Contact Dermatitis in Atopic Individuals

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Allergic contact dermatitis and atopic dermatitis are common inflammatory T cell-mediated diseases, that may also coexist. Both diseases show an increasing prevalence, although the prevalence of allergic contact dermatitis is quite difficult to establish. Nevertheless, longitudinal patch testing has demonstrated increasing numbers of sensitization to some allergens, like metals, fragrances, and preservatives [1–4]. In the USA, it is estimated that 4.17% of the population suffers from contact dermatitis, that levied a cost of $ 1.5 billion in 2013 [5]. Meanwhile, the prevalence of atopic dermatitis seems to have tripled in industrialized countries in the last three decades, affecting 15–30% of children and 2–10% of adults [6, 7]. Both conditions are associated with high costs for the health service, for loss of work or school days, and a reduced quality of life [8].

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19.1 Pathogenic Mechanisms

Even if allergic contact dermatitis and atopic dermatitis may seem clinically similar, and often coexist [9], the etiology, distribution and therapeutic options are often different.

Allergic contact dermatitis is a classic type IV immunologic reaction characterized by two phases, namely a sensitization and then an elicitation phase. The primary inflammatory signature is a T cytotoxic (Tc) 1 cell or T-helper (Th)1 response. However, Th 2, Th 17, and Th 22 responses also seem to play a role in the pathogenic mechanism, sometimes related to various allergens [10, 11]. It has been shown, for instance, that nickel is a potent inducer of the innate immune Th1, Th17, and Th 22 pathways, while fragrance and rubber promoted Th2 activity with less Th1 and Th17 involvement [12]. The potential role of Th17, demonstrated in various studies in humans [13–15], has also been shown in an experimental study in mice, where contact allergy reactions were reduced in the absence of IL-17 [16]. An elevated IL-9 expression has also been found in subjects with allergic contact dermatitis, in skin from positive patch test reactions, including reactions to metals, drugs, and polymers. IL-9 is also increased after a nickel challenge test in subjects who are allergic to nickel [17, 18].

Atopic dermatitis is a multifactorial immunologic disease with complex genetic, immunologic

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and environmental influences [19–21]. A subset of patients with atopic dermatitis have filaggrin gene (FLG) null mutations (in up to 20–50% of subjects of European or Asian descent) that are inherited in an autosomal semi-dominant fashion [22–24]. The mutation in FLG (filaggrin is a keratin *fil*ament-*aggr*egating prote*in*) severely compromises the epidermal barrier, predisposing patients to an increased skin absorption of irritants and allergens. This leads to a further breakdown of the skin barrier, raising the risk of penetration of the allergens [25, 26]. Exposure to various environmental factors (pollution, climate, chemicals, dust, pathogens) also contributes to impair the skin barrier, in turn increasing the penetration of allergens in predisposed subjects [24]. In fact, tape stripping tests have demonstrated that percutaneous permeation of the surfactant 1% sodium lauryl sulphate, a common irritant, was increased in uninvolved skin in patients with atopic dermatitis compared to control subjects [27].

As in allergic contact dermatitis, the skin's innate and adaptive immune systems are both activated in subjects with atopic dermatitis, too. The atopic dermatitis inflammatory signature is primarily $CD4^+$ Th 2 cells, especially in the acute phase. The Th 2 cascade induces the production of IL-4, IL-5, IL-13 and IL-31, eosinophil and mast cell recruitment, and the production of allergy-specific IgE immunoglobulin [28]. IL-4 and IL-13 promote skin barrier disruption. Th 2 cytokines also increase pathogen penetration [29]. Recent studies have demonstrated that in the chronic phase, atopic dermatitis is marked not only by Th 2 cells but also Th 1 cells. Recent studies have also demonstrated a possible role for the Th 9 and Th 17 pathways. IL-9, whose levels are high in both adults and children with atopic dermatitis and correlated with the disease severity, promotes the activity of mast cells, eosinophils, and innate immune cells [30, 31]. Moreover, IL-9 favors the secretion of IL-13, a key cytokine in the atopic dermatitis pathogenic mechanism. Th17 levels are correlated with the disease severity and play an even more important role in intrinsic atopic dermatitis [32].

19.2 Allergic Contact Sensitization in Atopic Dermatitis

Research into the relation between atopic dermatitis and allergic contact dermatitis dates back to the 1970s, when studies in murine and human models suggested that atopic dermatitis could be protective against allergic contact dermatitis: repeated exposure to common and potent allergens elicited reduced rates of sensitization [33–35]. This was attributed to the inability of subjects with atopic dermatitis to mount delayed hypersensitivity responses, owing to the relative cell-mediated immune deficiency (secondary to a predilection for Th 2 responses) and the skin barrier dysfunction [36].

However, more recent data have illustrated an increased risk of contact allergy in patients with atopic dermatitis, especially to weak sensitizers, that are the chemicals used for the topical treatment of the disease. There are various reasons why subjects with atopic dermatitis tend to have an increased risk of allergic contact dermatitis than non atopic subjects. Firstly, patients with atopic dermatitis have an altered skin barrier function, with an approximately two-fold increased skin contact absorption of irritants and allergizing substances [26, 27, 37]. Irritant chemicals, in turn, further affect the skin barrier, boosting the penetration of allergens and so increasing the risk of contact allergy [25, 27]. The chronic topical use of various emollients and antiinflammatory drugs (with a potential sensitizing action) to treat the disease should also be borne in mind [38, 39]. As stated above, more recently, potential immune pathways for subsets of atopic dermatitis and contact allergy, such as Th1, Th 2, Th 9, and/or Th17, have been demonstrated. Yet another factor is bacterial colonization in atopic dermatitis, that can lead to increased contact sensitization by inducing an inflammatory process [40, 41].

19.2.1 Evidence of Contact Allergy in Atopic Dermatitis

The true prevalence of allergic contact dermatitis in subjects with atopic dermatitis is unknown. In the literature, the rates of positive patch tests in children with atopic dermatitis range widely, from 27 to 95.6% [22, 42–58]. This wide range depends on a number of factors, such as the patch test time point (mild vs moderate vs severe atopic dermatitis), hapten profile, study designs, etc.

Two systematic reviews have recently updated the knowledge of contact allergy in atopic individuals. One of them took into account 31 studies in children, and demonstrated that the rate of allergic contact dermatitis was significantly higher in children without than with atopic dermatitis (46.6% and 41.7%, respectively), even if there were significant differences among the studies as regards study criteria [57]. The other review and meta-analysis, that included 74 studies, revealed an increased prevalence of contact allergy in patients with atopic dermatitis compared to the general population [48].

Personal Data. In a study we conducted over a period of 11 years in 1,899 consecutive children (aged 0–12 years) with suspected allergic contact dermatitis, no significant differences emerged in the frequency of positive reactions between patients with or without atopic dermatitis [51]. The incidence of contact allergy in children with atopic dermatitis was 21.6% versus 27.8% in children without atopic dermatitis. In the first group the incidence of contact allergy increased with age, from 0% in the first and second years of life, to 38.5% by the twelfth year of age. The most common culprit allergens were nickel, fragrances, thimerosal, wool alcohols, and neomycin. When the two groups of children were subdivided by age (0–6 and 7–12 years), it was seen that contact allergy to thimerosal was prevalent in the first group, while nickel was the most common allergen between 7 and 12 years [51].

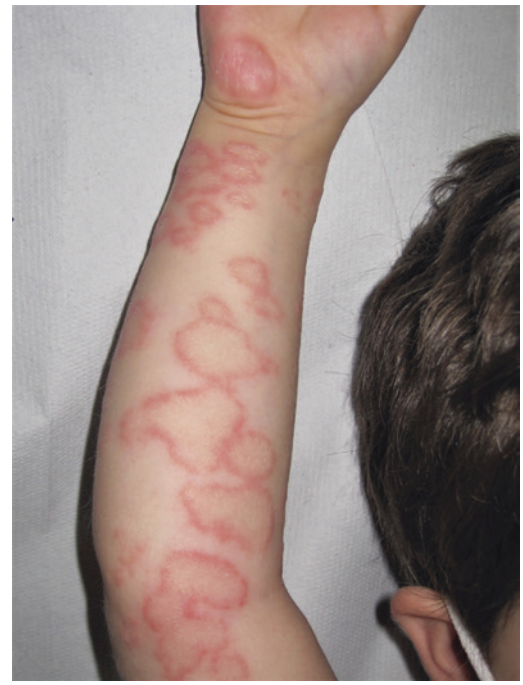

Fig. 19.1 Allergic contact dermatitis from neomycin

19.2.2 Relevant Allergens

Consideration of the above studies [42–58] shows that the most common allergens in subjects with atopic dermatitis are metals (nickel, cobalt, and chromium), lanolin, neomycin (Fig. 19.1), formaldehyde, sesquiterpene lactone mix, Compositae mix, and fragrances (Fig. 19.2).

It has been demonstrated that personal care products, even when they are claimed to be hypoallergenic, contain powerful contact allergens [38, 59]. Moreover, in children with atopic dermatitis, when frequent use is made of emollients increased urinary levels of allergens have been shown, in particular parabens and phthalate metabolites [60]. Retrospective Dutch and USA studies in populations with atopic dermatitis have demonstrated that the most common allergens are lanolin and fragrances [61, 62].

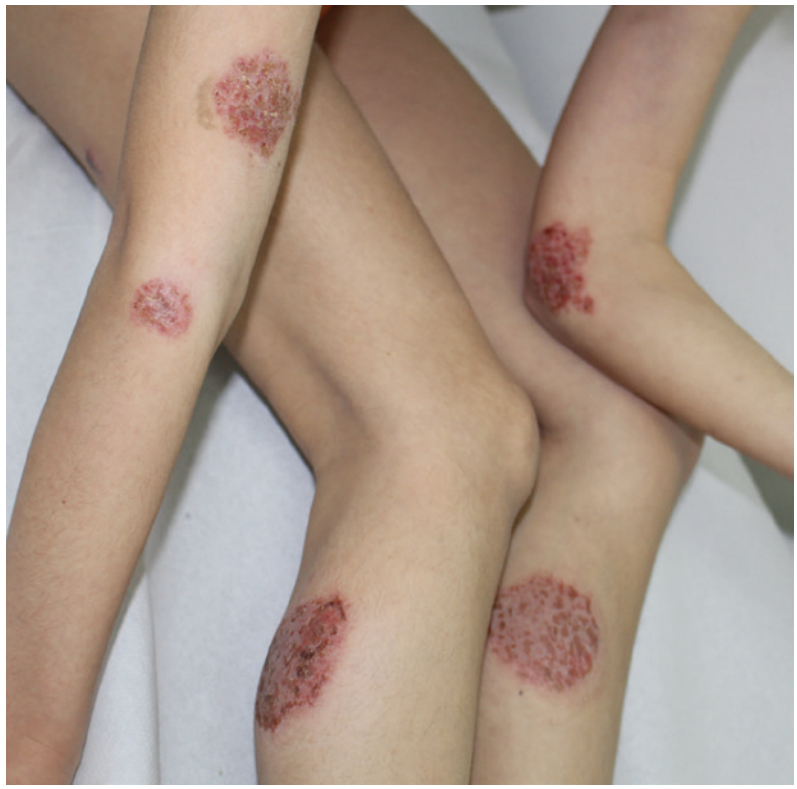

Fig. 19.2 Allergic contact nummular eczema due to fragrances

19.3 Patch Testing

Guidelines for patch testing in subjects with atopic dermatitis are available [63]. Testing is recommended in patients whose dermatitis does not improve with topical treatment; with an atypical or changing distribution of the dermatitis (involvement of the eyelids, head and neck, hand and foot, perioral); with hand eczema resistant to treatment in worker populations; with adult or adolescent-onset atopic dermatitis, since allergic contact dermatitis can occasionally present with a flexural distribution; before starting systemic immune suppressive treatment (identification and avoidance of the allergen can improve the dermatitis and hence prevent the need for systemic treatment). Also in the case of nummular eczematous lesions it is advisable to perform patch tests [22, 64]. In fact, nummular lesions are very frequent in subjects with atopic dermatitis, being a sign of allergic contact dermatitis [65–68]. Patch tests are also advisable in cases of a rebound of the dermatitis as soon as the treatment is stopped, indicating sensitization to ingredients in topical medicaments, such as corticosteroids.

By contrast, it is not advisable to perform patch tests in patients with stable, well controlled dermatitis, with flares, with dermatitis on the back and other potential test application sites, and if all the other common contraindications are present (topical or systemic immune suppressive treatment, exposure to ultraviolet therapy or excessive exposure to the sun, etc.).

When selecting the allergens to be tested, the geographic location (region or country), the limited area available for testing in children, the occupation, hobbies and recreations, and other specific types of exposure, such as to personal care products and topical medications, are all factors that need to be taken into account.

A study group recently proposed a baseline patch testing series comprising 38 allergens intended for children aged 6–18 years [69]. A European task force focused on allergic contact dermatitis in children has published a position paper with 9 test allergens, including nickel, fragrances, a rubber accelerator, and preservatives; a second list of allergens to be added to the above series is suggested, depending on the clinical history and exposures (including metals, corticosteroids, and antibiotics) [70].

Various pitfalls need to be considered when performing patch tests in subjects with atopic dermatitis. It is well known that these subjects have a lower irritancy threshold, even in non lesional skin far from areas of active inflammation, and that this can lead to irritant or false-positive reactions, in particular to metals (often giving rise to pustulous reactions or lesions with a follicular distribution), fragrances, formaldehyde, and lanolin [25, 51, 71]. Conversely, active or flaring atopic dermatitis may result in false-negative reactions due to the decreased contact sensitization [6, 22, 63, 72]. In short, the results of patch testing in patients with atopic dermatitis need to be interpreted with considerable caution.

19.4 Conclusions

Although the topic is still controversial, most of the data in literature support a significant, clinically important incidence of contact allergy in subjects with atopic dermatitis. The underlying relationship between the two disorders is complex and based on the skin barrier dysfunction and consequently increased allergen and irritant penetrance, chronic exposure to allergens due to the frequent use of topical medicaments and personal care products, and bacterial colonization that promotes inflammation and further boosts the absorption of extraneous substances and resulting contact allergy.

Patch testing is an important diagnostic tool in this patients population; the most common culprit allergens should be tested, and when reading the results, they should be interpreted with great caution.

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