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ATOPIC COMORBIDITIES OF ATOPIC DERMATITIS

Introduction

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory, multidimensional-burden skin disease. It is associated with numerous comorbidities, which have been summarized in the literature previously. This chronic inflammatory dermatosis is part of the atopic syndrome. This review will focus on atopic comorbidities of atopic dermatitis with specific attention to asthma, allergic rhinitis, and possible associated food allergies in the AD patient. We hope to help equip the dermatology outpatient practice with an economical, efficient, and validated tool which can be used to identify uncontrolled asthmatic patients who present with atopic dermatitis and to address questions commonly asked about the role of food allergies in atopic dermatitis.

Atopic Dermatitis and Asthma

Asthma is a complex, chronic inflammatory airway disease that manifests as inflammation and hyperresponsive airways. Approximately 3.8 million Canadians, 10 percent of the population, live with asthma.[1] Studies have indicated that AD and asthma may be correlated, with as many as 19 to 45 percent of asthmatic children having concomitant atopic dermatitis.[2] Atopic dermatitis in adults with asthma has been shown to be associated with a higher number of annual asthma exacerbations and more persistent asthma.[3]

The mechanism underlying AD's progression to asthma remains somewhat unknown, although recent findings suggest that defective epithelial barrier function plays a key role in the pathophysiology of airway inflammation in asthmatic patients.[4] The barrier consists of epithelial apical junctional complexes, which are multiprotein subunits known for their roles in cell-to-cell adhesion and barrier integrity.[4] These complexes can be compromised in asthmatic patients through numerous sophisticated pathways which are beyond the scope of this article. It should be noted that decades of studies suggest that the relationship between AD and asthma is more complicated than a direct causality.[5,6] A cluster analysis of 214 infants found that children with early-onset AD faced a higher risk of developing asthma if they had had multiple sensitizations to food allergens or a familial history of asthma.[7]

Uncontrolled asthma lowers health-related quality of life. A national survey of U.S. residents showed that children with uncontrolled asthma were rated by caregivers as having significantly lower physical and

psychological health, as well as missing significantly more school days than their controlled-asthma counterparts.[8] A large prospective cohort study corroborates these findings.[9]

The Asthma Control Test (ACT) may offer a convenient resource to detect and refer poorly controlled asthma patients in various clinical settings, such as dermatology outpatient clinics when evaluating atopic dermatitis patients. The ACT is a 5-item patient-completed questionnaire and asks about daytime and nighttime symptoms, medication use, and impaired productivity.[10] **(Figure 1)**. Scores range from 5 to 25, with well-controlled asthma yielding a score of 25. A score of 19 or lower indicates generally uncontrolled asthma; a score of 15 or lower is more concerning, as it indicates poorly controlled asthma[10]. Patients who score poorly should be referred to an allergist/immunologist or a respirologist. Schatz et al.[10] demonstrated that the ACT is reliable over time, internally consistent, and valid between baseline ACT scores, specialists' baseline asthma control assessments, Asthma Control Questionnaire scores, and percent predicted FEV[1] values. It was further found that ACT scores were lower in those with poorer asthma control (as judged by asthma specialists) than those with better asthma control, with percent predicted FEV[1] and therapy changes measuring "asthma control." The study additionally found that an ACT score of 19 indicated likely cause for concern; of patients with ACT scores lower than 19, only 27 percent were deemed to have well or completely controlled asthma. Conversely, of patients with ACT scores greater than 19, only 8 percent were deemed by an asthma specialist to have poorly controlled or not controlled asthma.

Asthma Control Test™

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
o	o	o	o	o
1	2	3	4	5

2. During the past 4 weeks, how often have you had shortness of breath?

More than Once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
o	o	o	o	o
1	2	3	4	5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all
o	o	o	o	o
1	2	3	4	5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
o	o	o	o	o
1	2	3	4	5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at All	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
o	o	o	o	o
1	2	3	4	5

Figure 1. Asthma Control Test (ACT); adapted from Schatz et al, 2006

As Schatz and colleagues remind us, "there is no gold standard for asthma control measurement".[10] Point-in-time measurements such as FEV[1] values often do not give a full picture of respiratory health and should not be used in isolation to diagnose asthma.[11] The ACT is a physician-tested screening tool that can be used to screen for uncontrolled asthma patients in the atopic dermatitis patient population.

Atopic Dermatitis and Allergic Rhinitis

Allergic rhinitis is an IgE-mediated reaction that, when triggered by aeroallergens, leads to sneezing, nasal pruritis, congestion, and rhinorrhea.[12] In a study of 2,270 children with physician-confirmed AD, Kapoor et al.[13] found that nearly two-thirds of subjects reported having either or both of allergic rhinitis and asthma. The presence of these comorbidities was found to correlate with poor AD control. These results indicate that when AD goes uncontrolled, respiratory health may decline.

A mouse-model study found that epicutaneous aeroallergen sensitization initiates T-helper Type 2 (Th2) immunity, priming for nasal hyperresponsiveness[14]. Akei et al. conclude that antigen sensitization can efficiently occur via skin.[14] Similarly, other mouse-model studies have demonstrated that epicutaneous sensitization to ovalbumin and peanut promotes Th2 immunity, as measured by increased Interleukin-4 secretion and high specific IgE and IgG1 levels.[15]

Exposure to aeroallergens can trigger AD-like symptoms[14]. House dust mites *Dermatophagoides pteronyssinus* and *farinae* are particularly pervasive and thus significant. In a multi-center, randomized, double-blind trial, Werfel et al.[16] administered subcutaneous immunotherapy (SCIT) to AD patients with Type I sensitization to house dust mite antigens over the course of one year. They found that SCORAD (SCORing atopic dermatitis) scores decreased, as well as the use of topical corticosteroids and oral antihistamines.

However, the triggers for AD are multifactorial and house dust mite allergy may be only one of several variables. It is thus unsurprising that other studies show little evidence to support the effectiveness of SCIT in treating AD patients. Therefore, desensitization of dust mite allergens in AD patients is an area of debate and higher quality research is required prior to drawing concrete conclusions.

Atopic Dermatitis and Food Allergies

Food allergy is defined by the National Institute of Allergy and Infectious Disease (NIAID) as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food"[17] and broadly comprises several types of reactions. Food allergies are commonly brought up by patients as potential triggers for their atopic dermatitis. Some patients describe anaphylaxis symptoms (immediate and IgE-mediated) while others report delayed dermatitis flares following ingestion. Generally, food allergies are more likely to develop in patients with earlier, more severe AD.[15]

Extensive literature review has demonstrated that 50 to 90 percent of presumed food allergies are not true allergies.[17] Self-reported food allergies can exceed true allergy incidence, as proven by an oral challenge, by a factor of 10.[18] The NIAID suggests that all suspected food allergies be confirmed using oral food challenges or further tests for sensitizations.[17] Patient history should only substitute for an oral challenge in the most unambiguous, clear-cut instances of acute and severe reactions. Further, patient history is often not clinically helpful when diagnosing delayed reactions to foods.[19]

With respect to IgE-mediated reactions, the suspected food allergen may be gradually re-introduced at home if the patient has a negative skin prick test (SPT), negative food-specific IgE test, and no history of immediate food allergy symptoms.[20] Those with a history of immediate food allergy symptoms, even in the presence of a negative SPT and food-specific IgE test, should undergo an oral challenge in a controlled clinical setting to confirm or exclude a true IgE-mediated reaction.[20]

Routine skin prick testing in the AD patient is generally not recommended for the purpose of diagnosing triggers. There is an approximately 40 percent chance of a false-positive reaction. If the patient has a false-positive reaction on a SPT, the patient should ideally undergo an oral challenge to confirm or rule out an IgE-mediated reaction.

Many patients and parents, however, are more frequently concerned with late eczematous reactions rather than IgE-mediated reactions. For this reason, this article will focus on late eczematous reactions.

The pathophysiology of these non-IgE mediated reactions is not fully understood. An oral food challenge in the AD patient can lead to 3 different outcomes:[18]

1. An immediate, IgE-mediated non-eczematous reaction
2. A delayed eczematous reaction (typically seen as an eczema flare 6-48 hours after ingestion)
3. A combination of an immediate non-eczematous reaction and a delayed eczematous reaction

Niggemann et al.[21] retrospectively analyzed the clinical outcome of 387 oral provocations using double-blind, placebo-controlled food challenges (DBPCFC) in 107 children with moderate to severe resistant AD. Of all positive challenges, 25 percent resulted in isolated, delayed reactions and 5 percent resulted in combined early and delayed reactions. Of all oral challenges with hen's egg, 70 percent resulted in positive reactions. This was followed by cow's milk, at 51 percent combined, cow's milk and hen's egg accounted for 83 percent of all positive oral challenges.

In a study by Breuer et al.[22], DBPCFC were administered to 106 children with AD. Food challenges included cow's milk, hen's egg, wheat gluten, and soy. Forty-six percent of all food challenges resulted in a positive reaction. Of these, 43 percent were immediate reactions, 12 percent were delayed eczematous reactions, and 45 percent resulted in combined immediate and delayed reactions. Hen's egg accounted for the highest proportion of positive reactions, at 62 percent, followed by cow's milk, at 47 percent. Isolated, delayed eczematous responses are generally seen 6 to 48 hours following ingestion and are thus not noted in many oral challenge studies.[23] Few studies have specifically observed these types of reactions and have found that 25 percent of delayed reactions occur 2 hours following ingestion, and 10 percent occur at least 16 hours following ingestion.[23]

Due to the delayed reaction, the patient's skin must be inspected by a physician for eczema area and severity index (EASI) and SCORAD scores both before the oral challenge and afterward. Patients who did not react after the first challenge should undergo further provocation with the same food for another 1 to 2 days.[18]

Food testing is not typically recommended with a new diagnosis of AD. However, testing may be helpful in certain types of patients. The NIAID expert panel suggests testing the following subsets:[17]

1. children <5 years of age who have intractable, moderate-to-severe AD despite optimal management and topical treatment
2. children who have experienced an immediate reaction following ingestion of a specific food

Testing processes should follow the diagnostic algorithm depicted in **Figure 2** below:

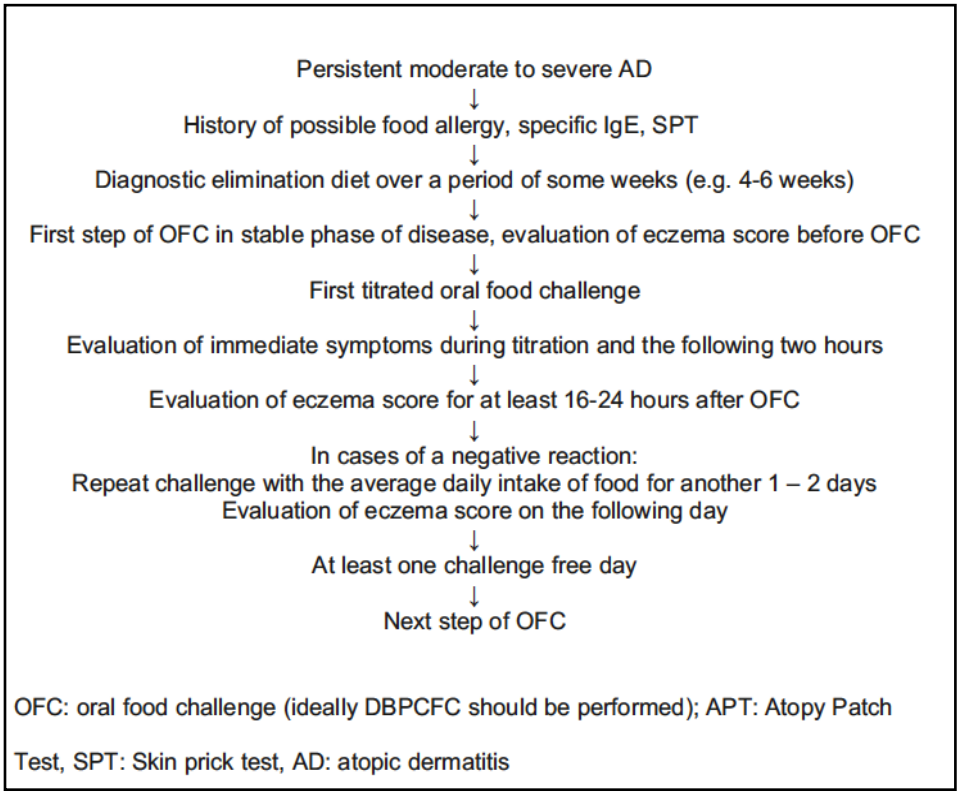

Figure 2. Diagnostic algorithm for the identification of food allergy in patients with AD; adapted from Sampson et al, 2012

Food elimination diets should not be recommended to all patients with AD. A review of 9 randomized, controlled trials measuring the effects of elimination diets on AD patients found that there was little evidence to support avoidance diets.[17] Furthermore, food elimination diets could introduce psychological and social burden, and acute, severe reactions upon re-introduction of food allergens.[24]

Oral challenges are still considered the gold standard for diagnosing IgE-mediated reactions. However, little quality data exists in diagnosing triggers for late eczematous reactions. This area is still developing and needs much research.

Conclusion

Atopic dermatitis is ultimately a complex and chronic inflammatory condition with many challenging comorbidities that impact patient quality of life, morbidity, psychological and economic burden. Although the mechanisms of AD correlation with asthma, food allergies, and allergic rhinitis are not entirely understood, AD patients see an increased likelihood of atopic comorbidities. Dermatologists are thus in the unique position to help screen and identify atopic comorbidities in AD patients to maximize AD control and improve patient outcomes.

Clinical pearls from our author

If a patient comes to us and is quite fixated that food allergies are triggering their atopic dermatitis, we carry forward with epicutaneous testing (i.e. skin prick testing) which is then followed by a supervised oral challenge. We strongly encourage most patients to avoid testing (unless history is suspicious for an IgE mediated reaction) because there is a risk of false positive reactions (~ 40%). If the patient still demands testing despite education AND if a patient has a positive skin test (in the setting of NON- IgE mediated symptoms), we follow through with a monitored 3- hour challenge. This helps us rule out immediate reactions (plus early delayed).

What about delayed reactions? Some of the newer clinics are certainly thinking about delayed reactions now but very few are actually carrying out delayed 6-12 hour challenges. Our practice is that patients get a call in the evening (6 hours after the initial challenge and we ask them to take pictures), then they come back 24 hours later, and then again 48 hours later for quick EASI scores, BSA, and IGA evaluation. This is cumbersome and resource intensive, but it seems to work and there is evidence in the literature to support this approach, though there are limitations even in the quality of literature. This is a new approach, however, there is certainly some merit and I am finding it is really convincing a majority of patients they don't have food allergies. The challenge is AD waxes and wanes and its course fluctuates many times. There are several triggers (i.e. heat, stress, sweat, irritants, etc.) and a controlled home setting is difficult to ensure. Almost all allergists are now carrying out immediate oral challenges in their clinics if the evaluation is being done right.

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