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When and how to perform allergy tests in children and adults with atopic dermatitis

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An allergy workup is carried out in many children with atopic dermatitis but both its appropriateness and practical benefit for disease management need to be questioned. This editorial emphasizes the need for a global assessment of the young patient, including compliance with previous treatments and evaluation of true disease severity. In this perspective, allergy testing should be considered as a second line option, integrated to global management, and including a survey of food, contact and environment allergens (atopens). Food allergy is found in one third of children with moderate/severe disease. Symptoms are not only limited to the skin, but avoidance diets in such patients may help reducing topical corticosteroid consumption, when skin symptoms are enhanced by food allergens. In adults with long lasting and severe disease, patients with multiple sensitisation to atopens have usually developed auto-immunization and their disease is not amenable to significant improvement with allergen avoidance, standard skin care and even phototherapies. Systemic therapy should address the auto-inflammatory element in priority, using immunosuppressants to stop the vicious circle of the disease. In milder and limited forms such as head and neck or hand dermatitis, local therapy and careful patch testing should be carried out to rule out common aggravating contact allergies. Apart from a better delineation of the indication of the tests, there is a need to make allergy workups more simple, and a better standardization of tests is needed.

Most of the workup in atopic dermatitis (AD) is today focused on allergy. However the appropriateness of this type of diagnostic intervention is rarely questioned. Our objective is to show that rather than being set apart, allergy tests should be integrated into the general management of atopic dermatitis.

The child with AD: a thorough clinical examination and history taking is needed before discussing allergy testing

The vast majority of infants and children seen at dermatology clinics are basically healthy, but it remains of paramount importance to take a careful history and to make a

complete clinical examination. Delayed growth is mostly caused by sleeplessness due to excessive scratching, rather than to an associated illness. Any unusual manifestation such as gastrointestinal symptoms or repeated infections should however prompt specific investigations.

Apart from some common skin conditions associated with pruritus (scabies) and involving flexures – asymmetric perilesional exanthem of children or APEC [1] –, which are frequently treated first as AD because of the argument of frequency of the latter, psoriasis and rarer disorders such as Langerhans cell histiocytosis can be misdiagnosed as AD.

Genetic conditions which present with atopic dermatitis-like symptoms must be considered in cases with unusual presentation. Those involving the epidermis and adnexae include ichthyosis vulgaris, a common phenotype whose limits are blurred with those of AD, as recently demonstrated by molecular genetics [2]. More rarely, several genetic types of hypohidrotic ectodermal dysplasia, where genes are important during development for TNF α signaling [3], carry symptoms like atopic eczema. Those involving the immune system include the common IgA primary deficiency, but also rare phenotypes such as the Wiskott-Aldrich syndrome, SCID and hyper IgE syndrome (Job-Buckley). Especially, hyper IgE syndrome is frequently confused clinically with atopic dermatitis. In infants, recurrent scalp staphylococcal abscesses are a good marker of the disease and later the coarse facial appearance is also diagnostic when associated with recurrent, deep, mostly staphylococcal infections [4].

Comel-Netherton syndrome is an inherited disorder associated with atopic dermatitis-like symptoms which involves both the immune system and skin, due to the lack of a serine protease inhibitor LEKTI, physiologically expressed in the stratum granulosum of the epidermis and in thymus epithelium. Comel-Netherton syndrome often presents in childhood with a failure to thrive and erythroderma, but can also have features of flexural atopic dermatitis with associated peripheral desquamation. Hair defects (bamboo hairs) are diagnostic, but immunohistochemistry staining of a skin biopsy has recently been undertaken to detect the absence of LEKTI, the protein encoded by the defective SPINK 5 gene [5].

After ruling out these unusual conditions which may present with eczema, assessment of previous therapies, both successful and unsuccessful, is essential and this will influence the severity grading of the disease. Experience suggests that treatment failure in atopic dermatitis is often associated with inadequate compliance and that bad communication of therapeutic objectives adversely affects the correct use of established treatments. A suitable method to assess the severity of atopic dermatitis is the SCORAD index, developed by the European Task Force on Dermatitis [6]. The system has been validated in both adults and in children. In our practice, it is the basis of a management schedule which includes criteria for allergy testing as summarised in *table 1* and a similar scheme is also part of the classification adopted by the European task force on AD [7]. In the case of moderate to severe disease, a validated stepwise allergy diagnostic procedure using skin tests (to food, contact allergens and atopens), and challenges if needed, preceded by intensive skin care. If allergy testing is indicated but cutaneous tests are not possible, specific IgE testing can be required first. Some thresholds for specific IgE to food allergens have a good predictive value of true allergy [8]. In any case, a careful assessment of the relevance of test results is essential.

Recommendations for allergy testing in children with AD

Without testing, it makes sense to implement avoidance on a probabilistic basis for example in the case of house dust mite, which is the most prevalent allergen in western households. However, testing remains mandatory to analyse the role of food or contact allergens.

Allergy testing has both benefits and drawbacks. Benefits include making a clear distinction between allergy and sensitisation at challenge tests. It will allow for a better avoidance when such a demonstration of true allergy has been carried out. Limits concern the variable or in some cases near-absent IgE dependency of the disease, e.g. the benefit of allergy testing in atopic dermatitis may not be as apparent as in allergic rhinitis when efficient hyposensitization follows. Furthermore, test procedures are time-consuming and costly, and interpretation is not always straightforward. Allergy testing during a flare-up often gives uninterpretable results (angry back or anergy). It may not always be possible to stop the current therapy, which if

continued could give false negative tests. Not to mention that reading requires experience, good lighting and interpretable controls.

The main issue in infants and young children concerns food allergy and its relevance to eczema. Around one-third of children with atopic dermatitis referred to a secondary care clinic have at least one positive immediate reaction to a food [9]. Egg is the most frequently encountered allergen, followed by either peanuts or cow's milk. Tolerance is most likely to develop with milk, then egg and least with peanuts. Delayed reactions as may occur with milk are difficult to detect, even using patch tests with food allergens in addition to skin prick tests. The Finnish experience with patch testing with foods shows clearly that patch testing with milk can increase the number of cases detected [10].

How relevant for eczematous lesions are food allergens? The careful study by Niggemann and colleagues [11] tried to address this, based on immediate and late reaction results to food challenges. Of 77 children with positive food challenges, 39 had early type I reactions, whereas 12 had late reactions and 17 combined early and late reactions. Early type I reactions were associated with skin (urticaria), respiratory and gastrointestinal symptoms. Late reactions were skin restricted (exacerbation of AD). Combined reactions were either skin restricted (early urticaria followed by exacerbated AD) or associated early GI symptoms and later exacerbation of AD.

The effect of avoiding documented food allergens on the severity of atopic dermatitis is not fully known. Food allergy is clearly an aggravating factor in a subset of patients. In hospital pediatric practice it is rarely a causative factor, because elimination diets in isolation do not cure patients. Some eczema patients outgrow their food allergy yet still have eczema. The reverse is also seen, e.g. urticarial rashes following egg consumption without remaining eczema. Thus, diet management should not be considered as the only endpoint in disease management and allergy testing is only included as part of second-line management in young children in our current approach.

Is it possible to simplify testing procedures, especially for food allergens?

If guidelines for testing procedures in AD children are needed, their simplification would be welcome. The 'gold standard' for food allergens still remains the double-blind

Table 1. Use of SCORAD index to allocate treatment and decide allergy workup in children with AD

SCORAD	Severity	Treatments
< 15	Minor/mild	Emollients, counselling (including diet).
15-40	Moderate	Topical steroids, plus/minus macrolactam derivatives (> 2 years); anti H1 agents and antibiotics for flares. <i>Allergy work-up if more than 30 g/month of topical steroids</i>
> 40	Severe	Compliance assessment; <i>Allergy workup and strict allergen avoidance if relevant</i> Consider hospitalisation if dermatological treatment ineffective. Phototherapy and systemic immunosuppressive treatments exceptionally needed

placebo-controlled food challenge introduced by Sampson [12], but single-blind challenges are also helpful. Tests can be done at a day hospital, the patient having stopped antihistamines five days beforehand. It is essential to clear the eczema with prior intensive treatment to assess food challenges properly.

Labial food challenge [13] (LFC) might be an alternative to classic food challenge, particularly when testing egg and peanut allergy. A drop of commercial food extracts or crushed food re-suspended in saline is applied to the lower lip. The result can be read after 15 minutes. Grading of the LFC is as follows: [1] swelling of the lip [2] erythema of the buccal area of the lip [3] contiguous urticaria [4] edema of the cheek, rhinitis and watery eyes and [5] systemic reaction. The test is simple and fast, but has a low sensitivity. It may be a useful screening test in busy clinics. However an international standardisation of the test and its validation is needed. For patch tests, a ready-to-use patch test to cow's milk has been developed recently [14] and exhibits a promising good sensitivity and specificity.

My personal approach with adults

The persistence into adulthood of AD can lead to a wide spectrum of disease severity. It is also becoming more and more common to diagnose AD in adults and even in elderly patients without a known personal history of eczema. In all these patients, it is important to determine if skin inflammation is primarily driven by allergy to atopens or contact allergens, or by other factors. In many patients with long lasting disease and poor response to topical treatments, including the newly introduced topical macrolactam immunosuppressants, auto-inflammation is probably the major force driving eczema. The groups of A Scheynius and P Schmid-Grendelmeier have already shown a mechanism of cross reactivity between superoxide dismutase in yeasts and human cells which can perpetuate auto-immunity [15]. How much of auto-inflammation is in a patient's skin would be the key question to making a good therapeutic choice. It is indeed clear that avoidance of proven allergies may not be sufficient in severe patients, who, moreover, are not amenable to skin testing due to the severity of their disease. If occupational allergy is not in cause, an option which is not always easy to clear, my personal preference, if well managed topical treatments and phototherapies fail, including supervision of treatment under inpatient care, or if disease recurrence or worsening occurs after several attempts, is to start an immunosuppressive treatment, cyclosporine 300 mg/day usually in young adults or azathioprine (100 mg/d) or methotrexate (15 mg/week) after 40 years of age [16, 17], under strict clinical and biological monitoring for 6 to 24 months, in order to switch again to local treatments and retest the patients. This approach may work if other variables, including indoor allergen avoidance and psychological interventions, are also managed during the period of systemic treatment, which allows the patient a kind of break in his suffering.

Can allergy testing offer clues to the aetiology of atopic dermatitis and other atopic disorders?

Based on the interpretation of the role of allergens in infantile eczema, several propositions have been made concerning its pathogenesis. Most pediatricians consider that food allergy is the most important factor, skin symptoms being only considered as the target of the effector arm of allergy. AD in infants may also involve the cutaneous expression on skin of a more mysterious atopic diathesis, also fitting this inside-outside hypothesis. However, if sensitisation to external agents is causative, the primary permissive defect may involve the skin. The hypothesis that infantile atopic dermatitis is merely the expression of increased skin penetration of allergens, corresponding to the penetration phase of the disease, has been proposed [18]. A strong argument is that the majority of infants with AD below the age of one year, without any other sensitization criteria (no detectable specific IgE, no positivity to skin prick tests), have a delayed eczematous reaction to aeroallergens such as house dust mites or pollens at skin patch tests. The elicitation of positive patch tests decreases with age, reflecting the delayed maturation of the epidermal barrier in atopic infants. This "penetration syndrome" step is probably underestimated given the importance of aeroallergens in the "atopic march" leading from AD to asthma and rhinitis.

Mouse models also show that it is possible to produce sensitisation through the skin leading to asthma [19]. Food allergens are probably of less importance than aeroallergens, because acquired tolerance is seen in most cases after infancy and childhood. ■

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