

3. Allergy workup: when and how for the child with atopic dermatitis?

ALAIN TAÏEB

An allergy workup is done in many children with atopic dermatitis but its practical benefit on disease management remains largely unproven. This paper emphasizes the need of a global assessment of the young patient, including compliance to previous treatments and disease severity. Allergy testing should be considered as a second line option, integrated to global management. True food allergy is found in one third of patients with moderate/severe disease, and avoidance diets in such patients help reducing topical corticosteroids consumption. Apart a better delineation of the indication of the tests, there is a need to make allergy workups simpler, and a better standardization of tests is needed.

INTRODUCTION

Before the discovery of the concept of allergy and anaphylaxis in the early 1900s, there was already much debate concerning the relative role of extrinsic and intrinsic factors contributing to the clinical entity we now call atopic dermatitis (AD). The role of external factors, such as microbial infection and irritants, was advocated by Unna & Hebra in the 19th century, whilst the role of intrinsic factors, loosely designated 'diathesis', was promoted by many authors, including Besnier who fathered the 'prurigo diathésique' in 1889 (1). Such a distinction (intrinsic vs extrinsic) remains the centre of the pathophysiological discussion today. The biological marker of the obscure diathesis is mostly considered today as the abnormal IgE response to common environmental allergens. However, what relevance the IgE response has to the clinical phenotype and its management remains elusive. Most of the workup in AD children is today focused on allergy, and our objective is to discuss if this is appropriate, and if yes, when and how this workup should be done.

THE INITIAL CLINICAL APPROACH TO THE CHILD WITH ATOPIC DERMATITIS: IS A WORKUP REALLY NEEDED?

The vast majority of infants and children seen at dermatology clinics are basically healthy. However, it is important 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 such as coeliac disease, cystic fibrosis or growth hormone insufficiency. Any unusual manifestation such as gastrointestinal symptoms or repeated infections should, however, prompt specific investigations. Genetic conditions which present with AD-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. More rarely, several genetic types of hypohidrotic ectodermal dysplasia, whose genes are important during development for TNF-alpha signalling, 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). These conditions are interesting from a pathophysiological aspect, because the genetic component of most of them is either already known or currently under close scrutiny. Hyper IgE syndrome is sometimes confused clinically with AD. The condition may present in infants with recurrent scalp staphylococcal abscesses (Fig. 1).

The Comel-Netherton syndrome is an inherited disorder associated with AD-like symptoms which involves both the immune system and skin, due to the lack of a serine protease inhibitor LEKTI physiologically expressed in stratum granulosum of the epidermis and in thymus epithelium. The Comel-Netherton syndrome often presents in childhood with a failure to thrive and erythroderma, but can also have features of flexural AD with associated peripheral desquamation (Fig. 2). Hair defects (bamboo hairs) are diagnostic, but an immunohistochemistry staining of a skin biopsy (2) has recently been implemented to detect the absence of LEKTI, the protein encoded by the defective SPINK 5 gene.

ASSESSING DISEASE SEVERITY COMES FIRST

Assessment of previous therapies, both successful and unsuccessful, is essential. Experience suggests that treatment failure in AD is often associated with inadequate compliance and that poor communication regarding therapeutic objectives adversely affects the correct use of established treatments. A suitable method to assess the severity of AD is the SCORAD

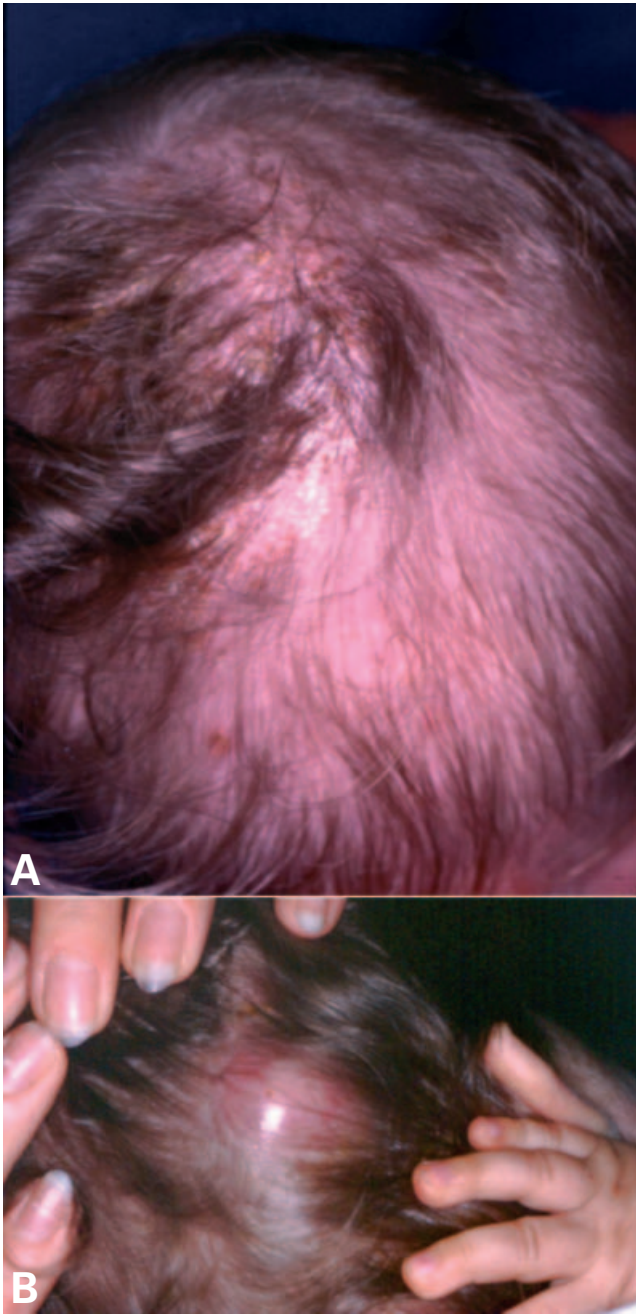


Fig. 1. Child with hyper IgE syndrome and scalp pustules (A) and abscesses (B).

index developed by the European Task Force on Dermatitis (3).

The system has been validated in both adults and children. In our hands, it forms the basis of a management schedule which includes criteria for allergy workup as summarized in Table I.

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Fig. 2. Comel-Netherton syndrome presenting with exfoliative erythroderma and failure to thrive.

RECOMMENDATIONS FOR ALLERGY TESTING IN CHILDREN WITH ATOPIC DERMATITIS

Allergen avoidance should only be used in a global management approach. Avoidance can be implemented either on a probabilistic basis – for example, in the case of house dust mite, which is the most prevalent in Western households – or in a more analytical way for food or contact allergens.

Allergy testing has both benefits and drawbacks. Benefits include making a clear distinction between allergy and sensitization at challenge tests. It will allow for a better avoidance when such a demonstration of true allergy has been done. Limitations concern the limited IgE dependency of the disease, e.g. the benefit of allergy testing in AD 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

Table I. Use of SCORAD index to allocate treatment and decide allergy workup in children with atopic dermatitis

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 <u>Allergy workup if more than 30 g/month of topical steroids</u>
>40	Severe	Compliance assessment <u>Allergy workup and strict allergen avoidance, if relevant</u> Consider hospitalization if dermatological treatment is ineffective Phototherapy and systemic immunosuppressive treatments exceptionally needed

continued, could give false negative tests. Readings require good lighting and interpretable controls.

The main issue in infants and young children concerns food allergy. Around one-third of children with AD referred to a secondary care clinic have at least one positive immediate reaction to food (4). Egg is the most frequently encountered allergen, followed by either peanut 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.

How relevant for eczematous lesions are food allergens? The careful study by Niggemann et al. (5) tried to address this on the basis of 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 had 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. It is essential to clear the eczema with intensive treatment beforehand to assess food challenges correctly. However, an example of urticarial food challenge to fish located on a zone of lichenified eczema is demonstrated in Fig. 3.

HOW DOES DIET MANAGEMENT AFFECT ATOPIC DERMATITIS IN CHILDREN?

The effect of avoiding documented food allergens on the severity of AD is not fully known. Food allergy is clearly an aggravating factor in a subset of patients. In hospital paediatric 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



Fig. 3. Urticarial wheals on lichenified site of atopic dermatitis following fish challenge.

following egg consumption without remaining eczema. Thus, diet management should not be considered as the only end point in disease management. Therefore, allergy testing is only included as part of second-line management in young children in our current approach. When decided, food allergy testing together with a more comprehensive allergy assessment is implemented (Table I).

IS IT POSSIBLE TO SIMPLIFY TESTING PROCEDURES, ESPECIALLY FOR FOOD ALLERGENS?

If guidelines for testing procedures in AD children are needed, a simplification of those would be welcome. The 'gold standard' for food allergens still remains the double-blind placebo-controlled food challenge (6), but single-blind challenges are also helpful. Tests can be done at a day hospital, the patient having stopped antihistamines 5 days beforehand. Labial food challenge (LFC) (7) might be an alternative to classic food challenge, particularly when testing egg and peanut allergy. A drop of commercial food extracts or crushed food resuspended in saline is applied to the lower lip. The result can be read after 15 minutes. Grading of the LFC is as follows: (i) swelling of the lip, (ii) erythema of the buccal area of the lip, (iii) contiguous urticaria, (iv) oedema of the cheek, rhinitis and watery eyes, and (v) 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 standardization of the test and its validation is needed.

CAN ALLERGY TESTING OFFER CLUES TO THE AETIOLOGY OF INFANTILE AD?

Based on the interpretation of the role of allergens in infantile eczema, several propositions have been made concerning its pathogenesis. Most paediatricians consider food allergy as the most important factor, skin symptoms being only considered as the target of the effector arm of allergy (inside-outside hypothesis). 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 sensitization to external agents is causative (outside-inside hypothesis), the primary permissive defect may involve the skin. The hypothesis that infantile AD is merely the expression of increased skin penetration of allergens, corresponding to the penetration phase of the disease, has been formulated (8). A strong argument is that the majority of infants with AD below the age of 1 year, without any other sensitization criteria (no detectable specific IgE, no positivity at 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. Consistently, mouse models show that it is possible to produce sensitization through the skin leading to asthma (9). Food allergens are probably of less importance than aeroallergens, because acquired tolerance is seen in most cases after infancy and childhood.

CONCLUSION

The basic assessment of the AD infant includes first, before any testing, a careful history taking and clinical examination, assessing type and topography of lesions. Severity assessment of skin lesions should be made simultaneously with possible associated signs and symptoms at examination, because it will determine the rest of the management. Rather than being set apart, allergy tests should be integrated in the general management of AD. When appropriate, based mostly on severity evaluation, a validated stepwise diagnostic procedure using skin tests will be needed, preceded by intensive skin care. If allergy testing is indicated, but cutaneous tests are not possible, specific IgE testing can be required first. In any case, a careful assessment of the relevance of test results is essential.

SUMMARY

- The results can be viewed in the same way as the superantigen story, the allergen increases the severity and may induce steroid insensitivity. Removal of the exacerbating factor allows control with less steroids
- Sensitization all comes back to the exacerbating action of IgE
- In our cases of eczema with food allergy, none get better without steroids, but removing the food allergy enables control at lower steroid doses

DISCUSSION

Thestrup-Pedersen; You suggest that a child has to have a SCORAD of 15–40 and be using more than 30 grams of steroids per month before you consider allergy testing. What percentage of your patients would that concern?

Taieb; In the general population about 5%.

Langley; In terms of patients we see the majority has allergy testing, but we are a specialized centre and see the more severe cases. It is important for those in

primary care to appreciate that the requirement for allergy testing is low.

Diepgen; There are some problems with allergy testing, what do the results mean, using a RAST test for milk and egg the results vary. However, for grass pollen we have seen a nice correlation between sensitization and severity of eczema.

Leung; Is grass pollen causing their eczema or is it just a marker for future development of rhinitis?

Diepgen; That is difficult to say, but we do know sensitization to grass pollen is a risk factor for eczema in some people.

Leung; The link is that IgE doesn’t cause eczema, but it does enhance it. It shifts the T-cell dose response curve to the right, i.e. reduces the amount of allergen needed to drive the response. IgE responses do not cause the eczema but can enhance severity. The percentage of patients involved is debatable, but probably around 5%. It is difficult to control the allergen in such cases, if it is house dust mite or grass pollen, but in food allergy we can remove the allergen more easily.

Langley; If we accept that 5–20% of patients attending clinics have some form of food allergy, in how many can you make significant improvement by controlling allergen exposure?

Taieb; There are no hard data available, but our impression is that with the global intervention program, there is benefit in that we can reduce the amount of steroid use.

Leung; The results can be viewed in the same way as the superantigen story, the allergen increases the severity and may induce steroid insensitivity. Removal of the exacerbating factor allows control with less steroids. Sensitization all comes back to the exacerbating action of IgE. In our cases of eczema with food allergy, none get better without steroids, but removing the food allergy enables control at lower steroid doses.

Langley; Removal of the food allergy is part of the adjunctive programme to control the disease.

Andersen; We have data on a random group of 562 healthy infants who were tested for food allergens from birth to 18 months. There was a high frequency around 80% of fluctuating low grade allergy. This population will be monitored prospectively concerning the development of atopic disease.

Taieb; In young infants the skin has not fully developed as a barrier (physical and immune) and this may skew

the early results. The results concerning the development of atopic disease will be very interesting.

Leung; If you agree with the data we have seen, you could conclude that AD is a cutaneous manifestation of a systemic disease. Just looking at skin testing in isolation is not ideal.

Taieb; It is unlikely that patients develop asthma purely as a result of percutaneous penetration of allergens. There is also penetration and sensitization via the bronchioles.

Leung; A high proportion of babies with egg allergy go on to develop asthma. Parents are very concerned that their children will go on to develop the atopic march and is there anything they can do to prevent this. A child with persistent allergy is more likely to go on to develop asthma. Egg allergy is a good predictor.

Thestrup-Pedersen; Can anything be done to stop this progression?

Leung; Parents could bring their children earlier, persistent coughing is a sign of asthma. Early presentation allows initiation of inhaler therapies.

Langley; Egg allergy seems a good predictor. Are there any others?

Leung; Allergy testing is not relevant in mild disease which is readily controlled by steroids. In moderate to severe disease about a third of patients may benefit from allergy testing. Whilst there is little we know which will prevent asthma developing in AD, parents should be instructed to look for early signs of the condition, persistent sneezing or nasal congestion, coughing and other signs of respiratory involvement. Allergy testing should be done only when it can actually help with disease management.

Langley; The atopic march is yet to be proven, yet identification of an allergen may be helpful in predicting asthma development, there is the increased allergen and cleanliness concept, but are there any data that what we do is actually going to be helpful? Can allergen avoidance prevent the development of other atopic disease?

Leung; We do not know yet.

McFadden; Allergy workup is beneficial in some patients, the problem is patients believe in the concept of one single allergen being the problem. It is difficult to educate them on this. The same patients may be reluctant to use the steroids as well.

Taieb; Allergy testing is very common in France, whereas in my view most of these tests are of no value.

Andersen; What do you use for the tests, commercial preparations or whole foods? What methods of IgE measurements are you using? The levels needed to indicate a positive test need careful defining. There is a general, but low and fluctuating degree of reactivity to food allergens in the general population. Perhaps we should consider as significant only positive reactions to three items or more.

Leung; You need to consider both laboratory tests and the clinical picture. As for the value of the tests, these are only of use when there is a clinical need and whenever avoidance of the allergen is possible.

Andersen; Yes, but you do need to establish the background reactivity to food allergens before you can interpret results in patients with eczema.

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