

EDITORIAL

The role of dust mite antigen sensitization and atopic dermatitis

Atopic dermatitis (AD) affects up to one in 10 children and, as with other atopic clinical syndromes, the prevalence is increasing steadily. Onset is usually in the first weeks and months of life and, while most affected people enter spontaneous remission, the dermatitis may persist into adult life. The condition causes major impairment of quality of life [1]. There are many factors including allergies, infections, emotional, climatic and other environmental influences that contribute to the causation of AD in genetically predisposed individuals. The role of airborne environmental allergens both in the initial sensitization of atopic individuals and the subsequent elicitation of the clinical symptoms, is the subject of intense interest.

Environmental allergen levels are probably the major determinant of whether sensitization of genetically predisposed individuals occurs. However, the time at which sensitization occurs whether intrauterine life or postnatally is the subject of many studies. It appears that priming of immune responses to a range of allergens may happen during intrauterine development [2,3]. Moreover, the sensitization is reflected by the presence of antigen-specific helper T lymphocytes and specific antibodies of IgE class. The normal fetal and neonatal immune system is characterized by a predominantly TH2-orientated immune response, and during the first 1–2 years of life, a maturation and drift towards a TH1-orientated response occurs [2]. In atopic subjects this maturation appears delayed [2]. There is discussion as to whether postnatal exposure to allergens somehow delays the maturation of the T-helper lymphocytes [2]. Also, the induction of sensitization may occur postnatally and during childhood. The corollary is that reduced exposure to allergens may be associated with diminished expression of atopic clinical syndromes. This is borne out in evidence from a range of sources. Thus, avoidance of exposure to house dust mite (HDM) and food allergens for the first year of life was associated with significant diminution in the proportions of clinically detectable eczema and asthma [4]. Babies born in autumn, when HDM numbers are highest, have a greater risk of sensitization by HDM [5] and children born just before the birch pollen season in Scandinavia have a higher risk of sensitization to birch pollen than those born after the season [6]. A recent Japanese study showed that if atopic babies (with detectable IgE antibodies to various foods but not HDM) were protected from contact with HDM by encasing their bedding in dust-proof bags, there was significantly less

sensitization to HDM, reflected by IgE and prick test response [7]. However, it was not followed through to see whether there was a reduction in associated clinical problems.

It has been proposed that the risk of becoming sensitized to HDM is greatly increased by exposure to 10 µg/g of Der p 1 while even 2 µg/g confers a significant risk [8]. However, there is uncertainty as to the route of exposure by which sensitization occurs — via mucosae or the skin. Eczema is usually the earliest clinical manifestation of atopy, and the antigens to which initial sensitization develops in infants are thought to be food derived [2,9,10]. It is one of the unsolved conundra as to why sensitization via the intestinal route results in a cutaneous inflammatory reaction. However, it may be supposed that once the eczematous skin reaction begins the permeability barrier is broken and penetration of the large protein allergens from dust mites for example, can occur, resulting in sensitization.

The role of aero-allergens such as HDM in provoking or maintaining AD has been the subject of controversy and uncertainty. Allergic sensitivity is reflected by the presence of specific IgE and immediate-type responses to prick test challenge. In addition, following intradermal challenge, after the immediate response, a 6-h late phase and a 24–48-h delayed-type hypersensitivity to allergens can be demonstrated [11]. Epicutaneous patch test challenge elicits a delayed-type response that clinically resembles the naturally occurring eczema [11–15]. These reactions are induced by various aero-allergens and most authors have found that they seem to be restricted to individuals with atopic eczema rather than those with respiratory or mucosal forms of atopy. Seidenari *et al.* [16] observed a significant proportion of individuals with mucosal allergies and high specific IgE levels reacted to mite culture supernatants. The proportion of individuals with AD that exhibit positive allergen-induced patch test reactions varies with technical aspects of how the challenge is performed [17,18]. The large protein allergens do not usually penetrate intact epidermis so different manipulations have been used to facilitate allergen entry. The most commonly used one is repeated application of adhesive cellophane tape to strip away the stratum corneum which provides the permeability barrier. The frequency of positive patch tests rises to about 85% with increasing numbers of tape strips and high allergen concentrations [17]. The patch test challenges are usually found in people with high specific IgE, but they can be

dissociated [19]. Similarly, strong positive prick test responses with high specific IgE are often found in the absence of positive patch test responses to the same allergen.

The patch test responses, which are characterized by infiltration of T lymphocytes and eosinophils [20], have been investigated as a 'model' of the naturally occurring dermatitis. The generation of these delayed-type responses via T-cell-mediated mechanisms has been shown in a number of ways. Firstly, allergen-induced lymphocyte proliferative responses *in vitro* are found in many patients with AD and there is a correlation with the presence of positive patch test responses to the same allergen [21–23]. Several groups have cloned the lymphocytes from patch test reactions and obtained antigen-specific T cells, predominantly of a TH2 phenotype [11,24–26]. Also, following the expression of cytokines during the evolution of patch test reactions, initially TH2-type cytokines are expressed, but as the reaction proceeds, there is a progressive increase in TH1-derived cytokines [26,27]. Interestingly, in the natural dermatitis, cytokines of both TH1 and TH2 types are expressed. As the dermatitis resolves in response to treatment with long-wavelength ultraviolet, the TH1 cytokine message is down-regulated while the TH2 message persists [28]. This indicates that the eczematous process seems to depend upon a TH1 component even though a TH2 contribution appears to be an early part of the process.

There is evidence to indicate that IgE plays a part in the presentation of atopic allergens to T cells. IgE is found on the surface of Langerhans' cells, the epidermal antigen-presenting cells, in individuals with atopic dermatitis [29]. Langerhans' cells express both FcεR1, the high-affinity receptor for IgE as well as CD23, the low-affinity receptor. In an *in vitro* lymphocyte-stimulation system, IgE⁺ on the surface of Langerhans' cells allows T cells to respond to 1000-fold lower concentrations of the antigen [30]. Also, after epicutaneous application of HDM allergens, IgE dust mite antigen-bearing Langerhans' cells are found in the epidermis [31]. In the naturally occurring eczema, dust mite antigen-bearing Langerhans' cells are found in both the epidermis and dermis [32].

There is uncertainty as to the clinical significance of positive patch test reactions to aero-allergens. Various authors have presumed the presence of such responses can be taken as a clear indicator that the eliciting allergen is a clinically important provoking factor for the eczema. There is indeed clear evidence that HDM and their allergens are of pathogenetic significance in the provocation or maintenance of AD. A double-blind, placebo-controlled trial was performed of a regimen of house dust mite eradication measures, including encasing of mattress and bedding, vacuum cleaning and use of a spray with acaricidal and allergen-denaturing properties [33]. The active treatment

resulted in major reductions in the quantities of Der p 1 in the bed and carpets and this was associated with a highly significant clinical benefit in both children and adults with moderate to severe AD. In the study by Tan *et al.* [33] no effort was made to relate results of tests indicating allergic sensitivity in individuals with the clinical outcome. Before patients can be given firm recommendations about whether they would benefit from the institution of anti-dust mite measures, it is necessary that some form of robust predictive test can be applied. Although evidence on the usefulness of the dust mite-induced patch test reaction is not solid, it was the hope of clinicians that it would become clearly established. However, the paper by Gutgesell *et al.* [15] in this issue of the journal reports findings that throw an interesting new light on the significance of this reaction. They show firstly that there is no correlation between the amount of Der p 1 in the mattress and the severity/activity of the eczema which appears to argue against the causal role of dust mite allergens in atopic eczema. However, it has yet to be determined where in the domestic environment the clinically important contact with allergens occurs. It is presumed that the bed is the place of closest and most prolonged skin contact. However, the finding by Tupker *et al.* [34] that eczema can flare after inhalation challenge with Der p 1, indicates that skin contact is not necessarily the only important route of contact. Secondly, Gutgesell *et al.* [15] confirmed the lack of correlation between positive responses to epicutaneous patch test challenge with allergen and IgE RAST score. Lastly, they show that there was a negative correlation between the amount of Der p 1 on the mattress and positive patch test responses to Der p 1. They argue that this could indicate that high allergen levels down-regulate the patch test response. If the patch test response is a real reflection of the eczematous process, it might hence be expected that there would also be a negative correlation between the amount of environmental Der p 1 and the activity of the eczema. One aspect of the whole area that is not well understood is how induction and expression of sensitization to an allergen evolves over time and how it is affected by continuing exposure to the allergen. It is conceivable that responses in patch test challenges reflect sensitization and reactivity determined at the time of first exposure to the allergen rather than reflecting present exposure levels to the allergen. In any event the significance of the allergen patch test and its value in identification of the allergens of major clinical relevance for the provocation and perpetuation of atopic eczema remains to be clarified.

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