Current Issues in Atopic Comorbidities and Preventing the Atopic March

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The individual, family, and public health burden of atopic dermatitis (AD) is considerable. The prevalence of AD is high, the signs and symptoms of the disease adversely affect quality of life for patients and their families, and the comorbid conditions associated with AD can increase considerably the negative impact of the disease. These comorbid conditions patients with AD are susceptible to include skin infectious, IgE-mediated diseases, and mental health disorders. New research identifies the skin barrier as not only an important initiator of atopic dermatitis but may even be a site for allergic sensitization to protein antigens. The skin barrier represents a potential new target for novel atopic prevention strategies.

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Atopic dermatitis (AD) is a common disorder, becoming more prevalent in developing countries around the world. AD often negatively affects the lives of children and has a major impact on an entire family. AD also predisposes a child to multiple comorbid conditions, such as skin infections, food allergy, asthma, and psychological issues. Because of the high disease prevalence and its impact on patients and families, finding a way to prevent the development of AD has become a focus of intensive research. Additionally, preventing AD may prevent or reduce the burden of multiple comorbidities that often occur in children who develop AD. Herein, we discuss recent advances regarding AD comorbidities and present a novel skin barrier approach to prevent the atopic march.

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Atopic Comorbidities

Mechanisms of Sensitization

In the past, the clustering of IgE-mediated conditions led to the assumption that AD is a disease driven by allergic mechanisms. Indeed, several single nucleotide polymorphisms in genes encoding for immune elements have been found in AD populations.¹ However, in light of the robust data implicating the skin barrier gene filaggrin as a strong predictor of AD development, IgE sensitization and allergy are no longer viewed as causes of AD, but as possible consequences. Protein exposure through a defective skin barrier may be an important mechanism of IgE sensitization in young children, although more direct human data are needed to better understand the importance of transcutaneous sensitization.

Gideon Lack and his team of pediatric allergists conducted one of the first clinical studies to suggest IgE sensitization and allergy may be associated with protein exposure to the skin. This group demonstrated that the strongest predictor of peanut allergy in a cohort of children in the UK was the use in infancy of topical moisturizers containing peanut oil.² This suggested IgE sensitization to peanut proteins was occurring via a transcutaneous route. Lack and colleagues³ also demonstrated that food protein concentrations in house dust was strongly associated with an increased risk for peanut allergy.

Studies in both the murine model and in humans support this concept of transcutaneous sensitization. In mouse models, Beck and Leung⁴ showed that applications of protein allergen to abraded skin would produce high levels of IgE to that protein, to a degree greater than that found with sensitization via other routes. In clinical studies, it has been demonstrated that a filaggrin skin barrier gene defect not only increases the risk for AD, but also increases the risk for asthma and allergic sensitization. Most recently, Brown and colleagues⁵ reported that filaggrin defects increase the risk for developing peanut allergy even in the absence of AD development, further highlighting the importance of the skin barrier in peanut sensitization.

Food Allergy

The prevalence of food allergy is increased in patients with AD compared to control populations, although the strength of that risk is not clear. Recent population-based studies show that previous estimates of 30% to 60% may be too high, and the risk is probably closer to 15%.^{6,7} In addition, several papers have been published recently indicating that positive allergy tests in AD have poor predictive value—that is, the presence of a positive test is not a reliable predictor of either an immediate or delayed clinical reaction.^{8,9} Indeed, an estimated 50% of the U.S. population will have positive results on an allergy test with no history of allergy.¹⁰

Recently, the National Institute of Allergy and Infectious Diseases published new guidelines on the diagnosis of food allergy with recommendations for the management of food allergy for patients with AD.^{11,12} Among the changes incorporated by the independent panel of allergists and dermatologists responsible for updating the guidelines is that the di-

agnosis of allergy should not be based solely on positive results of allergy testing, but also requires demonstration of an “adverse health effect.” The updated NIAID guidelines further state that patients with AD should not be routinely tested for food allergy unless signs are evident of a type 1 reaction (for example, vomiting, urticaria, or angioedema), or unless a patient has been adequately treated with appropriate topical skin care without significant improvement.

Asthma

There is at least a two-fold increase in asthma risk in children with AD. In addition, asthma severity is known to be worse in patients who also have AD.¹³ The type of asthma that is most common in patients with AD is allergic asthma. The mechanisms of asthma development in AD are not clear. One possibility is that IgE sensitization, either through immune dysregulation or transcutaneous sensitization, drives allergic asthma. Several studies have suggested that that early exposure to respiratory syncytial virus may dramatically increase the risk for asthma, especially in patients predisposed to atopic disorders.^{14,15}

Behavioral/Emotional/ Psychological Issues

General clinical experience and numerous published studies have shown that children with AD have an increased prevalence of emotional, behavioral, and psychological issues compared to children without AD. These issues include irritability, fussiness, clingy behavior, restlessness, and scratching the skin as an attention-getting behavior.¹⁶

In addition, accumulating evidence suggests that children with AD may be at increased risk for defined mental health disorders, including attention deficit-hyperactivity disorder (ADHD) and autism. Prompted by epidemiologic evidence demonstrating an increased prevalence of asthma in children with ADHD, Schmitt and colleagues¹⁷ hypothesized that the immunologically related condition of AD might be linked to ADHD symptoms. They studied the possible relationship in a study of more than 1400 German children. These investigators found that the prevalence of ADHD in the subjects with AD was 5.2%, and in controls, it was 3.4%, a statistically significant association (odds ratio, 1.54; 95% CI, 1.06-2.22; $p=0.02$), and possibly indicating a severity-related independent association between AD and ADHD.

However, the authors also point out that their results “require cautious interpretation,” noting that even if the association is a real one, it may relate to atopy in general and may not be specific for AD. In addition, they delineate methodologic issues that prevent the establishment of a causative relationship between AD and ADHD. Finally, they indicate that AD-related pruritus, sleep disturbance, and other factors may have been factors in their results.

Our group recently conducted a study of mental health disorders in children with AD in large populations in the United States that confirm the initial study from Europe. This study demonstrated that pediatric AD is associated with

ADHD, depression, anxiety, and autism with the greatest risk being associated with more severe skin disease.¹⁸

A prevailing opinion regarding the underlying mechanisms of behavioral/psychological problems in children with AD is sleep disturbance. Studies have shown that children with AD commonly experience disturbed sleep, both in duration and quality. Disturbed sleep for just a few consecutive nights can manifest in behavior that resembles that associated with ADHD, and children with AD often experience many months and years of poor-quality sleep. It is not yet clear whether the behavioral/psychological problems in children with AD are fully explained by sleep disturbances, or are the result of other mechanisms entirely.

One other proposed mechanism that may explain—or contribute to—the link between AD and ADHD or autism is systemic inflammation. The theoretical possibility must be considered that cutaneous inflammation may lead to a systemic inflammatory state leading to altered brain development. Children with ADHD and autism have elevated levels of proinflammatory cytokines.^{19,20} Proinflammatory cytokines have been thought to influence brain development, as cytokine receptors can be found in the developing brain.

Infections

Patients with atopic dermatitis are at increased risk for *Staphylococcus aureus* colonization and infections. In addition, patients with AD also get exaggerated presentations of viral infections, particularly to herpes simplex virus (eczema herpeticum), which is associated with a dramatic spreading of viral lesions over the skin, lymphadenopathy, fever, and malaise. Eczema herpeticum can be severe and even life-threatening. Patients with AD also are at increased risk for eczema vaccinatum, a viral skin infection that results from direct vaccination with the smallpox vaccine or, more likely, from close contact with another individual who has been vaccinated.

Understanding of the role and nature of microbial skin infections has been enhanced recently by the work of Capone and colleagues²¹ and of Kong et al,²² groups who published groundbreaking articles on the human skin microbiome in infants²¹ and in patients with AD. The skin microbiome is, essentially, the genetic signature of all microorganisms on the skin. These microbiome studies have provided a richer understanding of the microbial diversity and dynamic nature of skin microbes in patients with AD. Kong et al²² demonstrated that flares of AD actually are correlated with a lack of microbial diversity. Staphylococci appear to proliferate in the setting of reduced microbial diversity, although the exact order of events is unclear. Studies of the microbiome provide opportunities for the development of novel strategies in patients in whom recurrent cutaneous infections may be a problem.

Strategies for Prevention

A systematic review determined that 91% of previous eczema prevention strategies were based on allergen avoidance or on attempts to alter allergic responses. Some of these examples

include the use of hypoallergenic formulas, dietary allergen avoidance, environmental allergen avoidance, and dietary supplements to alter immune reactions in the gut. Unfortunately, after decades of research and more than 100 published studies, no generally accepted prevention strategy for AD exists.²³

The use of probiotic supplementation and hypoallergenic formulas have shown some recent promising results, but these strategies have not been consistently effective.^{24,25} In part, this may be because allergic mechanisms are not an important driving factor in atopic dermatitis as previously discussed. Attempting to repair a defective skin barrier early in life represents a new strategy for preventing AD.

In the first study examining a skin barrier approach to AD prevention, Simpson and colleagues used full-body emollient to prevent the initial flare of AD. This approach was studied in a cohort of 22 babies at high risk for developing eczema (one first-degree relative with a history of atopic disease).²⁶ After over 1 year of treatment, the cumulative incidence of AD was lower than what would be expected using historical controls. These open-label results were recently confirmed in a small, controlled feasibility trial—the Barrier Enhancement for Eczema Prevention (BEEP) study, a collaborative effort between the U.K. and the U.S. involving 124 neonates.²⁷ Although the study was not powered to assess efficacy, the results indicated that the approach appears to be safe, feasible, and was associated with significant efficacy in reducing the incidence of AD. The caveats to these results include the fact that it was only a 6-month study and three different emollients were used. However, the results provided a basis on which to further explore this strategy.²⁸

Conclusion

Atopic comorbidities include IgE-mediated diseases, infections, and behavioral and emotional problems. An obvious goal in prevention of AD is to avoid the skin signs and symptoms, but also to prevent these various allergic, infectious, and mental health comorbidities.

Although currently there are no generally accepted, or objectively proven, prevention strategies for AD, results from the BEEP feasibility study suggest that measures to protect and enhance the skin barrier from birth may be a promising avenue for future research.

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