

Original article

Environmental prevention in atopic eczema dermatitis syndrome (AEDS) and asthma: avoidance of indoor allergens

Indoor allergens represent an important precipitating factor for both asthma and atopic eczema dermatitis syndromes (AEDS). There is also accumulating evidence that sensitization to those allergens is associated with the onset of atopic disorders. Patients with AEDS present aeroallergen-specific T-cell responses associated with worsening of symptoms when exposed to specific aeroallergens. Furthermore, application of indoor allergens to the skin of patient with AEDS induces a local eczematous response in one-third of these patients. Exposure to high concentrations of mite allergens in early infancy have been demonstrated to be a risk factor for developing atopic dermatitis during the first 3 years of life. Moreover, a clear dose–response relationship has been documented between mite exposure and disease activity. Primary prevention of AEDS by avoiding indoor allergen exposure has been proved to be effective only when allergenic foods have also been avoided. Mite allergen avoidance in infants with AEDS and food allergy may however, prevent mite sensitization and the onset of asthma. Indoor allergen avoidance has been demonstrated to be effective in the majority of studies performed in patients with established AEDS. Negative results may be explained either by individual susceptibility variation, by long duration of disease with the consequent irreversible pathological changes in the target tissue or by exposure to allergens outside the house. Education of the patients and public consciousness of the problems are crucial for the efficacy of indoor allergen avoidance in allergic diseases.

C. Capristo¹, I. Romei², A. L. Boner²

¹Department of Pediatris IInd University of Naples, Italy; ²Department of Pediatrics University of Verona, Italy

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C. Capristo
Department of Pediatris
IInd University of Naples
Italy

Introduction

There is strong evidence that indoor allergens constitute important precipitating factors both for patients with asthma (1–5) as well as for those with the atopic eczema/dermatitis syndrome (AEDS) (6–8). Epidemiological studies have demonstrated that there is also a close relationship between exposure to indoor allergens and the origin of asthma in some individuals (1,5,9). The best evidence for a role of an environmental allergen in asthma causation is that for house dust mite (HDM) antigens (1,10). In communities where the mean group I mite allergen concentration in bedding is more than 2 µg/g of dust, for example, sensitization to mites has been documented as a risk factor for asthma with an odds ratio ranging from 6.6 up to 9.7 µg/g (11). Although recent observations suggest that environmental factors, such as HDM allergen, may also play a crucial role in the development of AEDS, a disease entity strongly associated with asthma (1–11), the precise pathogenetic role of these factors remains unclear (8). The purpose of the present communication is to review the evidence supporting the preventive role of environmental control in the AEDS.

Role of indoor allergens in AEDS

Studies of children from China who emigrate to Hawaii and of Tokelau immigrants in New Zealand have shown large increases in the prevalence of atopic eczema in the migrant children, compared to those children of similar genetic background who remain in their country of origin (12,13). The same is true for black Caribbean children born in London compared to similar children living in Jamaica (14). These migrant studies support the concept that environmental factor(s) associated with the western life style are important in the pathogenesis of AEDS. There are, of course, several factors associated with urbanization and in this presentation only the role of indoor allergen exposure will be considered.

The relationship between exposure to inhalant allergens and atopic dermatitis was demonstrated as early as 1918 (15) when Walker first reported that several of his patients had exacerbations of their atopic dermatitis on exposure to horse dander, ragweed pollen, or timothy grass (15). Subsequently, in 1949, Tuft first confirmed this observation (16) and later, it was shown that the eczematous skin reaction can be provoked in patients

with AEDS by the epicutaneous application of aeroallergens by the atopy patch test (APT) (17,18).

Positive APT reactions have not only been more frequently demonstrated in patients with a typical eczematous distribution pattern characteristic of the aeroallergen-induced disease (19), but have also been found to show significant concordance with history, skin prick test, and radioallergosorbent test for *Dermatophagoides pteronyssinus*, cat dander and grass pollen allergens ($P < 0.001$) (20). Positive reactions have been observed with a wide variety of allergens including HDM, animal danders, moulds, weeds and pollens (21).

Although several immunological mechanisms are thought to be the basis for the APT, a positive response may be expression of either a T-cell-mediated immune reaction or an immunoglobulin E (IgE) -mediated late phase reaction (22). Type IV and type I reactions can be concomitantly or separately present in patients with AEDS (23). In subjects with AEDS there have been demonstrations of increased frequency of aeroallergen-specific T-cell responses producing both increased interleukin-4 (IL-4) and IL-5 (24,25) or marked secretion of IL-2 and interferon- γ (26) when exposed to specific aeroallergens. These clones may be involved in the development of allergic inflammatory reactions. Recent studies, in this regard, indicate that both T helper type 2-(Th2) and Th1-type cytokines contribute to the pathogenesis of skin inflammation in AEDS, with Th1 cytokines primarily involved in chronic lesions and Th2 cytokines involved in acute phases of the disease (27). Most patients with AEDS have increased serum levels of inhalant allergen-specific IgE and IgG antibodies (28,29), which represent specific responses to antigens to which the individual has been exposed (27). Not only is it known that patients with AEDS produce mite-specific IgE antibody, but also that adult patients with moderate to severe AEDS produce a higher quantity of IgE antibody to *D. pteronyssinus* than asthmatic patients and controls. Indeed, in the study of Scalabrin et al. (31), 95% of sera from AEDS patients had IgE to house mites compared with 45% of asthmatics.

The fact that patients with AEDS react consistently to dust mites supports the view that mite exposure is a major cause of the disease. This is further supported by the evidence that application of purified mite allergen to the skin of these patients can induce a local eczematous response in one-third of these patients (31,32). The same proportion of reacting subjects was observed when patients with AEDS were challenged with the allergen *Coprinus comatus*, a species of basidiomycete which occurs in the air in high concentrations in many parts of the world and which has been recovered in remarkable quantities from house dust (33). In this study, 32% of the patients reacted to the patch test with *C. comatus* with the development of eczematous skin lesions in unaffected skin areas. These findings demonstrate that indoor antigens may be rapidly absorbed from the skin where they induce

an initial infiltration of basophils, eosinophils and monuclear cells (34) replaced by skin mast cells after repeated application of the allergens (35). IgE bound on Langerhans cells facilitate binding of allergens to these cells themselves prior to the processing and presentation of antigen. In this regard, IgE-bearing Langerhans cells from AEDS skin lesions, in contrast to those that lack specific surface IgE, are capable of presenting HDM allergens to T cells (36). Moreover, immunohistochemical studies focusing on the localization of HDM antigen in naturally occurring lesions of AEDS have demonstrated the presence of HDM antigens in the epidermis and dermis only of patients with HDM-specific IgE antibody (37). Not all patients, however, react to the application of mite allergen on skin and this may be explained by the fact that the frequency of clonal expansion of *D. pteronyssinus*-specific T-cell clone types in the skin of AEDS patient is rather limited (38). Nonetheless, because it is known that T-cell clones specific for seasonal and perennial allergens can persist for years in the skin of patients with AEDS (39), it will be important to evaluate, in future studies, whether the lack or presence of clonal expansion is a constant feature of some individuals or if, whether it may change with time in relation to different environmental conditions.

Allergen avoidance

There are several studies evaluating the effects of allergen avoidance on asthma (reviewed in 40–44). Even though avoidance of sensitizing allergens is an obvious task in the management of the asthmatic patients, the issue of avoiding indoor allergen is still not completely resolved (41). Here we will concentrate on avoidance of indoor allergens in patients with AEDS since several review articles in allergen avoidance on asthma have been recently published (40–44).

Exposure to high concentrations of mite allergen in early infancy have been demonstrated to be a risk factor for developing atopic dermatitis during the first 3 years of life. Infants exposed to $> 1 \mu\text{g/g}$ of Der p1 tend to be affected more often by AEDS than those exposed to $< 1 \mu\text{g/g}$ Der p1 (21.6% vs. 5.3%, $P = 0.0156$; 45). Furthermore, a clear dose–response relationship has been documented between mite exposure and disease activity (46). This was confirmed in a recent study where significant associations were found between severity score of AEDS and concentrations of specific IgE for mite ($P = 0.032$) and cat ($P = 0.014$) allergens (47).

Several studies have also examined whether avoidance of indoor allergens results in clinical improvement of AEDS. The initial reports were uncontrolled clinical trials in which patients who were removed from their usual environments and placed in mite-free environments showed an improvement of their skin conditions (48–53). Subsequently, placebo controlled trials were

performed either to evaluate the effectiveness of mite allergen avoidance on the appearance of sensitization and on the onset of atopic dermatitis (*primary prevention*) and on the improvement of symptoms once sensitization has occurred and the disease is established (*tertiary prevention*). Studies on *secondary prevention* aimed at evaluating the possibility of disease prevention, i.e. appearance, in subjects already sensitized have not been performed in subjects with AEDS.

The first study on primary prevention was conducted on the Isle of Wight on 120 infants with a positive family history of atopy and high (>0.5 KU/l) cord blood concentrations of total IgE (54). In the prophylactic group ($n = 58$), lactating mothers avoided allergenic foods (milk, egg, fish, and nuts) and avoided feeding their infants these foods as well as soya, wheat, and orange up to the age of 12 months; the infants' bedrooms and living rooms were treated with an acaricidal powder and foam every 3 months and mattresses were covered with polyvinyl materials impermeable to HDM allergens. In the control group ($n = 62$), the diet of mothers and infants was unrestricted; no acaricidal treatment was instituted and no special mattress covers were used. In the prophylactic group the mean Der p1 concentrations for bedroom carpets was $25.9 \mu\text{g/g}$ of dust at birth and $6.0 \mu\text{g/g}$ of dust at 9 months. Baseline values were similar in the control group and remained constant through the study period. At 12 months the prevalence of atopic dermatitis was 3% in the active group and 19% in the control group ($P < 0.05$). These differences were significant and were maintained at follow-up after 24 and 48 months (13.8% vs. 24.2% at both ages, $P < 0.05$; 55,56). The odds ratio for developing atopic dermatitis in the control group was 3.59 at 12 months and 3.4 at both 24 and 48 months (54–56). In two other studies, on high-risk infants, one performed in the UK (57) and the other in the Netherlands (58), the use of mite avoidance measures (the application of HDM allergen-impermeable mattress covers), starting during pregnancy was not found to be associated with a reduction in the prevalence of eczema in the first year of life (57,58). The prevalence of eczema in the active group compared to the placebo group was 40 vs. 37% in the study performed in England (57), and, respectively, 13.3 vs. 14.9% in the study performed in the Netherlands (58). However HDM allergen levels were low both in the intervention and in the placebo group both in the Dutch study ($0.913 \mu\text{g/g}$ vs. $1.468 \mu\text{g/g}$ Der p1; 59), and in the English trial ($0.10 \mu\text{g/g}$ vs. $0.37 \mu\text{g/g}$) (60). Therefore the difference in allergen exposure between the active and placebo groups might have been too small to show a difference. Furthermore, an additional confounding feature in one study was the fact that 67% of the children in the active group attended day-care centres by the age of 1 year (58) and it is known that day-care attendance is known to be an important source of mite allergen exposure (61–63). Moreover, food allergens were not avoided in these two studies and

this may also, in part, explain the negative results. Food allergy exerts a prominent role in the pathogenesis of AEDS in young children and in the age group below 2 years sensitization to food precede sensitization to inhalants (6).

Additional studies have evaluated the role of HDM reduction in the treatment of established atopic eczema (64–70). Two studies (64,65) demonstrated that intensive vacuum cleaning were associated with significant clinical improvement of atopic dermatitis symptoms while the use of a spray to kill house dust mites was not effective (65). In three other studies, encasing mattresses and pillows with HDM allergen impermeable covers significantly reduced HDM exposure in bed and eczema severity (66–68). In one study (68) the positive effect was observed also in patients not sensitized to mite, a result which was attributed to a reduction of other important allergens, super antigens or irritants in beds.

In this regard, it is also known that mattress covers used for avoiding mite exposure effectively reduce also the growth of fungi in the mattresses (71). In two other studies, the use of allergen-impermeable mattress encasing in adults with atopic dermatitis resulted in a reduction in allergen exposure, but this was not associated with significant changes in clinical parameters between active and placebo groups (69,70). It is therefore possible that reduction of allergens in other environments (work, school, and outdoors) might be equally important for the improvement of symptoms. Moreover, because only one-third of patients with atopic dermatitis and with specific IgE to mites show worsening of symptoms after mite allergen exposure, it is expected that only a proportion of mite-sensitive patients will improve after mite allergen avoidance. In the future it will be therefore important to identify which groups respond best, which interventions are most cost effective and how broad these interventions need to be to result in effective control. Since both negative studies (69,70) were performed in adults, the effects of age and the duration of disease before the application of avoidance measures need to be evaluated in future studies.

From atopic dermatitis to asthma: prevention possibilities

Atopic dermatitis and HDM sensitization in early childhood have been demonstrated to be significant risk factors for wheezing in later childhood (72–74). Frequently, AEDS is the first manifestation of atopic diathesis, which occurs in genetically predisposed individuals and which also includes asthma and allergic rhinitis (74). Up to 80% of children with AEDS will eventually develop allergic asthma later in childhood, particularly those who are already sensitized to foods allergens, egg in particular (75–77). This raises the interesting possibilities that effective environmental control in children with AEDS may reduce the risk of subsequent development of respiratory allergy.

In a placebo-controlled study on 57 Japanese infants with atopic dermatitis and high IgE antibodies against either egg white, cow's milk or soy bean, but not against HDM, encasing with special anti-mite covers for quilts and mattresses of all family members markedly reduced mite exposure (3.0 µg/g of dust for placebo and 0.77 µg/g dust for active treatment $P < 0.001$) and also prevented the appearance of HDM-specific IgE ($P < 0.05$) at the 12-month follow-up (78). Skin prick tests with HDM extract were positive in 63% of children in the placebo arm and in 31% of patients using active covers ($P < 0.02$). During the study, wheezing episodes were observed in 37% of children using placebo and in 11% of patients in the actively treated group ($P < 0.05$). This study suggests that mite sensitization may precede the onset of asthma in children with atopic dermatitis. This was subsequently confirmed in another study which evaluated a larger group of Japanese infants with AEDS who were free from wheezing at enrolment. Of the 169 infants included in the study, 45% experienced asthma-like respiratory symptoms in the 4-year follow-up and 35% had a physician diagnosis of asthma (79). Children who developed asthma showed early appearance of HDM-specific IgE which was identified to be the most significant risk factor for developing asthma symptoms in these patients (79).

Positive skin prick test and atopy patch test responses to HDM as well as elevated environmental allergen exposure levels have been documented to have significant predictive power with AEDS duration (80). Therefore, adequate environmental control in infants with AEDS has the potential to prevent asthma development and to alleviate the course of AEDS itself.

Why indoor allergen avoidance may not work?

There are several reasons for the failure of allergen avoidance in improving clinical symptoms (Table 1). If the allergen selected for avoidance is not relevant to the development and progression of the disease and sensitization is only an epiphenomenon, of course, there is no reason for improvement even with appropriate avoidance. For example, the application of mite allergen on the skin of patients with AEDS is associated with the appearance of symptoms in approximately one-third of the patients, despite up to 80% of them showing HDM-specific IgE

(31–33). Consequently, two-thirds of those patients may not improve after mite allergen avoidance simply because other causes are involved in the pathogenesis of the disease. Furthermore, sensitization to multiple allergens is common in atopic patients and children tend to develop multiple sensitivities within a few years of exposure (81). Obviously, avoidance of multiple allergens is a more difficult task. Sometimes nonefficacious measures have been offered to patients. For example, studies with acaricides have shown that even the use of a good active compound does not necessarily equate with good mite allergen control and subsequent improvement of symptoms (41,82,83). Vacuum cleaning alone, not combined with steam cleaning (84), does not remove deeply imbedded allergens and does not reduce the number of live mites (82). Air filtration is not effective for mite allergen avoidance and has a limited efficacy also for pet allergen control (85). Furthermore, lay advertising advocating the use of foam mattresses and pillows in allergic patients should be the object of careful revision by the scientific community. The basis for this are the numerous demonstrations that the use of synthetic bedding is known to be a risk factor for severe atopic disease (45,86) because these materials are conducive to higher contents of mite and pet allergens in foam mattresses compared to spring mattresses (87) and in synthetic pillows compared to feather ones (88,89). In contrast, more traditional mite-avoidance measures, such as encasement of mattresses and box spring, removal of carpeting, and replacing upholstered furniture, can reduce the allergen burden and alleviate mite-induced atopic disease. However, these avoidance measures are poorly adhered to (90,91). With usual clinic-based education efforts, only 17% of patients have completely adherence to the prescribed avoidance plan (92) and this percentage rises to 39% with the use of a computerized education programme (93). Reasons for nonadherence include lack of understanding of the role of allergens in allergic disease, lack of spouse support, the time required, and the need to alter the life style (93). Low socioeconomic status may be another reason (94) even though 10–20% of the patients do not use dust mite-proof bedding covers even when they are given without cost in clinical trials (95,96). The failure to use measures of hot-washing the covers may also be a common cause of reduced efficacy because it is known that hot water is a requirement for an acaricidal effect. When first introduced, it was clear that cover mattresses were able to reduce mite allergen levels up to 100 times but it was also clear that after 6 weeks of use, mite allergen levels began to rise again on top of the cover (97). With this in mind, a recent trial evaluating the use of allergen-impermeable bed covers for adult asthmatics failed to be effective (98). But in this study the concentration of Der p1 in mattress dust was significantly lower in the active-intervention group at 6 months (geometric mean, 0.58 µg/g vs. 1.71 µg/g in the control group; $P = 0.01$) but not at 12 months (1.05 µg/g vs. 1.64 µg/g, $P = 0.74$) as could be expected when no

Table 1 Possible causes of allergen avoidance failure

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| 1 The allergen which is avoided is not relevant to the aetiopathogenesis of the disease; |
| 2 Multiple allergens are involved in the aetiopathogenesis of the disease; |
| 3 Non-efficacious measures have been suggested; |
| 4 Low adherence to the suggested measures; |
| 5 Exposure to the responsible allergen outside the home; |
| 6 Long-term duration of the disease with irreversible pathological changes in the target organ. |

washing instructions are provided and consequently no regular hot washing of the covers is performed.

Given the adherence problems with allergen avoidance a new measure has been proposed: the medical indoor environment counsellor (MIEC) (99). It has been shown that home visits by a MIEC increased the compliance to mite reduction methods advised, induced a significant difference in mite reduction levels on mattress and on carpets, and avoided nonestablished avoidance advice. There are other reasons for failure despite adherence to allergen avoidance at home, which includes exposure to allergens in public places (61–63), particularly for pet allergens (100–104), and even in private cars (105).

Long-term established disease is also less likely to respond to allergen avoidance: effectively a negative effect of allergen avoidance is mainly observed for both AEDS and asthma in adult patients (69,70,106). In long-lasting diseases irreversible pathological changes in the target tissue organ may obviously be more difficult to reverse.

Conclusions

Environmental factors seem to be at least as important as genetic factors in determining the expression of asthma

and atopic eczema (2–13). The challenge is now to find effective public health interventions capable of reducing the burden of atopic diseases, especially those that involve avoiding exposure to factors, such as indoor allergens, for which there is good evidence for a causal relationship (107–109). The information and education process should be part of a public health policy. Parental history of atopic disease is a strong risk factor for atopic outcome in the offspring, but the majority of infants who develop an atopic phenotype and sensitization do not have atopic parents (110). Therefore, to be effective, interventions aimed at reducing the onset of atopic diseases (primary prevention) should be directed at a population level. The same is true for most of the cases of secondary and tertiary prevention because exposure to allergens outside the house does not depend on and cannot be controlled by the individual patient.

Identification of risk factors is the first point (10) that education needs to follow. Unfortunately this is still limited even in the parents of atopic children (111,112).

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