Can Atopic Dermatitis and Allergic Contact Dermatitis Coexist?

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PRACTICE **POINTS**

- Although it previously was thought that atopic dermatitis (AD) and allergic contact dermatitis (ACD) could not coexist due to their polarized immune pathways, current evidence suggests otherwise.
- When both diagnoses are suspected, patch testing should be considered as well as therapeutic strategies that can treat both AD and ACD simultaneously.

Due to their seemingly divergent immune pathways, it previously was thought that atopic dermatitis (AD) and allergic contact dermatitis (ACD) could not occur together. However, novel research suggests that the 2 conditions may be more closely related than previously understood. Herein, we discuss the overlapping relationship between AD and ACD and review the evidence for their coexistence. We also review management strategies to consider for patients with dual diagnoses of AD and ACD.

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Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are 2 common inflammatory skin conditions that may have similar clinical presentations. Historically, it was thought that these conditions could not be diagnosed simultaneously due to their differing immune mechanisms; however, this belief has been challenged by recent evidence suggesting a more nuanced relationship between the 2 disease processes. In this review, we examine the complex interplay between AD and ACD and explain how shifts in conventional understanding of the 2 conditions shaped our evolving recognition of their ability to coexist.

Epidemiology of AD and ACD

Atopic dermatitis is the most common inflammatory skin disease in children and adolescents, with an estimated prevalence reaching 21%.[1] In 60% of cases, onset of AD will occur within the first year of life, and 90% of cases begin within the first 5 years.[2] Resolution may occur by adulthood; however, AD may continue to impact up to 8% to 9% of adults, with an increased prevalence in those older than 75 years.[1] This may represent an underestimation of the burden of adult AD; one systematic review of 17 studies found that the pooled proportion of adult-onset AD was greater than 25%.[3]

In contrast, ACD previously was assumed to be a disease that more commonly impacted adults and only rarely children, primarily due to an early misconception that children were not frequently exposed to contact allergens and their immune systems were too immature to react to them even if exposed.[4,5] However, it is now known that children do have risk factors for development of ACD, including a thinner stratum corneum and potentially a more absorbent skin surface.[4] In addition, a 2022 study by the North American Contact Dermatitis Group (NACDG)

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found similar rates of ACD in children (n=1871) and adults (n=41,699) referred for patch testing (55.2% and 57.3%, respectively) as well as similar rates of having at least 1 relevant positive patch test (49.2% and 52.2%).[6]

In opposition to traditional beliefs, these findings highlight that AD and ACD can occur across age groups.

Immune Mechanism

The pathogenesis of AD represents a multifactorial process involving the immune system, cutaneous flora, genetic predisposition, and surrounding environment. Immunologically, acute AD is driven by a predominantly T_H2 helper T-cell response with high levels of IL-4, IL-5, and IL-13[7]; T_H22, T_H17, and T_H1 also have been implicated.[8] Notably, T_H17 is found in high levels during the acute eczema phase, while T_H1 and T_H22 are associated with the chronic phase.[7]

The pathophysiology of ACD is not completely understood. The classic paradigm involves 2 phases: sensitization and elicitation. Sensitization involves antigen-presenting cells that take up allergens absorbed by the skin to present them in regional lymph nodes where antigen-specific T lymphocytes are generated. Elicitation occurs upon re-exposure to the allergen, at which time the primed T lymphocytes are recruited to the skin, causing inflammation.[9] Allergic contact dermatitis initially was thought to be driven by T_H1 cytokines and IL-17 but now is understood to be more complex.[10] Studies have revealed immune polarization of contact allergens, demonstrating that nickel primarily induces a T_H1/T_H17 response, whereas fragrance and rubber accelerators skew to T_H2; T_H9 and T_H22 also may be involved depending on the causative allergen.[11,12]

Of note, the immunologic differences between AD and ACD led early investigators to believe that patients with AD were relatively protected from ACD.[13] However, as previously described, there are several overlapping cytokines between AD and ACD. Furthermore, research has revealed that risk of contact sensitization might be increased in the chronic eczema phase due to the shared T_H1 pathway.[14] Barrier-disrupted skin (such as that in AD) also may increase the cytokine response and the density of antigen-presenting cells, leading to a proallergic state.[15] This suggests that the immunologic pathways of AD and ACD are more intertwined than was previously understood.

Underlying Risk Factors

Skin barrier dysfunction is a key step in the pathogenesis of AD. Patients with AD commonly have loss-of-function mutations in the filaggrin gene, a protein that is key to the function of the stratum corneum. Loss of this protein may not only impact the immune response as previously noted but also may lead to increased transepidermal water loss and bacterial colonization.[16] Interestingly, a 2014 review examined how this mutation could lead to an increased risk of sensitization to bivalent metal ions via an impaired chelating ability of the skin.[17] Furthermore, a 2016 study conducted in Dutch construction workers revealed an increased risk for contact dermatitis (irritant and allergic) for those with a loss-of-function filaggrin mutation.[18]

Importantly, this same mutation may explain why patients with AD tend to have increased skin colonization by *Staphylococcus aureus*. The abundance of *S aureus* and the relative decrease in the diversity of other microorganisms on the skin may be associated with increased AD severity.[19] Likewise, *S aureus* may play a role in the pathogenesis of ACD via production of its exotoxin directed at the T-cell receptor V beta 17 region. In particular, this receptor has been associated with nickel sensitization.[17]

Another risk factor to consider is increased exposure to contact sensitizers when treating AD. For instance, management often includes use of over-the-counter emollients, natural or botanical remedies with purported benefits for AD, cleansers, and detergents. However, these products can contain some of the most prevalent contact allergens seen in those with AD, including methylisothiazolinone, formaldehyde releasers, and fragrance.[20] Topical corticosteroids also are frequently used, and ACD to steroid molecules can occur, particularly to tixocortol-21-pivalate (a marker for class A corticosteroids) and budesonide (a marker for class B corticosteroids).[21] Other allergens (eg, benzyl alcohol, propylene glycol) also may be found as inactive ingredients of topical corticosteroids.[22] These exposures may place AD patients at risk for ACD.

The Coexistence of AD and ACD

Given the overlapping epidemiology, immunology, and potentially increased risk for the development of ACD in patients with AD, it would be reasonable to assume that the 2 diagnoses could coexist; however, is there clinical data to support this idea? Based on recent database reviews, the answer appears to be yes.[20,23-26] An analysis from the Pediatric Contact Dermatitis Registry revealed that 30% of 1142 pediatric patch test cases analyzed were diagnosed as AD and ACD simultaneously.[24] The NACDG found similar results in its 2021 review, as 29.5% of children (n=1648) and 20.7% of adults (n=36,834) had a concurrent diagnosis of AD and ACD.[20] Notably, older results from these databases also demonstrated an association between the 2 conditions.[23,25,26]

It remains unclear whether the prevalence of ACD is higher in those with or without AD. A comprehensive systematic review conducted in 2017 examined this topic through analysis of 74 studies. The results demonstrated a similar prevalence of contact sensitization in individuals with and without AD.[27] Another systematic review of 31 studies conducted in 2017 found a higher prevalence for ACD in children without AD; however, the authors noted that the included studies were too variable (eg, size, design, allergens tested) to draw definitive conclusions.[28]

Even though there is no clear overall increased risk for ACD in patients with AD, research has suggested that certain allergens may be more prevalent in the setting of

AD. An NACDG study found that adults with AD had increased odds of reacting to 10 of the top 25 NACDG screening allergens compared to those without AD.[20] Other studies have found that AD patients may be more likely to become sensitized to certain allergens, such as fragrance and lanolin.[14]

Considerations for Management

Diagnosis of ACD in patients with AD can be challenging because these conditions may present similarly with chronic, pruritic, inflammatory patches and plaques. Chronic ACD may be misdiagnosed as AD if patch testing is not performed.[29] Given the prevalence of ACD in the setting of AD, there should be a low threshold to pursue patch testing, especially when dermatitis is recalcitrant to standard therapies or presents in an atypical distribution (ie, perioral, predominantly head/neck, hand and foot, isolated eyelid involvement, buttocks).[4,30] Various allergen series are available for patch testing adults and children including the NACDG Standard Series, American Contact Dermatitis Society Core Allergen Series, or the Pediatric Baseline Series.[31-33]

If potentially relevant allergens are uncovered by patch testing, patients should be counseled on avoidance strategies. However, allergen avoidance may not always lead to complete symptom resolution, especially if AD is present concomitantly with ACD. Therefore, use of topical or systemic therapies still may be required. Topical corticosteroids can be used when dermatitis is acute and localized. Systemic corticosteroids are utilized for both diagnoses when cases are more severe or extensive, but their adverse-effect profile limits long-term use. Other systemic treatments, including conventional agents (ie, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil), biologics, and small molecule inhibitors also may be considered for severe cases.[34,35] Dupilumab, a monoclonal antibody targeting IL-4/IL-13, is approved for use in moderate to severe AD in patients 6 months and older. Recent evidence has suggested that dupilumab also may be an effective off-label treatment choice for ACD when allergen avoidance alone is insufficient.[36] Studies have been conducted on secukinumab, a monoclonal antibody against IL-17; however, it has not been shown to be effective in either AD or ACD.[37,38] This indicates that targeted biologics may not always be successful in treating these diagnoses, likely due to their complex immune pathways. Finally, there is an emerging role for JAK inhibitors. Three are approved for AD: topical ruxolitinib, oral abrocitinib, and oral upadacitinib.[39] Further investigation is needed to determine the efficacy of JAK inhibitors in ACD.

Final Interpretation

Evolving evidence shows that AD and ACD can occur at the same time despite the historical perspective that their immune pathways were too polarized for this to happen. Atopic dermatitis may be an important risk factor for subsequent development of ACD. Management should include a low threshold to perform patch testing, while pharmacotherapies utilized in the treatment of both conditions should be considered.

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