

Original article

When allergies complicate allergies

The 'allergic march' is a term used to describe an individual's progress from one clinical manifestation of allergy to another, with age. Not all sensitized children will join the allergic march, but it appears that individuals who do not join the allergic march have a greater risk of displaying symptoms of allergic disease in adulthood. Consequently, there is a need for early diagnosis of allergy in children. Immunoglobulin E (IgE) antibody quantification is increasingly used for this purpose. However, rather than making a diagnosis based on single positive IgE antibody results only, it may be more efficient to test a profile of airborne and food allergens and use the sum of IgE antibody concentrations ≥ 3.5 kU_A/l in combination with the number of allergens that elicit positive results tests. Allergic diseases often co-exist in patients, and the combination of several exposures at a given time (the allergen load) is related to disease severity. Therefore, a reduction of the allergen load is a key to successful treatment.

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For a quarter of a century, the prevalence of allergic diseases has increased among children, although this increase has recently been suggested to level out (1, 2). In Europe, one in four children suffer from an allergic disease and questions have been raised as to how this situation may develop in the future (3).

The allergic march

A number of studies have demonstrated that sensitization to food and airborne allergens may predict the development of allergic airway disease in later life, and young, nonsensitized children with wheeze seem to go into remission more often than recurrent wheezers who are sensitized (4–8). Besides, sensitization to airborne allergens in subjects with asthma is an age-independent risk factor for an increased severity of disease (9–11).

In an ongoing birth cohort study in Stockholm involving around 4000 children [Barn (children)–Allergy–Milieu–Stockholm–Epidemiology, BAMSE], Wickman et al. (12) determined immunoglobulin E (IgE) antibody levels in 2614 children when they were 4 years of age. The analyses were performed using the Pharmacia CAP systemTM (Pharmacia Diagnostics; Uppsala, Sweden, Phadiatop[®] and food mix fx5[®]), and an antibody level ≥ 0.35 kU_A/l was considered as positive. The children were classified as having asthma, allergic rhinitis, eczema or gastrointestinal allergy based on a questionnaire of parental-reported symptoms. In asthmatic children, a close association was found not only between the number of episodes of wheeze and the level

of IgE antibodies to airborne allergens (Phadiatop[®]), but also between the number of episodes of wheeze and the level of IgE antibodies to food allergens (fx5[®]) (Fig. 1). In particular, in boys with asthma, a positive Phadiatop[®] test was significantly related to limited peak flows, compared with a negative test result.

It is not uncommon for individuals to progress with age from one clinical manifestation of allergy to another. This observation is also included in the concept of the 'allergic march' (Table 1 and Fig. 2). Allergy early in life often involves eczema and food allergy, which may resolve as respiratory symptoms develop. Several hypotheses exist

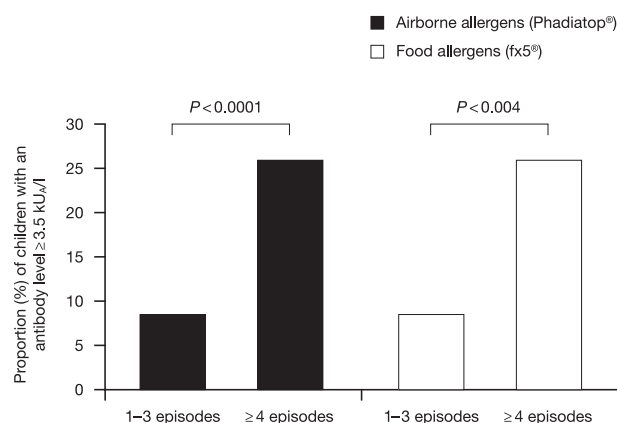


Figure 1. Association between the severity of wheeze and sensitization to airborne and food allergens (12). Reproduced with permission from Blackwell Publishing.

Table 1. Key points of the allergic march

- Early sensitization, in particular to inhalant allergens, predicts allergic airway disease
- Sensitization and allergic symptoms in early childhood lead to an increased risk of allergic disease in adulthood
- Young asthmatic children sensitized to airborne or food allergens are at risk of experiencing increased disease severity compared with nonsensitized asthmatic children
- Children with high levels of IgE antibodies to a particular allergen have a poorer prognosis and an increased risk of reactions after exposure

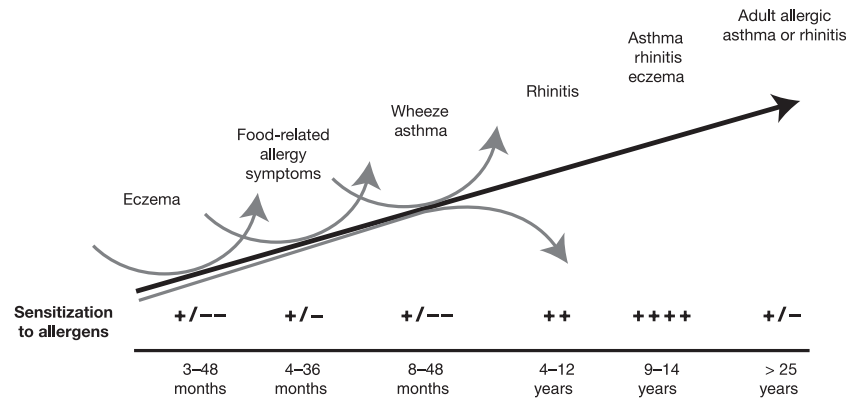


Figure 2. The allergic march.

that may explain the immunological mechanisms behind the allergic-march phenomenon.

Not all sensitized children will join the allergic march. The majority (70%) of young children with wheeze will be symptom-free at school age (13). In children with food allergy, declining levels of food-specific IgE antibodies indicate an increased likelihood of developing tolerance to that food, in particular, if the IgE antibody levels were low from the beginning (14, 15). However, individuals who do not join the allergic march still appear to be at a greater risk of displaying symptoms of allergic disease as adults.

Consequently, there is a need for early diagnosis of allergy in children and identification of the offending allergens, but there is also a need for quantification of IgE levels over time for monitoring and re-evaluation purposes. This is a prerequisite for the success of secondary measures, such as specific treatment levels, allergen avoidance where possible and appropriate family education, and to prevent exacerbation of disease (16).

Approaches to assess sensitization and probability of allergic disease

There is a growing interest in the use of IgE antibody quantification for the diagnosis of allergy in children (14, 17).

The BAMSE study demonstrated that the occurrence of IgE antibodies ≥ 3.5 kU_A/l to both Phadiatop[®] and fx5[®] in combination in young children could reveal a predicted likelihood of any suspected allergic disease (asthma, rhinitis, eczema or food allergy) of 97.4% (12). However, in the same study, the presence of IgE

antibodies ≥ 3.5 kU_A/l to either Phadiatop[®] or fx5[®] used as a single test only was far less efficient in predicting any allergic disease. The authors suggested that quantification of IgE antibodies with multi-allergen tests could facilitate the diagnosis of allergic disease and could also indicate the severity of asthma. At the 4-year follow-up of the BAMSE project, it was further investigated whether the following approaches to assess sensitization could help in identifying children with allergic disease: determination of the sum of allergen-specific IgE-antibody levels, determination of the number of allergens in the Phadiatop[®] and fx5[®] mixes that elicited positive test results, or a combination of these two approaches. When the sum of specific IgE antibody levels towards the selected allergens was at least 34 kU_A/l or, alternatively, more than four of the 14 allergens in the two mixes elicited a positive result, there was a 75% likelihood that an allergic disease was present (Fig. 3). It was found that the combination of the sum of specific IgE antibody levels and the number of allergens that elicited positive results was significantly associated with the likelihood of asthma — an important point for identifying those with asthma (Fig. 4).

The authors concluded that, in 4-year-old children, allergic disease was frequently not associated with single positive IgE antibody results, whereas an increased sum of IgE antibody levels was significantly more prevalent among those with allergic disease. Thus, testing a certain profile of airborne and food allergens and utilizing the sum of IgE antibody levels in combination with the number of allergens that elicit positive test results may represent a more efficient diagnostic tool than using single positive IgE antibody results only. The number of allergens for which an individual tests

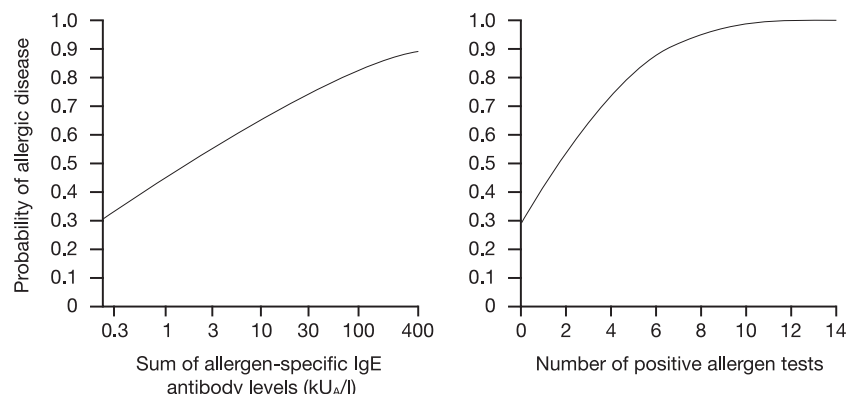


Figure 3. Association between the sum of specific IgE antibodies ≥ 0.35 kU_A/l or the number of allergens in the Phadiatop® and fx5® mixes that elicited a positive result, and the likelihood of developing allergic disease (asthma, allergic rhinitis, eczema or gastro-intestinal allergy) (20). Reproduced with permission from Blackwell Publishing.

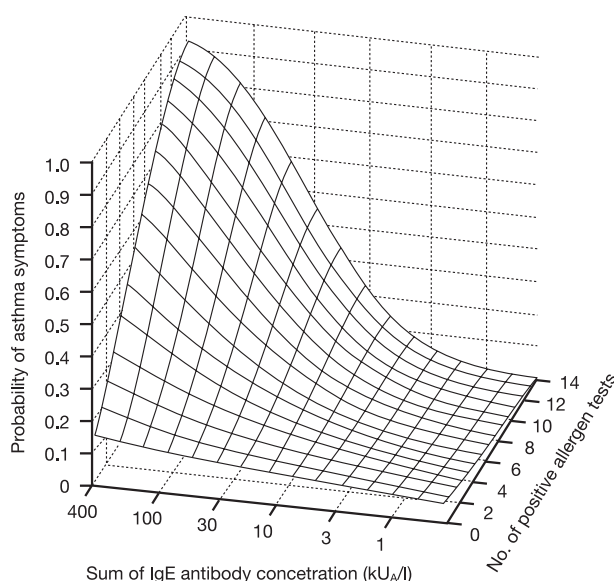


Figure 4. Association between the sum of specific IgE antibodies ≥ 0.35 kU_A/l, the number of allergens that elicited a positive result and the likelihood of asthma (20). Reproduced with permission from Blackwell Publishing.

positive can also be used as an indicator of allergic status.

Continuous exposure, sensitization to single and multiple allergens and deterioration of disease

Allergic diseases often co-exist in patients; for example, younger children often experience both eczema and food allergy, and many schoolchildren and adults suffer both asthma and allergic rhinitis. This is perhaps not surprising in view of the close proximity of the upper and lower airways. It is important to note that patients may be

sensitized to an allergen but remain asymptomatic, suggesting both the involvement of tolerance mechanisms and a threshold level for disease. For instance, at moderate levels of birch pollen, the majority of individuals sensitized to this allergen will experience problems involving the upper airways only, but when the allergen levels are high, an increasing proportion will also experience symptoms involving the lower airways. Furthermore, individuals may be asymptomatic to a specific allergen, but when they are concurrently exposed to a second allergen, they may become symptomatic.

Thus, several allergens (the allergen load) may act together to exceed an individual's threshold. If the allergen load is reduced through avoidance of one or more of the relevant allergens, this may eliminate the need for pharmacological treatment.

An understanding of this concept allows physicians to manage their patients' allergies more effectively. For example, an individual who experiences allergic symptoms most noticeably during the pollen season, but presents with some symptoms throughout the year, may find symptoms reduced throughout the year by effectively avoiding an allergen to which they have minimal symptomatic sensitivity.

It has also been suggested that sensitization to one allergen may facilitate sensitization to another without the involvement of cross-reaction mechanisms. Kihlström et al. (18) investigated the relationship between early allergen exposure, sensitization and development of atopic disease in 583 children with atopic heredity born between 1992 and 1994; the children were examined when they were 4.5–5 years old. Children born before spring in 1993, when the birch pollen counts were 10 times higher than in other years, had a significantly increased risk of sensitization to birch pollen, compared with children born in 1992 or 1994. Furthermore, children born before spring in 1993 who had a cat at home, exhibited a threefold increased risk of sensitization to cats. These

data could be confirmed by results from the 4-year follow-up of the BAMSE study. Children sensitized to birch and not to timothy, compared with children sensitized to timothy and not to birch, were significantly more often sensitized to cats (M van Hage Hamsten, personal communication).

Allergen exposure is one of the keys to disease severity in symptomatic and sensitized individuals. Patients with asthma who are exposed to allergens to which they are sensitized have a more severe form of the disease than asthmatics who are not exposed. In a study by Langley et al. (19), patients who are both sensitized and exposed to high levels of sensitizing allergen were found to have significantly lower forced expiratory volume (FEV1) percent predicted values and more severe airways reactivity, compared with participants who were not sensitized.

Conclusion

Some key points can be concluded concerning the diagnosis of multiple allergies. In clinical practice, the interpretation of allergy test results and the information given to patients should be differentiated according to several factors, including age, magnitude of sensitization

(number of allergens that tested positive, specific IgE levels) and geographical circumstances. Quantification of serum IgE levels may not only be beneficial for the diagnosis of allergic diseases, but also serve as a marker for disease severity and help to estimate prognosis, especially in young children, as it gives an indication of the atopic constitution. Finally, when there is exposure to >1 sensitizing allergen, the effect of the allergen load needs to be taken into consideration.

Key points

- Not all sensitized children will join the allergic march, but those who do not still have a greater risk of displaying symptoms of allergic disease in adulthood.
- Combining the sum of IgE antibody concentrations for those allergens for which a patient tests positive with the number of positive allergen tests may represent a more efficient diagnostic tool than single positive IgE antibody tests alone.
- Diagnosing the nature of a specific allergy is useful for obtaining an estimate of prognosis, especially in young children.

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