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Contact Dermatitis (SE Jacob, Section Editor)

Allergic Contact Dermatitis in Atopic Dermatitis

Suwimon Pootongkam, MD
Susan Nedorost, MD[*]

Address
*Department of Dermatology, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 3500, Cleveland, OH 44106-5028, USA
Email: Susan.Nedorost@UHhospitals.org

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Opinion statement

Atopic dermatitis (AD) is a common chronic inflammatory skin disease resulting from a disrupted barrier function and an altered immune mechanism. Sometimes, it is difficult to distinguish between AD, irritant contact dermatitis (ICD), and allergic contact dermatitis (ACD) because they all present as eczematous dermatitis and may co-exist. Impaired barrier function in AD predisposes to the development of both ACD and ICD, as these three conditions share some mechanisms. The prevalence of ACD is at least as common in AD patients as in the general population; therefore, patients with chronic recalcitrant dermatitis should be evaluated for and considered for patch testing. Patch testing should also be undertaken in difficult-to-control or new-onset dermatitis in patients with AD, as avoiding the culprit allergen(s), along with barrier repair and infection control, will lead to improvement of symptoms. There are some special considerations when patch testing in patients with AD. Patch testing should include a standard basic screen in addition to the components of the emollients and cleansers, topical antibiotics, and topical corticosteroids used by the patient. 'Hypoallergenic' products without fragrances and strongly allergenic preservatives are commonly recommended in order to minimize the risk of irritation and sensitization via inflamed skin; however, AD patients are often sensitized to weakly potent allergens. Therefore, testing for an extended series of weak allergens used in personal care products and medicaments is critically important. Atopy patch testing (APT) may be also performed as an additional test to detect food and aeroallergen triggers of dermatitis in AD, if clinically indicated. This type of testing is also indicated in patients with a history of perioral eczema and no history of immediate hypersensitivity symptoms to the specific food tested. Aeroallergen APT is specifically indicated in seasonal dermatitis on exposed skin.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease commonly found in children with a prevalence rate of 6 % in the USA [1]. A majority of cases have onset within the first 5 years of life. AD

clears in about 40 % of children and may persist in some adults [2].

Symptoms of AD result from multiple factors, including genetic predisposition, impaired barrier functions, and altered immune mechanisms against environmental triggers and microbes.

Irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) often co-exist with AD, and the three share some common cellular mechanisms [3, 4•]. Loss-of-function mutations of the filaggrin gene have been associated with AD. Filaggrin function has an effect on moisture retention in the epidermis [5]. Previous studies have shown that AD patients with filaggrin gene mutations have an increased risk of developing chronic ICD [6]. A disrupted barrier in AD leads to increased antigen penetration, activation of innate immunity, increased access of surface antigens to dendritic cells, and activation of the T helper (Th) 2 immune response. Th2 and Th17 predominate in patients with acute AD and Th22 and Th1 in patients with chronic disease [4•]. In addition, danger signals produced in inflamed skin of AD or ICD predispose to sensitization [7]. AD patients have baseline danger signal production from barrier impairment that predisposes to sensitization of weak allergens (Kohli N, Nedorost S, unpublished data).

The presence of IgE receptor molecules on epidermal Langerhans cells from patients with AD [8] may explain the higher possibility of cutaneous sensitization to large molecules such as proteins in patients with AD. When an allergen is captured by an IgE molecule, it can then bind to the IgE receptor on an antigen presenting cell and be presented for immune recognition. Antigen presentation results in a T cell-mediated allergen-specific immune response that is responsible for the subsequent eczematous reaction [9].

Prevalence of allergic contact dermatitis (ACD) in atopic dermatitis (AD)

There are multiple factors that may affect the association between AD and contact sensitization, e.g., environmental exposures, diagnostic factors, and specific allergens considered [10•, 11–13].

In early studies, contact sensitivity to dinitrochlorobenzene (DNCB) in patients with AD was less than in control subjects [14] and severity of AD was inversely associated with contact sensitization. DNCB sensitization was positive in 33 % of severe, 95 % of moderate, and 100 % of mild AD patients [15]. However, patients with severe AD do not have severe disease at all times, and therefore they may become sensitized during periods of milder disease activity. We speculate that severe AD in the setting of exposure to a strong sensitizer such as DNCB, which functions as its own irritant, may negatively affect dermal dendritic cell function. It has long been known that other noxious conditions such as ultraviolet B will cause migration of dendritic cells away from the epidermis where antigens enter the skin and induce immune tolerance [16].

Contact sensitization and the atopic march

Patients with AD tend to develop IgE sensitization to proteins such as pollen, foods, and animal dander. Even though the antigen may penetrate the skin to an equal degree in atopic and non-atopic patients, AD patients are more likely to exhibit a Th2-skewed antigen response [17••]. AD patients with barrier dysfunction are also at increased risk of become sensitized to large protein allergens via skin contact, such as plant-derived

proteins. These constituents may also be added to personal care products because of their moisturizing properties; oat and wheat, for example, may be used as ingredients and the risks of sensitization may need to be considered [18]. Type I and type IV reactions from skin contact (and systemic route in some cases) can occur [19–21].

Identification of contact allergens in AD allows management by modification of lifestyle and diet

Standard allergens included on most patch test screening series are as follows:

- Metals: AD patients with frequent episodes of hand eczema show a strong association between filaggrin gene mutations and contact sensitization to metals including, but not limited to, nickel [22–24].
- Medicaments: The most common allergens include neomycin [25], antiseptics, and antimicrobials such as chloroxylenol [26].
- Corticosteroids: Positive patch tests to tixocortol-21-pivalate were found in 2.5 % of AD patients. Risk factors associated with positive patch test reactivity were AD severity, onset before the age of 6 months, IgE-mediated sensitization [27], and weak sensitizers (Kohli N, Nedorost S, unpublished data). In another study, 48 % of AD patients had an allergic reaction to at least one allergen, and 12.8 % had an allergic reaction to at least one corticosteroid [28].
- Fragrance: A German study found no difference in the prevalence of fragrance sensitization in patients with or without AD [29]. However, other studies (specifically in the last decade) have found a higher prevalence of fragrance sensitization in patients with AD than in controls [30–32].
- Preservatives: Recent data show increased risk of sensitization to some preservatives and surfactants in AD patients [33, 34]. We caution against the authors' interpretation of this data that patients with AD should avoid certain sensitizers while favoring others, because exposure and concentration was not controlled in these retrospective studies.
- Plant resins: Higher prevalence of sensitization to plant members of the Compositae family has been observed in patients with AD in some studies [26, 35, 36]. Paulsen and Andersen suggest that patients with AD may become sensitized to Compositae at any age, both occupationally and non-occupationally [36]. Several centers test children with seasonal flares on exposed skin to dandelion.

Emerging technique: atopy patch tests

Atopy patch tests (APT) are performed by epicutaneous application of protein allergens, usually used to elicit standard IgE-dependent reactions tested by skin-prick test (SPT) [37], such as foods and aeroallergens.

- Foods: AD flares by foods have been reported [38]. Some patients benefit from avoidance of milk, egg, soy, or birch-related foods [39] identified by APT.
- Aeroallergens: AD patients develop flexural contact dermatitis in later childhood and some of them have exacerbation of AD after contact with or inhalation of aeroallergens, e.g., house dust mites, pollen, or animal dander, and improve after avoidance [40].

The sensitivity and specificity varies widely depending on allergens [41]. SPT, specific IgE (sIgE), and APT have been studied for detecting food and aeroallergen sensitization in AD patients; they have been considered as diagnostic tools, but their predictive capacity varies by allergen and also for detection of early or late-phase reactions [42]. SPT and sIgE detect immediate-type hypersensitivity, whereas APT may have a role in detection of delayed-type hypersensitivity reactions. Further research to standardize and validate APT is needed.

Testing indications

Patch test indications

- New pattern of dermatitis
- Dermatitis fails to respond to previously successful treatment
- Suspicion of occupational dermatitis

Patch test preliminaries

- Test when back is dermatitis free in the test area, and patient is preferably off both topical and systemic corticosteroids
- Treat superficial/secondary infections with antibiotics before testing
- Treat post-pubertal patients with head and neck/textile pattern dermatitis with systemic anti-yeast antibiotics before testing

Patch test selection

- Allergens to be patched should be customized for each patient by detailed history and physical examination. A majority of AD cases are children and sometimes space on the patient's back is limited
- Test personal care products and medicament components in all patients
- Test occupational contactants when indicated
- Test foods in children with a history of perioral involvement
- Test aeroallergens in patients with seasonal flares of exposed skin
- Test for systemic contact dermatitis, e.g., to propylene glycol or benzoic acid, in patients with recurrent dermatitis in the same areas

Factors that may affect patch test results

- Irritant, angry-back reactions may occur. Delayed reading (at 96 and 120 h) helps reduce false positive interpretations due to irritant reactions. AD patients may have a follicular response from occlusion with patch-test tapes. Bacterial proliferation under patch-test occlusion may occur and cause flares of AD. We recommend pre-treating adult AD patients who have active disease with systemic anti-staphylococcal and anti-yeast antibiotics before patch testing.

Education on allergen avoidance and treatment of ACD in AD

Education on allergen avoidance

- Patients must be educated on alternative medicaments and personal care products in order to completely avoid identified allergens. If the allergen may be ingested and systemic contact dermatitis is suspected, then instruction should be given in dietary avoidance. In our Midwestern US population, this is most common with food allergens such as oats, and food additives such as propylene glycol and benzoic acid.
- Education and counseling to the patient, parents of afflicted children, and primary health care providers is one the most important factors in helping with treatment of ACD in AD. Counseling is the most time-consuming, and most critical, aspect of treating AD.
- Education of other health care providers involved in the patient's care is also essential. These providers must know to avoid prescribing medications for the dermatitis that may contain the patient's allergens. Topical therapies with corticosteroids, emollients, calcineurin inhibitors, and oral corticosteroids may contain identified allergens as active or inactive ingredients such as propylene glycol and benzoic acid.

Treatment of ACD in AD

- The treatment approach should include the need to optimize skin barrier functions and prevent and treat bacteria and infection. In post-pubertal patients sensitized to yeast [43], efforts to maintain skin decolonization of yeast are also important.
- As historical treatment of AD is primarily based on basic skin care and long-term topical treatments with emollients and topical corticosteroids, focusing on the potential for past or future sensitization to anything that comes into contact with the skin, including topical formulations used to treat AD, is critical. Introducing new products on inflamed skin should be avoided as this may increase the risk of sensitization.

- Use bleach baths to reduce commensal bacteria in the biofilm. Follow bleach baths with low pH emollients to promote filaggrin function and improve skin barrier [44–46].

Prevention of ACD

- Avoid contact of food with skin until tolerance is well-established. Even mild AD promotes sensitization; try to avoid skin contact with new foods until established feeding allows mucosal contact to induce tolerance. Prohibiting self-feeding in infancy might help with this.
- Avoid self-feeding in infants with hand eczema.

Pediatric considerations

- The overall prevalence of relevant positive patch tests reported by the NACDG (North American Contact Dermatitis Group) does not differ between children (51.2 %) and adults (54.1 %). Among positive reactions, 34.0 % of children had AD compared with 11.2 % of adults [47]. The data suggest that AD is a more important risk factor for ACD in children than in adults. However, this could be because AD is more common in children [47].
- Children with AD demonstrate contact allergy to components of personal care products and clothing such as nickel, neomycin, disperse dyes, and *Myroxylon pereirae* [25].

Compliance with Ethics Guidelines

Conflict of Interest
Suwimon Pootongkam declares that she has no conflict of interest.
Susan Nedorost declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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