation.[2] It is characterized by pruritus and skin changes such as xerosis, erosions, and excoriations. Even mild cases can have a profound impact on patient quality of life. Although it has been known for many years that atopic dermatitis and FA are highly associated, the role of FA in the pathogenesis and severity of atopic dermatitis is still a subject of controversy.

FAs affect approximately 4%-6% of children and 3%-4% of adults.[3,4] The prevalence of FA is significantly higher in those with atopic dermatitis, affecting approximately 15% of these patients.[5,6] The most common FAs in this population include egg, milk, peanut, soy, wheat, tree nuts, fish, and shellfish.[3,4] FAs are more likely to play a factor in infants and young children with atopic dermatitis and are more common with moderate to severe atopic dermatitis that is refractory to skin care treatment.[7] Some children with atopic dermatitis may have eczematous exacerbations with exposure to certain foods.[8] Patients with a history of atopic dermatitis are also at higher risk for IgE-sensitization, which may not be associated with clinically relevant FAs, yielding false positive skin prick and specific IgE tests.[9,10] These data suggest that although atopic dermatitis and FA are strongly associated, it is difficult to define their relationship.[11]

Pathogenesis and Risk Factors

Several theories exist regarding the role of FAs in the pathogenesis and severity of atopic dermatitis. Major theories support an immune-mediated inflammatory reaction to food allergens causing exacerbation of atopic dermatitis. IgE may contribute to the characteristic inflammation seen in the skin of patients with atopic dermatitis.[12] Many patients have elevated serum concentrations of total and food-specific IgE.[12] Studies in mice demonstrated an antigen-specific IgE-mediated activation of basophils, mast cells, and eosinophils in the skin.[13] In a study by Sampson et al,

AIT	Allergy immunotherapy
DBPCFC	Double-blind placebo-controlled food challenge
FA	Food allergy
FLG	Filaggrin
OIT	Oral immunotherapy

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patients with food hypersensitivity as demonstrated by double-blind placebo-controlled food challenge (DBPCFC) that frequently ingested the offending food allergens had higher rate of "spontaneous" basophil histamine release at baseline.[14] When the offending food allergen was eliminated from the diet, significantly lower rates of spontaneous basophil histamine release were recorded, along with improvement of atopic dermatitis symptoms. Basophil-mediated inflammation may play a role in both sensitization to FAs and secondary worsening of atopic dermatitis.

Other studies show that food allergen-specific T cells may play a role in the pathogenesis of FAs and atopic dermatitis. Systemic contact dermatitis is thought to be a form of delayed-onset, cell-mediated atopic dermatitis and occurs in persons who have been sensitized to a substance through skin contact. Re-exposure by ingestion then causes dermatitis. In fact, primary cutaneous exposure is more sensitizing than primary oral exposure through a distinct Th2 cell-mediated immune reaction and may even prevent oral tolerance later in life, leading to the development of IgE-mediated FA.[11,15,16] Once sensitized, re-exposure to environmental food allergens through oral ingestion can then worsen skin symptoms.[11,17] Studies have also found food allergen-specific T cells in the skin of children with atopic dermatitis.[18,19] Sicherer and Sampson showed that elevated levels of food-allergen specific T cells correlate with an increased homing of these T cells to the skin which may influence the pathogenesis of atopic dermatitis.[5]

There is evidence of a genetic component in the development of FA and atopic dermatitis. Filaggrin (FLG) mutations appear to play a role in the pathogenesis of the atopic march given their association with atopic dermatitis, allergic rhinitis, asthma, and FAs.[20] FLG is a skin matrix protein present in the stratum corneum that promotes keratin aggregation and is essential in the regulation of epidermal homeostasis.[21] Mutations in FLG can lead to epidermal barrier dysfunction, an increased risk for dry and irritated skin, and are the most recognized genetic risk factor for atopic dermatitis. Even in patients with atopic dermatitis without mutations in FLG, there is a downregulation in expression of this gene.[21] Approximately 50% of moderate to severe cases and about 15% of mild to moderate atopic dermatitis are associated with some form of FLG mutation.[21] Margolis et al[22] performed a longitudinal cohort study on patients with atopic dermatitis with and without FLG mutations and found that those with FLG mutations do not respond to treatment as robustly. This suggests that patients with atopic dermatitis with FLG mutations should be evaluated and treated earlier and more aggressively than those without this mutation.

FLG mutations have also been found in children with FAs. Studies by Asai et al[23] and Brown et al[24] showed that FLG loss of function mutations are associated with peanut allergy even after controlling for occurrence of atopic dermatitis (OR 3.8). FLG mutations are also independently associated with food sensitization without clinical symptoms of FA. FLG is not found in either the respiratory or gastrointestinal system and, therefore, the risk for FA might not be attributed to sensitization through these routes. The presence of atopic dermatitis, particularly severe atopic dermatitis, during the first 6 months of life is associated with an increased risk of peanut allergy.[11] It is suspected that the epidermal barrier dysfunction caused by FLG mutations allows increased exposure to environmental and food allergens through the skin leading to early sensitization.[23] Low-dose cutaneous exposure to food allergens occurs frequently through household surfaces, dust, and hands.[25] Repeat exposure to these allergens then causes an immune response that contributes to local inflammation and worsening of the skin barrier defect leading to a flare of atopic dermatitis symptoms.[21]

Diagnosis of FAs in Atopic Dermatitis

The approach to diagnosis of FA in patients with atopic dermatitis consists of a detailed history, including dietary history (or maternal dietary history if breast-fed), tests for sensitization such as skin prick testing and serum food-specific IgE levels, and assessment of the clinical significance of positive tests.[4,26] In 2010, the National Institutes of Health and National Institute of Allergy and Infectious Disease sponsored a panel of experts to publish clinical guidelines for diagnosis and management of FA.[27] In these guidelines, a FA was defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." The guidelines recommend testing for FA in all children who have experienced an immediate reaction following ingestion of a specific food. Although FA is more prevalent in children with atopic dermatitis, routine screening of all children with atopic dermatitis is not recommended. The expert panel stated that, in individuals without documented or proven FA, avoiding potentially allergenic foods as a means of managing atopic dermatitis is not recommended. The expert panel did suggest that children less than 5 years of age with moderate-to-severe atopic dermatitis should be considered for FA evaluation for milk, egg, peanut, wheat, and soy if: (1) the child has persistent atopic dermatitis in spite of optimized management and topical therapy; and/or (2) the child has a reliable history of an immediate reaction after ingesting specific foods.[26,27]

Tests for sensitization, such as skin prick testing and serum food-specific IgE levels, are designed to detect the presence of food-specific IgE, a marker of food sensitization.[28] Because over 90% of FAs in children are due to milk, egg, peanut, wheat, and soy, the initial approach recommended by the expert panel involves screening for reactions to these common food allergens.[27,28] Many patients can have sensitization to a food allergen without development of clinical symptoms, leading to a high false-positive rate to either specific IgE testing or skin prick testing.[10] For instance, consider testing for a cow's milk allergy, where in 1 study skin prick test had a sensitivity of 0.85 and a specificity of 0.75.[29] If we estimate the prevalence of milk allergy to be 5% (higher than in most studies, but useful for this exercise), 50 individuals would have true allergy in a population of 1000. With a