

REVIEW

Further marches: allergic and non-allergic

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The allergic march

The allergic march has been described as IgE-related atopic dermatitis, sometimes accompanied by allergic gastrointestinal disease, starting in infancy and progressing to respiratory allergy [1]. Initial IgE reactivity is to food allergens; later reactivity to inhaled allergens develops [1]. Initial sensitization may be via the skin and there is a strong genetic influence [2].

Later allergy development

However not all allergies begin in early childhood. The Isle of Wight cohort study demonstrates that 11.2% of children had delayed atopy only apparent at 10 years [3].

Seasonal allergic rhinitis (AR) in many parts of the world also probably involves *de novo* allergic disease appearing in later childhood – prevalence is consistently higher in 13–14 than in 6–7-year-olds in the International Study of Asthma and Allergies in Childhood (ISAAC) reports. The prevalence of AR, as evidenced by repeated use of the same ISAAC questionnaire, has increased in 13–14-year-olds in many parts of the world between the mid 1990s and early 2000/2001 [4–8]. New hayfever also presents in adult life [9].

Local IgE production has been demonstrated in the nose in AR [10]. In children with a clear history of seasonal allergic rhinitis skin prick tests (SPT) are sometimes initially negative, but become positive after a year or two (personal observation). Thus later allergic sensitization appears to be via the airway.

Progression of sensitization

There is no cohort study examining the progress of these patients. Certainly some lose their rhinitis, however in others there appears to be a progression from mono- to poly-sensitization as noted in the control subjects in an immunotherapy trial [11]. Of 1214 control patients mono-sensitized at the start of the study and treated by pharmacotherapy, 69.03% were poly-sensitized at 4 years, 76.7%

by 7 years. A possible reason for this is that pollen not only carries antigens into the respiratory tract, but is also a source of bio-active lipids which attract neutrophils and eosinophils, and a source of E phytoprostanes which inhibit IL-12 and modulate dendritic cell function towards T-helper type 2 (Th2) polarization [12].

Progression to asthma

Rhinitis shares a similar epidemiological distribution with asthma involving high prevalence in English speaking countries with Western lifestyles [13]. Most asthmatics have rhinitis and both allergic and non-AR are risk factors for the subsequent development of asthma with an odds ratio of around 3 [14, 15].

Similarly in occupational disease rhinitis is almost always the first manifestation of an airways problem. It may accompany or precede the development of asthma. In a recent prospective study 11.6% of the 3637 occupational rhinitis patients developed asthma i.e. 19/1000 of population per year. In occupational diseases other than rhinitis there were 972 incident cases of asthma (3.1%) in 31 457 individuals, an incidence of 4/1000 per population per year. Relative risks compared with the reference population were 4.8 for occupational rhinitis, 5.4 for compensated occupational rhinitis, 3.7 for unaccepted occupational rhinitis and seven for farmers and wood workers with occupational rhinitis [16].

Both asthma and rhinitis are eosinophilic disorders and there is a correlation between the eosinophil numbers in upper and lower airways both in simple uncomplicated AR [17], and in rhinosinusitis [18]. This is probably accounted for by the recent demonstration that allergen challenge in the nose excites an eosinophilic reaction not only in the upper, but also in the lower airways and vice versa [19, 20]. There is an undoubted systemic link with immature eosinophil egress from the bone marrow, some maturation in the circulation and extravasation from blood vessels, both at the initial site of inflammation and in other areas of the respiratory tract [21].

Progression to rhinosinusitis

Rhinitis also can progress to involve other parts of the respiratory tract. Rhinosinusitis usually commences with

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rhinitis symptoms, this is poorly documented for AR, but is particularly evident in aspirin exacerbated respiratory disease where, as the AIAANE network demonstrates in data from 500 patients in Europe, there is a sequential pattern. Individuals begin with a persistent rhinitis, SPT negative in two thirds, at around 29.7 ± 12.5 years. Then nasal polyposis, asthma and aspirin intolerance develop with a variable time course. The disease is earlier and more severe in females. Atopic individuals (one in three), show earlier rhinitis and asthma, but there is no difference in the timing of the development of aspirin sensitivity [22]. Thus this is an atopy-independent disease progression.

Recent mouse experimental evidence suggests that many of the T cells present in asthma are not allergen-specific Th2 cells, but natural killer T cells activated by bacterial glycolipids [23]. Recent work on nasal polyposis in man has also demonstrated that many of the T cells present respond to staphylococcal superantigens by local production of polyclonal IgE [24]. This may also be true of the lower airways in severe asthma [25]. This suggests the possibility of an initial allergic phase to inflammation in the airways with a subsequent less antigen-specific inflammation in response to superantigens. Thus allergen avoidance measures and specific allergic therapy such as allergen immunotherapy would be more likely to be effective in the early-phase of disease.

Effects of treatment

There is evidence that allergen-specific treatment of AR may modify disease progression. Immunotherapy for seasonal rhinitis reduces bronchial hyper-reactivity and seasonal asthma [26–28]. In children with AR immunotherapy reduced the development of new asthma with an odds ratio of 2.52 at 3 and at 5 years [29]. There is also evidence that injection immunotherapy can reduce new sensitization [11, 29]. Sublingual immunotherapy has been less extensively investigated [30]. In a recent study in 511 AR patients with and without asthma, of whom 319 were treated with sublingual immunotherapy, there was a decrease in positive methacholine challenge and a reduction of new allergic sensitizations in the immunotherapy group compared with those treated with pharmacotherapy alone [31]. It is thought that both injection and sublingual immunotherapy may act via the generation of T-regulatory cells [32].

Conclusion

Thus there appear to be at least two allergic marches: the first with a strong genetic component starting in early childhood with atopic dermatitis with sensitization occurring possibly via the skin; the second starting later in life with a strong environmental component and

sensitization starting in the respiratory tract. Progression of sensitization and progression from rhinitis to asthma and probably to rhinosinusitis can occur. The contribution of micro-organisms to these processes remains to be determined.

There is also a similar, but non-atopic disease progression from rhinitis to polypoid rhinosinusitis and asthma in which bacterial superantigens are involved in promoting local polyclonal IgE.

This has important research and therapeutic implications.

Genetic pre-dispositions may differ between the first and second allergic marches. Asthma and allergy researchers should be careful to differentiate very clearly the history of trial subjects.

Future trials should address the identification of those in whom later onset allergic disease is likely to progress. Early specific immunotherapy to those individuals may reduce progression and the costs of long-term chronic respiratory disease.

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