

The Role of Contact Dermatitis in Patients with Atopic Dermatitis

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Because both atopic dermatitis (AD) and contact dermatitis (CD) are characterized by a similar morphologic appearance and similar distribution of skin involvement, the diagnosis of CD in AD has been difficult. Historically, it was thought that patients with AD were unable or less likely to develop CD due to various studies in which patients with AD stimulated with strong allergens failed to develop sensitization at rates similar to patients without AD. However, more recent evidence from the United States and Europe has shown that patients with AD have similar if not higher rates of positive patch test results to common contact allergens, including metals and fragrance, than those patients without AD. In this review, we highlight evidence for and against the role of contact allergy in patients with AD and seek to give clinically relevant management recommendations for the evaluation of CD in the patient with AD. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:382-7)

Key words: Allergic contact dermatitis; Irritant contact dermatitis; Atopic dermatitis; Patch test

Contact dermatitis (CD) is a chronic skin disease characterized by itch and rash that can present as erythematous papules, vesicles, and/or crusted lichenified lesions based on its time course. It is estimated that up to 15% to 20% of the general population has CD.^{1,2} According to a 2005 report by the Society for Investigative Dermatology and the American Academy of Dermatology, CD was associated with more than 10.6 million physician office visits with direct costs estimated at \$1.6 billion and indirect costs of \$566 million from lost work, school, and productivity.³

The relationship of contact allergy of patients with atopic dermatitis (AD) is complex, and the incidence of allergic contact dermatitis (ACD) in patients with AD is unknown.⁴ There still is

conflicting evidence as to whether patients with AD are at a higher overall risk of contact sensitization compared with non-atopic dermatitides. On one hand, patients with AD have impaired skin barrier function that may potentially increase allergen penetration. Mutations in the filaggrin gene have been associated with occupational chronic irritant CD in some studies.^{5,6} The patient with AD also is exposed to numerous topical treatments, including lotions, creams, ointments, and medications, often on a long-term daily basis. This repetitive application of topical medications and emollients that often contain fragrances and preservatives can be sensitizing. On the other hand, it was traditionally believed that patients with AD are not capable of developing CD due to a shift away from cytokines that are responsible for delayed hypersensitivity responses. It is important to diagnose CD in patients with AD as atopy amplifies the effects of contact irritants and allergens on the skin. This is seen with hand eczema in patients with AD of certain occupations (hairdressers, cleaners, metalworkers, mechanics, and nurses). Contact sensitization may negatively influence the skin of AD, thus identifying an aggravating factor, such as a contact allergen, and avoidance of the allergen can lead to improvement of the dermatitis.⁷

Clinically, it is difficult to differentiate CD from AD, especially in the common areas of involvement, such as the eyelids, lips, hands, and flexural areas of the neck, and even dermatitis with scattered generalized distribution. A patch test (PT) is useful in this regard to determine sensitization to specific allergens. However, the clinical relevance of positive PT reactions should be established by carefully correlating the patient's history, including where exposure to the allergen is occurring (work, home, hobby) and what type of exposure (How much allergen? How frequently? Body site?) with the test results. It is the role of the clinician to determine if a positive PT result is relevant or not, and it often is one of the most difficult aspects of PT. Reported relevance in published studies is determined by standards used by the North American Contact Dermatitis Group (NACDG).⁸

NACDG defines current relevance as definite if the PT with the suspected item is positive, probable if the antigen is present in known skin contactants and the clinical presentation is consistent with that exposure, or possible if skin contact with materials known to contain the allergen was likely. The most concrete proof of relevance is if the dermatitis improves or resolves after avoidance of the positive allergen.⁹ Past relevance is considered if the PT is positive, but the exposure was in the past, and the patient is not currently exposed to that allergen.^{8,10}

IMPAIRED SKIN BARRIER FUNCTION AND POTENTIAL INCREASED ALLERGEN PENETRATION WITH AD

Do patients with AD develop more contact sensitization due to barrier defects, for example, increased water loss? A European

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Abbreviations used

ACD- Allergic contact dermatitis
AD- Atopic dermatitis
CD- Contact dermatitis
DNCB- Dinitrochlorobenzene
NACDG- North American Contact Dermatitis Group
PT- Patch test

group¹¹ examined the relationship between transepidermal water loss and stratum corneum hydration on the forearm and nasolabial fold in adult patients with AD-, rosacea-, and sex-matched healthy controls. The results showed that transepidermal water loss was higher and stratum corneum hydration was lower in patients with AD at both locations compared with healthy controls. Is there increased susceptibility to irritation in patients with AD due to higher skin permeability? One study looked at the penetration of 1% sodium laurel sulfate in the uninvolved skin of 20 patients with AD and 20 healthy controls by tape stripping of the stratum corneum. Again, here transepidermal water loss was higher in the AD group.¹² The diffusivity of the sodium laurel sulfate was higher in the normal skin of patients with AD compared with the healthy controls.

FILAGGRIN GENE MUTATION HAS BEEN REPORTED IN BOTH AD AND CD

Loss-of-function mutations in the filaggrin gene responsible for ichthyosis vulgaris have been reported in subtypes of AD, including early onset AD, severe persistent AD, and eczema herpeticum with AD.¹³ Filaggrin gene mutations also have been examined in patients with CD.^{5,6,14,15} A case control study from Europe looked at filaggrin gene polymorphisms (R501X, 228del4) in 296 patients with occupational-induced chronic irritant CD and in 217 controls.⁶ Heterozygotes were more frequent among subjects with chronic irritant CD than the controls (13% vs 7%), with an odds ratio of 1.91. However, two other European studies did not find an overall association with hand eczema and filaggrin null mutations.^{14,15}

COMMON AREAS OF INVOLVEMENT IN CD AND AD

AD and CD have common areas of involvement, including the lips, eyelids, hands, and flexural areas, which oftentimes makes it difficult to diagnose one disease instead of the other. For example, patients who present with flexural dermatitis may be diagnosed with AD but in fact have CD instead. Czarnobilska et al¹⁶ evaluated 143 children and adolescents with PT. Among children and adolescents who had flexural eczema, 20% of children and 52% of adolescents were diagnosed with ACD while having insufficient features for Hanifin and Rajka¹⁷ criteria of AD.

STUDIES THAT COLLABORATE ACD IN AD

An in-depth review of this topic by the authors was published in 2010.¹⁸ Here we aim to highlight the newest evidence while reviewing some of the previously published studies (Table I). A French study looked at ACD to medications in 641 children with AD.¹⁹ All the patients were tested to antiseptics, topical corticosteroids, and their current emollient. Forty-one positive PT results were obtained in 40

TABLE I. Key points

CD and AD may present with similar morphologic lesions and skin distribution
If CD is suspected in the patient with AD, then a PT is a diagnostic tool that can help determine positive allergens
Metals, fragrances, emollients, topical antibiotics, preservatives, and topical corticosteroids are some allergens that may be positive in the patient with AD who also has ACD
Once positive relevant positive allergens are identified, management includes avoidance

children of the total 641 children tested (6%). Interestingly, emollients were the most positive allergen on PT followed by antiseptics. The following were associated with contact sensitization in patients with AD: (1) onset of AD before 6 months of age, (2) more-severe AD, and (3) IgE sensitization. Contact sensitization has been found to be an early phenomenon. Belloni Fortina et al²⁰ investigated 321 children younger than 3 years of age with PT to a standard series of 30 allergens. At least 1 positive PT reaction was seen in 200 children (62%). Contact sensitization was equally seen in those patients with and those without AD (61% vs 63%).

In the United States, a review of 2305 patients who had a PT for ACD by the standard NACDG panel found that patients with AD defined by the criteria of Hanifin and Rajka¹⁷ (n = 297) were more likely than patients without AD (n = 2008) to have at least 1 positive allergen on the PT and a positive PT to a metal.²¹ A retrospective chart review of pediatric patients who underwent PT with T.R.U.E. Test (Thin-layer Rapid Use Epicutaneous Test; Smart Practice, Phoenix, Ariz) found at least 1 positive allergen with 89% of patients with atopy and with 66% of patients without atopy.²² AD was diagnosed by using the criteria of Hanifin and Rajka.¹⁷ These patients with AD had statistically significant differences in positive PT to fragrance mix and Balsam of Peru. A few studies looked at both positive PT results and assessed the relevance of these positive allergens. A prospective study from Tunisia of 89 children and adults with AD found a relevant positive PT test in 38% (34/89).²³ Interestingly, the more severe the AD, the more frequently PT was positive. Metals were the most common positive allergens.

In a recent review of contact allergy in children from publications over 11 years, the prevalence of positive PT results in selected populations (children with suspected ACD, recalcitrant AD, or eczema) ranged from 27% to 96%, with relevance established in 52% to 100%.²⁴ A total of 2309 children from 8 studies with and without AD in relation to positive PT found similar sensitization rates between both groups (56% vs 55%), similar to the findings of Belloni Fortina et al.²⁰ In summary, based on the above-mentioned European and US studies (mostly in children but also in adults), patients with AD have at least the same rate of positive PT as patients without AD, with some studies that reported even higher rates in patients with AD. The allergens with the most positive PT results in patients with AD are metals and fragrances. Contact sensitization of patients with AD may be seen in very young children. Many investigators advocate that, if ACD is suspected, then a PT should be considered in the evaluation of a patient with AD and with disease that is difficult to control, fails to improve with therapy, or spreads to new or previously unaffected areas in concordance

TABLE II. Review of the current literature for ACD in patients with AD

Study, y	Criteria for AD diagnosis	Patient characteristics	PT used	PT results
Studies that support ACD in AD				
Beattie et al, ⁴⁷ 2007	83 (75%) with history of AD, AR, or AA	114 Children: 48 boys, 66 girls	66, European series; 48, British Contact Dermatitis Group series	PT+ in 54% patients; nickel, 20%; rubber, 10%; fragrance, 7%
Belhadjali et al, ²³ 2008	Hanifan and Rajka ¹⁷	63 Children, 26 adults	European Standard series with the addition of special series and personal products for some patients	PT+ in 43% patients: nickel, 25%; chrome, 8%; cobalt, 8%
de Waard-van der Spek and Oranje, ²⁵ 2009	Not stated; 47 patients with AD	79 Children: 31 boys, 48 girls	T.R.U.E. Test, tixocortol 17 pivalate, budesonide, and 3 emollients; supplemental allergens with some patients	47% of patients with AD had at least 1 PT+; nickel was the most positive allergen in all children
Herro et al, ²² 2011	Hanifan and Rajka criteria in 54 patients (53%)	101 Children: 48 boys, 53 girls	T.R.U.E. Test standard series	PT+ in 89% of patients with atopy; PT+ in 66% of patients without atopy; nickel, 31%; wool alcohols, 18%; PTBPF, 15%; Balsam of Peru, 12%
Landeck et al, ⁴⁸ 2011	172 Patients with a history of atopy, either AD, AR, or AA	172 Patients with atopy, 1075 patients without atopy	Standard series with supplemental PT in some patients	PT+ in 65% of patients with atopy; PT+ in 58% in patients without atopy; nickel, first; fragrance mix, second; Balsam of Peru, third in both groups
Mailhol et al, ¹⁹ 2009	United Kingdom Working Party; 43% moderate-to-severe AD	641 Children: median age, 3.4 y; 48% boys, 52% girls	Chlorhexidine, hexamidine, budesonide, tixocortol pivalate, budesonide, sodium fusidate, and emollient	6% PT+: emollients, 48%; chlorhexidine, 43%; hexamidine, 8%; tixocortol pivalate, 3%
Malajian and Belsito, ²¹ 2013	Hanifan and Rajka criteria in 297 patients (12.9%)	297 Patients with AD, 2008 patients without AD: 825 males, 1478 females	NACDG standard allergen series	PT+ in 65% of patients without AD; PT+ in 71% patients with AD: nickel first in both groups
Silny et al, ⁴⁹ 2013	Hanifan and Rajka	104 Children with AD: 51 boys, 53 girls; 36 healthy controls, 15 with seborrheic dermatitis	In patients age 5 y or younger, 12 were allergens used; in patients older than age 6 y, a European standard series	PT+ in 45% of patients with AD; in healthy controls, 14% had PT+; in patients with seborrheic dermatitis, 7% had PT+
Thyssen, ⁵⁰ 2012	United Kingdom Working Party	3202 Adults from a population study that reported a history of AD: 1428 men, 1774 women	T.R.U.E. Test (panels 1 and 2)	10% PT+: nickel, 6%; fragrance mix, 2%; contact sensitization to at least 1 allergen was significantly associated with AD
Neutral studies				
Heine et al, ⁵¹ 2006	Hanifan and Rajka; in 9020 patients	9020 Patients with AD; 15,263 age-matched, without atopy	Standard series and, in some patients, additional allergens	No difference in frequency of no. of PT+ reactions was seen in both groups; sensitization to budesonide, rubber, disinfectants, and fragrances were seen more frequently in the AD group
Belloni Fortina et al, ²⁰ 2011	Hanifan and Rajka; in 137 children (43%)	321 Children: 144 boys, 177 girls	Series of 30 allergens	Prevalence of contact sensitization, similar with children with (61%) and without AD (63%)
Hogeling and Pratt, ⁵² 2008	Hanifan and Rajka; in 41 patients	100 Children: 38 boys, 62 girls	NACDG standard series, supplementary and personal products with some patients	70% PT+; children with AD (74%) were as likely as those without AD (67%) to have a positive reaction; nickel was the most common allergen
Paulsen and Andersen, ⁵³ 2013	History of past or current AD; history of childhood flexural eczema; history of childhood eczema and a positive skin prick test	46 Adults and 5 children, 16 males and 35 females, with Compositae CD and atopy vs 245 with Compositae CD without atopy	T.R.U.E. Test and Compositae allergens	Compositae sensitization did not differ greatly between patients with atopy and those without atopy; patients with atopy were younger, and dandelion was an important allergen, especially in patients with atopy and with hand eczema

Schena et al., ⁵⁴ 2012	Hanifan and Rajka; in 123 patients (35.3%)	349 Children: 156 boys, 193 girls; mean age, 8.4 y	Societa Italiana di Dermatologia Allergologica Professionale and Ambientale series	PT+ 69%; nickel, 16%; cobalt, 7%; Kathon/potassium dichromate, 5%; sensitizers were similar in children with and without AD
Seidenari et al., ⁴⁶ 2005	Hanifan and Rajka; in 404 patients (36.9%)	1094 Children: 509 boys, 585 girls	30 Allergens in 997 patients, 46 allergens in 97 patients	570 (52%) had a PT+ reaction; the frequency of PT+ did not differ significantly between patients with AD and those without AD; nickel and Kathon methylchloroisothiazolinone/methylisothiazolinone higher in patients with AD
Studies that do not support ACD in AD				
Onder, ³⁶ 2008	Hanifan and Rajka; in 4 children	360 Children	European standard series and supplemental allergens	118 PT+, 4 of whom had AD
Newell et al., ³⁷ 2013	Not stated	Patients with AD and without filaggrin mutation, patients with AD and with filaggrin mutation and healthy controls	Sensitization with DNCB	DNCB penetrated all skin groups equally; less skin reactivity was seen 1 mo later in patients with AD vs controls

+ Positive; AA, allergic asthma; AR, allergic rhinitis; Kathon, methylchloroisothiazolinone/methylisothiazolinone; PTBPPR, p-tert-butylphenol formaldehyde resin.

with the evaluation of other etiologies for difficult-to-control AD.^{22,25-28}

STUDIES THAT DO NOT SUPPORT ACD IN AD

The theory that patients with AD are less likely to develop ACD than patients without atopy came from evidence in the 1960s to 1980s when some patients with AD who had repeated applications of dinitrochlorobenzene (DNCB) did not display sensitization (Table I). In the study performed by Rogge and Hanifin,²⁹ 6 of 7 patients with AD did not respond to DNCB on repeated applications. In 1990, Rees et al³⁰ reported that exposures to DNCB of subjects with atopy and subjects without atopy showed that fewer subjects with atopy became sensitized, which suggests that the presence of inflammatory mediators in AD may inhibit the acquisition of delayed hypersensitivity.^{31,32} The study performed by Uehara and Sawai³³ tested a large number of patients with AD (n = 150) with varying levels of disease. Sensitization was seen in 87% of patients with AD. Patients with severe AD were less likely to respond to DNCB than patients with mild-to-moderate disease. All the patients with mild AD (n = 40) and 95% of patients with moderate AD (n = 82) had a positive response, whereas only 33% of patients with severe AD (n = 8) had a positive response. Interestingly, of those patients with severe AD and initial negative DNCB sensitization (n = 16), who then attained improved skin control, all but two were able to mount a response to a second challenge test.

Forsbeck et al³⁴ evaluated sensitization to DNCB and NDMA (p-nitrosodimethylamine) of patients with mild dermatitis (dermatitis that involves less than one-third of the body surface area) against those with severe dermatitis (dermatitis that involves more than one-third of the body surface area). They found that patients with mild dermatitis were sensitized to both DNCB and NDMA or either one 84% of the time versus 52% in the severe dermatitis group. Jones et al³⁵ looked at contact sensitization to the *Rhus* plant in 171 patients, 40 of whom had AD based on dermatitis distribution and compared them with age-matched controls (n = 44). Positive PTs with *Rhus oleoresin* were obtained in 61% of healthy patients without atopy versus only 15% of patients with atopy, which was statistically significant. Onder and Adisen³⁶ looked at ACD of children in Turkey by using the European Standard Series and supplemental allergens as needed. Of the 360 children assessed for suspected CD, 118 had a positive PT (32%), with only 4 children with a diagnosis of AD (0.03%) by criteria by Hanifin and Rajka.¹⁷

A recent study by Newell et al³⁷ relooked at sensitization to DNCB in unaffected skin of patients with AD and with filaggrin mutation, patients with AD and without filaggrin mutation, and healthy controls. The penetration of DNCB was equivalent for all 3 groups measured by fluorescence of anti-DNCB. A rechallenge with DNCB 1 month later showed that patients with AD (n = 16) had reduced contact hypersensitivity measured by significant decreases in erythema and skin-fold thickness compared with controls (n = 10). Spiewak³⁸ looked at 135 randomly selected patients in a general Polish population and performed aeroallergen skin testing and PT, and obtained serum-specific and total IgE levels. A positive PT was seen in higher frequency in patients with high IgE levels (>120 kU/L) but did not reach statistical significance. The study concluded that atopy and contact hypersensitivity were independent phenomena. Although the investigator remarked that “contact allergy should

be considered in every patient with atopic eczema, and topical drugs along with emollients are frequent sensitizers and should be included in routine patch testing in this group.”³⁹

Evidence against ACD in AD comes from primarily older studies in which patients with atopy failed to respond to sensitizers such as DNCB, NDMA, or *Rhus*. However, there was a difference in sensitization rates noted based on the degree of AD severity in which patients with milder disease, in fact, were able to mount a response, whereas patients with severe disease were not.^{33,34} Thus, even though there is still debate among whether or not patients with AD are as likely or less likely to develop ACD, patients in these series did have positive results on PT, such that PT is still advocated by investigators if clinically indicated.³⁹⁻⁴¹

DIAGNOSIS OF CD IN PATIENTS WITH AD

There are no standard guidelines available to aid in the evaluation and management of the patient with AD suspected of having CD. Thus, the diagnosis of CD in patients with AD is the same as in any patient suspected of having CD. The first step is to consider CD as part of the differential diagnosis and to perform PT when clinically suspicious. PT remains the criterion standard for the diagnosis of ACD. Consider CD in patients with AD and who have disease that is difficult to control, worsens with therapy, or spreads to new or previously unaffected sites once other factors, including noncompliance with medical management and bacterial or viral coinfection have been investigated.

PTs can be performed with a preloaded series (T.R.U.E. Test) or allergens that are manually loaded onto chambers. However, it is important to note that, even when using commercially available series, positive allergens can be missed. Two recent multicenter reviews of PT in the United States in allergy and dermatology practices found that PTs with only the standard allergens found in the T.R.U.E. Test series would completely identify allergens in only 28% to 57% of patients.^{42,43} In addition, the use of supplemental allergens is highly recommended. The NACDG found that nearly a fourth of 4454 patients displayed at least 1 relevant positive PT to a supplemental allergen.⁹ In particular, the use of personal products as supplemental allergens is suggested in patients with eyelid, facial, lip dermatitis, and suspected cosmetic dermatitis.^{44,45} In our opinion, it is reasonable to perform a PT on patients with AD suspected of having ACD with metals, fragrances, preservatives, topical emollients, topical corticosteroids, topical antibiotics, and antiseptics,¹⁹ and the patient's own personal care products.

Once contact allergens have been identified from PT and relevance is established, avoidance of the allergens is indicated. The advantage of allergen identification is the implementation of an avoidance regimen. A period of 8 to 12 weeks of allergen avoidance has been suggested before the assessment of clinical improvement.⁶ It is essential to provide patients with suitable lists of products that are safe for them to use. There are 2 available resources for patients and physicians, the American Contact Dermatitis Society Contact Allergen Management Program (acdscamp.org) and the Contact Allergen Replacement Database (www.preventice.com/card).

MANAGEMENT RECOMMENDATIONS

Because there is a lack of established guidelines, the following are our management recommendations based on review of

the recent dermatology and allergy literature and personal experience.

1. Patients with AD are at risk for contact sensitization, even young children.^{20,46}
2. Suspect ACD to topical corticosteroids, antiseptics, antibiotics, and emollients of patients with AD, especially when topical therapies fail to control²⁷ or worsen AD.
3. Consider PT to metals, fragrances, topical antibiotics, topical corticosteroids, and personal products of the patient with AD if there is strong suspicion of ACD.
4. When relevant contact allergens are identified, allergen avoidance is indicated, which includes providing the patient with alternative safe products to use.

KNOWLEDGE GAPS

The largest knowledge gap that exists is the unknown prevalence of ACD in patients with AD and that the utility of PT in this patient population has not been determined to date. Gaps that exist for the procedure of performing a PT include not knowing which allergens to use; which allergens are the most likely to be positive based on the location of dermatitis; and using supplemental allergens, including personal products for testing. Efforts need to be made to overcome barriers to testing for ACD, including apprehension on the part of the physician to place PTs on children, and the physical barriers that may be present with our patients with AD (dermatitis that involves the back and no suitable place for PT; the back has been treated with topical corticosteroids, phototherapy, or immunomodulators, and/or patients are ingesting oral corticosteroids or other immunomodulators that can suppress positive results; the small surface area of children to apply PT). Some of these physician barriers can be addressed during training of our allergy/immunology fellows. Although desirable, the PT is still not a required skill in allergy/immunology training and the diagnosis of CD may not be adequately addressed in these formative years. A greater focus on allergic skin diseases has been targeted at our annual meetings, which address some of these gaps.

CONCLUSIONS

Contact sensitization in patients with AD is likely underestimated and the exact prevalence and incidence of the disease is still unknown (Table II). If present in the patient with AD, then contact sensitization may exacerbate skin lesions. Thus, a high index of suspicion is needed for the diagnosis of ACD in these patients. The PT remains the criterion standard in the diagnosis and management of ACD. If a positive result on PT is obtained, then its relevance must be established in the context of the patient's own personal history, including home, hobby, and work exposures. The clinician needs to aid the patient in instruction and implantation of relevant allergen avoidance and give a suitable list of products that do not contain the positive relevant allergens.

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