

Predictive features for persistence of atopic dermatitis in children

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Allergen exposure plays an important role in atopic dermatitis (AD). Because immunological mechanisms underlying asthma and AD have great similarities, we evaluated whether features such as allergen sensitization, immune response, disease severity and duration or allergen exposure could be considered predictive for AD persistence. Seventy-one AD children (age range 14–158 months) were enrolled and followed for 3 consecutive years for AD severity using the SCORAD index (SI). At enrollment, reactivity to inhalant and food allergens using the skin prick test (SPT) and house dust mite (HDM) atopy patch test (APT), and HDM allergens in house dust were evaluated. After 3 years, 38 children outgrew their AD (AD⁻ group), while in 33 AD persisted (AD⁺ group). At enrollment, AD⁺ children had a higher SI, higher rate of positivity to SPT and APT for mites ($p = 0.001$), and higher environmental exposure to HDM allergens ($p = 0.035$). The AD⁺ children developed more respiratory symptoms in comparison to AD⁻ children ($p < 0.001$). None of the AD⁻ children presented APT positivity. In our study population, positivity of SPT and APT for HDM, environmental allergen exposure levels and severity of the disease at enrollment presented a significant predictive power towards AD persistence. Subjects with positive skin reactivity to HDM should be considered at risk of AD persistence and of possible development of allergic respiratory disorders.

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Atopic dermatitis (AD) usually appears early in life and 90% of patients develop skin lesions before 5 years of age (1). AD is often associated with a family history of atopy and frequently predates the development of allergic rhinitis and/or asthma later in life (2, 3). Exposure to allergens plays an important role in AD exacerbations as well as micro-organism infections, stress, sweating and climate (4). As recent studies suggest that the immune mechanisms underlying asthma and AD have greater similarities than differences (5), we evaluated in a cohort of children whether features such as allergen exposure and sensitization, immune response, severity and duration of the disease could be considered predictive for AD persistence.

Methods

Study design

A cohort of 71 AD children (age range 14–158 months) attending consecutively the outpatients' clinic for AD was followed for 3 consecutive years. The diagnosis of AD was according to the criteria of Hanifin and Rajka in children (6), and Sampson for diagnosis in infancy (7). Severity scoring for AD and associated symptoms were performed using the SCORAD index (SI) (8) at inclusion and repeated every year in the follow-up. Parents or guardians were asked to fill in a validated questionnaire on allergic diseases (9). The same physician (GBP) was in charge for patients' follow-up. At the end of the

3-year observation period, patients were evaluated and divided into two groups according to the SI values. AD clinical remission was considered when the SI decreased and was ≤ 10 for two consecutive visits (8) performed 1 year apart and parents reported no active disease.

At enrollment, atopy patch test (APT) for house dust mite (HDM) and skin prick test (SPT) for HDM (*Dermatophagoides pteronyssinus* and *D. farinae*), pollens (*Parietaria judaica*, *Phleum pratense*, Grass mix, *Artemisia*, *Olea europaea*), animal dander (Dog, Cat) and molds (*Cladosporium* and *Alternaria*) (ALK-Abellò, Milan, Italy) were performed. SPT for food allergens (milk, egg, fish, wheat, peanut, tomato, snail, and peach) were performed with fresh material according to the prick-by-prick technique (10).

Atopy patch test

APT was performed using a 8-mm aluminum cap (Finn Chambers, Epitest Ltd, Oy, Finland) filled with a 20% dispersion in petrolatum of crushed whole bodies of HDM (*D. pteronyssinus* and *D. farinae* 1:1) (Allergopharma-Bracco, Milan, Italy) and placed by means of hypoallergenic adhesive tape on non-abraded, uninvolved skin of the back of each child (11). The aluminum cap was removed 48 h later, and the reading took place after 30 min and again 24 h after the first reading. Glycerin, the APT vehicle, was used as a negative control. The APT was scored as negative if two independent tests run after a 7- to 14-day interval were both negative.

HDM allergen exposure

To assess HDM exposure, samples of dust were collected by means of a vacuum cleaner from children's bed mattresses at enrollment. A standard area was vacuum cleaned for 3 min. Samples were analyzed in duplicate in the same experiment for mite Group 1 (Der p 1 and Der f 1) content with an immunoassay method using specific monoclonal antibodies (11).

Patients' treatment

Children were regularly treated with bathing to hydrate the skin, followed by application of an effective moisturiser and on an as need basis with topical steroids, mainly hydrocortisone, for 7–10 days according to symptom severity.

The use of cover mattresses and cover pillows was not suggested and only standard environmental measures were recommended. No patient received antihistaminic treatment the week

before the SPT and APT tests. Patients treated with systemic steroids in the previous 3 months were excluded.

Statistical analysis

The χ^2 test was used to analyze the relative frequency for independent values, and the McNemar test was used for non-independent data. The likelihood ratio and its statistical significance were also calculated for relative frequency data. A parametric test (*t*-test) was used for statistical analysis of parametric data whereas non-parametric data were analyzed by means of the Mann–Whitney *U*-test. A standard statistical package was utilized (BMDP, Los Angeles, CA, USA).

The study was performed with the approval of the local Ethical Committee, and the children's parents gave their written informed consent.

Results

Thirty-eight children outgrew their AD (AD^- group); in 33 AD persisted (AD^+ group). Demographic data as well as age at first diagnosis of AD, age at enrollment, mean value and range of the SI in both groups of children are shown in Table 1. The two groups turned out to be well balanced for gender and no differences between groups for age at first diagnosis of AD were observed (NS). However, AD^+ children showed at enrollment a significantly higher SI compared with AD^- ($p < 0.001$). During the 3 year follow-up, AD^+ children developed more respiratory symptoms in comparison to AD^- children [16/33 (48.5%) vs. 2/38 (5.3%), respectively,] ($p < 0.001$). AD^+ children were exposed at inclusion to a significantly greater amount of environmental HDM allergens (mean $1.82 \pm 2.72 \mu\text{g/g}$; range 0.01–9.40) in comparison to the AD^- group ($0.74 \pm 1.38 \mu\text{g/g}$; 0.01–6.60) ($p = 0.04$).

A SPT positive response to HDM was significantly more frequent in AD^+ children compared with AD^- children [18 (54%) vs. 6 (15%)

Table 1. Demographic data

	AD^+ children	AD^- children
Total number	33	38
Male/female	14/19	16/22
Age at first diagnosis of AD, mean in months (range)	14.1 (2–71)	10.8 (1–39)
Age at enrollment, mean in months (range)	18.4 (4–90)	15.1 (4–41)
SI at enrollment, mean value (range)	57.06 (20–89)	21.79 (10–42)

subjects, $p = 0.001$], whereas an APT positive response was obtained in 21 AD⁺ children (63%), but in none of the AD⁻ children ($p < 0.001$). Some AD⁺ children presented also with sensitization to other inhalant allergens, all AD⁻ children were negative by SPT to the other inhalant allergens. Even though food allergen sensitization was more frequent in AD⁺ children (45%) compared with AD⁻ children (29%), there was no statistical significant difference between the two groups (NS).

Persistence of AD was more likely in children with a positive SPT to HDM compared with children with a negative SPT to HDM (likelihood ratio 12.22, $p = 0.001$). On the other hand, persistence of AD was even more likely in children with a positive APT as compared with children with a negative APT (likelihood ratio 42.97, $p < 0.001$).

Discussion

The clinical phenotype of AD is the final result of complex interactions between genetics, individual immunologic characteristics and specific environmental conditions (12, 13). A cause-effect link between food allergy and AD in children has been established (13–15), and sensitization to hen's egg is considered a strong predictor for AD persistence (16). However, recently importance has been given to HDM, because it was observed that hypersensitivity to HDM can give rise to eczematous reactions (17). Furthermore, HDM is now considered to be an aggravating factor in AD patients (18), becoming increasingly relevant during childhood and adolescence (19). In our study we observed different environmental exposure to HDM and different immunologic responses between children in whom AD persisted (AD⁺) and those where the skin disease cleared during the follow-up period (AD⁻). Children in the AD⁺ group were exposed to higher environmental levels of HDM allergens and showed a higher rate of SPT positivity to HDM (54% vs. 15% in AD⁺ and AD⁻, respectively). The association between degree of sensitization to aeroallergens and the severity of atopic eczema as well as the correlation between exposure to high concentration of HDM allergens in early infancy and the development of AD was previously documented (20, 21). In our study we further expected this association, having observed an increased risk of persistence of the disease in children with an immunologic reaction to mites. The different immunologic responses between our two groups were even sharper when the response to APT was considered: 63% of the

children in the AD⁺ group showed a positive result as compared with none in the AD⁻ group. Doubts have been recently raised on the variability in the performance and interpretation of APT for aeroallergens (22), and mainly when non-standardized testing materials are used (23). However, APT reproducibility had been previously shown as highly satisfactory in AD patients and in healthy individuals and satisfactory in non-eczematous atopic subjects (24). The possibility that APT responses merely reflect the increased irritability of the skin in children with more severe disease rather than a specific effect of sensitization of HDM is unlikely. If the response was related to irritant factors present in the material used for APT, we should have observed at least some children with an APT response in the AD⁻ group. Moreover, the majority of children with a positive APT had also specific IgE, i.e. SPT positivity, for HDM.

The relevance of HDM in the pathogenesis of AD is documented by previous studies showing that the activity of the disease can be greatly reduced by effective HDM avoidance covering beds with appropriate barrier materials (25, 26). In our longitudinal observational study, we did not give parents' specific information concerning effective allergen avoidance measures such as the use of cover mattresses and cover pillows. The relationship between the degree of allergen exposure sensitization and disease activity can be better evaluated by primary prevention studies on AD in healthy infants and by secondary prevention of asthma in children with AD. This is particularly important because also in our population the relative frequency of asthma was higher in the AD⁺ group compared with the AD⁻ group (48% vs. 5%), according to previous reports (27). It is well known, on the other hand, that AD in early infancy is predictive of later allergic airway disease (28) and that it might be partially prevented by house dust mite avoidance (29).

In conclusion, in our study population a positive response to SPT and APT for HDM, environmental allergen exposure levels and severity of the disease at enrollment presented a significant predictive power towards AD persistence. Our results support the assessment of sensitizations by SPT and mainly by APT to HDM as a marker to discriminate between patients that are more likely to outgrow AD compared with patients who will not. These data could be used to predict both the natural history of the disease and the possible later occurrence of bronchial asthma. The association between sensitization to HDM and ongoing AD repre-

sents an intriguing field for improving diagnostic methods for a more precise definition of the disease. Further therapeutic trials aimed at possible control through an early allergen avoidance regimen, an appropriate pharmacological treatment and immune modulation are required.

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