

EDITORIAL

Clinical and Experimental Allergy

The allergic march in early childhood and beyond

This editorial discusses the findings of the paper in this issue by Asarnoj et al. [3].

A. Linneberg

Research Centre for Prevention and Health, Glostrup University Hospital, The Capital Region of Denmark, 57 Nordre Ringvej, Building 84/85, DK-2600 Glostrup, Denmark

Atopy is defined as a personal and/or a familial tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins [1]. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, eczema and food allergy. Atopy may thus be viewed as a risk factor or an intermediate phenotype of these atopic (or allergic) diseases. The prevalence of allergic diseases has increased in developed countries and this trend is supported by documented increases in objectively measured atopy [2]. The incidence of atopic eczema and food allergy seems to peak already within the first 2 years of life, and these infants are at increased risk of later manifestations of allergic disease such as asthma and allergic rhinitis. This phenomenon of switching from one clinical manifestation of allergy to another is often referred to as 'The allergic march'.

Knowledge about the natural (or spontaneous) course of atopy and its relation to the manifestations of allergic disease is important in risk stratification of patients and may further provide clues to the causes of the allergy epidemic as well as increased insights into the mechanisms underlying the development of disease. This knowledge is best obtained by longitudinal studies of general populations. In this issue of Clinical and Experimental Allergy, Asarnoj et al. present important data on the development of sensitization (serum allergen-specific IgE) during early childhood (from 4 to 8 years of age) from a population-based birth cohort study: the BAMSE birth cohort [3]. They report a remarkably high incidence of IgE sensitization to inhalant allergens during this period of life, adding fuel to the continuation of the allergic march beyond early childhood. The high incidence and the persistence of sensitization resulted in a marked increase in the prevalence of sensitization to

inhalant allergens from 15% to 25% over this 4-year period. The persistence of sensitization was generally high for all inhalant allergens [3]. For example, 97% of children sensitized to birch pollen at 4 years of age were still sensitized to birch pollen at 8 years, i.e. a remission rate of 3%. This is a remarkably low remission rate emphasizing the persistent nature of IgE sensitization to inhalant allergens in this period of life. From a biological point of view, the 'true' remission rate may be even lower, because measurement error and seasonal variation in levels of serum-specific IgE are likely to decrease the reproducibility of test results.

There is evidence that the persistent nature of IgE sensitization to inhalant allergens goes beyond early childhood. Thus, Rhodes et al. performed repeated follow-ups including measurement of sensitization from birth to 22 years of age in a high-risk birth cohort [4]. The prevalence of IgE sensitization to inhalants continued to increase over the whole time span, supporting both the high incidence and the chronic nature of inhalant sensitization up to the age of 22 years. Even in much older populations, the remission of sensitization to inhalant allergens appears to be low. In a prospective study of a general population of 18–69 year olds, the 8-year remission rates of serum-specific IgE sensitization to pollen allergens and dust mite/pet allergens were 6% and 11%, respectively [5]. The rates of remission for specific allergens are shown in Table 1. The 8-year remission rate for grass pollen sensitization in this adult population was 12%, which was remarkably similar to the 4-year remission rate for grass pollen sensitization observed in the much younger BAMSE cohort (13%). Hence, although we need more data on the natural course of atopy and its clinical manifestations, it is becoming clear that inhalant sensitization is more persistent than previously recognized.

In contrast to the persistent nature of sensitization to inhalant allergens, food allergen sensitization tends to be more transient. The incidence of food sensitization peaks during infancy, while the incidence of inhalant sensitization peaks later in childhood. In the German Multicenter

Correspondence:

Allan Linneberg, Research Centre for Prevention and Health, Glostrup University Hospital, The Capital Region of Denmark, 57 Nordre Ringvej, Building 84/85, DK-2600 Glostrup, Denmark. E-mail: alli@glo.regionh.dk

Table 1. Eight-year remission rates of serum-specific IgE sensitization (negative test in persons with positive test at baseline, IgE ≥ 0.35 kU/L) to different inhalant allergens in a general population aged 18–69 years (adapted from reference [5])

Allergen sensitization	Eight-year remission rate percentage (n/total n)
Birch	9.6 (13/136)
Grass	12.1 (18/149)
Mugwort	19.7 (12/61)
<i>Dermatophagoides pteronyssinus</i>	7.9 (5/63)
Cat	13.7 (10/73)
Dog	28.6 (14/49)

Allergy Study, the incidence of food sensitization peaked during the first year of life and decreased until the follow-up at 6 years of age [6]. In contrast, the incidence of inhalant sensitization was low during the first year of life, but continued to increase up to 6 years. Transient sensitizations to food allergens were far more common than transient sensitizations to inhalant allergens. It is sometimes stated that the allergic child is likely to outgrow its allergies. However, although this may be true for food allergy, it does not seem to relate to inhalant allergy. Furthermore, epidemiological birth cohort studies have taught us that sensitization is a dynamic process and the food-allergic infant is at high risk of entering the allergic march and develop ('switch to') inhalant sensitization and clinical manifestations of allergic respiratory disease. In the BAMSE cohort, food allergen sensitization and food hypersensitivity at 4 years of age was a strong predictor of inhalant sensitization as well as asthma, eczema and allergic rhinitis at 8 years of age [3, 7]. Various phenotypes of asthma have been described, and it seems reasonably clear that allergic sensitization in early childhood is a very strong determinant of the development of so-called atopic asthma later in childhood [8]. Transient wheezing during the first 2–3 years of life is not related to atopy and should probably not be viewed as an atopic manifestation [9].

The apparent discrepancy between the course of food and inhalant allergen sensitization remains unexplained. A potential explanation was put forward by Patrick Holt, who noted that the dose of allergens introduced to the immune system is quantitatively manifold higher for food allergens (doses in the range of microgram to grams) as compared with inhalant allergens (doses in the range of nanograms) [10]. Thus, the lower prevalence and transient nature of food allergy might be due to tolerance induced by the high allergen dose obtained from foods and the fact that for many food allergens, e.g. cow's milk proteins, avoidance of exposure is difficult.

The finding that the dynamic process of development of novel sensitizations to inhalant allergens is working at full speed already in pre-school age [3] emphasizes the need for measures for early intervention. However, based on the

present scientific evidence it is not easy to make clear recommendations on how to change the course of allergic disease and reverse 'the allergic march'. Studies like the BAMSE birth cohort provide valuable information about the course of disease and may generate evidence of risk factors that may become future targets of interventions. Randomized intervention studies have so far failed to document beneficial effects of allergen avoidance as primary prevention against allergic diseases [11]. Allergen-specific immunotherapy (SIT) has documented beneficial effects on symptoms of allergic rhinitis [12] and allergic asthma [13] in adult patients. A long-term effect after discontinuation of treatment has been shown, indicating that SIT can potentially induce long-term tolerance and change the course of the disease [14]. The results of the preventive allergy treatment (PAT) study suggest a long-term preventive effect of SIT against asthma development in allergic children [15]. The high rates of development of novel sensitizations to inhalant allergens in early childhood suggest that early intervention with SIT would be a potential strategy for reversing 'the allergic march'. However, the role of SIT in this age group is still debated. More trials in this age group are warranted. Sublingual-administered SIT is an option that may facilitate large-scale randomized studies in children, even at an early stage in 'the allergic march' as a secondary preventive measure (in children at high risk of allergic disease, but without clinical manifestations). The effects of other interventions, e.g. dietary interventions or interventions emerging from the 'Hygiene hypothesis' such as treatments using microbial products, probiotics or even live micro-organisms, still need more documentation.

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