

THE ATOPIC MARCH

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ABSTRACT

The atopic march refers to the natural history of allergic or atopic manifestations characterised by a typical sequence of clinical symptoms and conditions appearing during a certain age period and persisting over a number of years. In general the clinical features of atopic eczema occur first and precede the development of asthma and allergic rhinitis.

This article outlines a number of studies that have demonstrated the atopic march in infants and young children. Early markers are noted and prevention methods outlined.

The atopic march is better known as the 'allergic march' in South Africa. This latter term is also better understood by parents and patients when used during explanation at consultations in allergy practice. However most international publications now use the term the 'atopic march'.

Atopic diseases such as asthma, allergic rhinitis and eczema are allergic conditions that tend to occur in families and are associated with the production of specific IgE antibodies to common food and environmental allergens.

The atopic march refers to the natural history of allergic or atopic manifestations characterised by a typical sequence of clinical symptoms and conditions appearing during a certain age period and persisting over a number of years. Characteristic of the clinical signs is that some features become more prominent with time whereas others diminish or disappear completely.¹ In general the clinical features of atopic eczema occur first and precede the development of asthma and allergic rhinitis (Fig. 1).

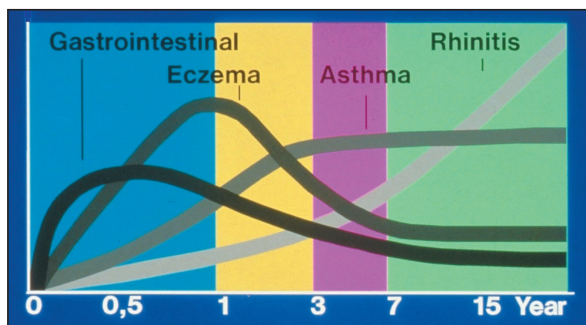


Fig. 1. Incidence of atopic disease in early childhood.

Several studies have demonstrated the atopic march from atopic eczema to the development of asthma and allergic rhinitis. In the UK Rhodes *et al.*² studied 100 infants from atopic families over a 22-year period. The

prevalence of atopic eczema reached a peak in 20% of children at 1 year of age and then declined to just under 5% at the end of the study. The prevalence of allergic rhinitis increased from 3% to 15% over the study period. Parent-reported wheezing increased from 5% during the first year of life to 40% of the study group at 22 years of age. Sensitisation to allergens as determined by skin-prick tests to 6 common allergens (*D. pteronyssinus*, mixed grasses, dog, cat, egg, milk) increased to a peak of 36% at 22 years of age. The major risk factor for adult asthma was early sensitisation to either foods in the first year of life or aeroallergens in the first 2 years of life.

A recent study in Germany³ has thrown further light on the atopic march. The large Multicentre Atopy Study (MAS) demonstrated the features of the atopic march in 1 314 children over a 7-year study period. A high-risk group comprising 38% of the children was identified where at least two family members had atopic diseases or a cord-blood IgE greater than 0.9 kU/l was present at birth. In this group 69% of infants who had developed atopic eczema by 3 months of age were sensitised to aeroallergens by the age of 5 years. The rate of aeroallergen sensitisation increased to 77% in all high-risk children. At 5 years, 50% of children with early atopic eczema and a positive family history of allergy had developed asthma or rhinitis compared with only 12% of children without eczema or a positive family history of allergy.

THE RELATIONSHIP BETWEEN ATOPIC DERMATITIS AND OTHER ALLERGIC DISORDERS

Dohi *et al.*⁴ studied 8 patients with asthma without atopic eczema and 8 patients with atopic eczema without asthma for house-dust mite sensitisation. Both groups had inhalation challenges to acetylcholine, a non-specific bronchodilator, and to house-dust mites. Both groups showed airway hypersensitivity to mites and the response of the atopic eczema patients to acetylcholine ranged from normal to the asthmatic range. These findings suggest that patients with skin sensitisation to house-dust mites can develop airway sensitisation to the same allergen.

Skin sensitisation evokes a systemic allergic response involving the upper and lower airways. Evidence that skin sensitisation can lead to airway sensitisation comes from an experimental study in a mouse model of allergy. Spergel *et al.*⁵ applied ovalbumin to the stripped skin of mice in order to induce dermatitis and specific IgE production. This group of mice was compared with a group where only saline was applied. The ovalbumin sensitised mice showed marked epidermal infiltration of CD3+T cells and eosinophils. Increases in the expression of both T-helper 2 (TH2) and TH1 cytokines (interleukin 4 (IL-4), IL-5 and interferon-gamma (IFN- γ)) were noted consistent with the increase of these cytokines in atopic eczema. The sensitised mice were subsequently challenged with a single exposure to inhaled ovalbumin and bronchoalveolar lavage (BAL) fluid was examined. The treated mice showed a significant increase in eosinophils in the BAL fluid compared with saline-sensitised mice. The ovalbumin mice

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were later shown to have a tenfold greater sensitivity to methacholine than the saline group. Thus the typical airway hyperresponsiveness associated with asthma followed cutaneous sensitisation in this group of mice. IgE-mediated allergic reactions are largely regulated by T-lymphocytes. Two types of T- helper lymphocytes have been identified, TH1 and TH2 cells.

It is generally accepted that the increased prevalence of allergic diseases during recent years is due to a disturbed TH1-TH2 balance leading to greater expression of the TH2 features resulting from the secretion of the cytokines IL-4, IL-5, IL-10 and IL-14. These cytokines are able to induce IgE production and to activate eosinophils leading to allergic inflammation. The exact reasons for the skewing of the TH1-TH2 balance towards the TH2 profile in allergic individuals is unknown but has been attributed to a Western lifestyle.

Decreased postnatal microbial stimulation results in an increased possibility of ongoing postnatal TH2 reactions. Modern lifestyle resulting in decreased bacterial stimulation (improvements in public health, reduction in family size with fewer infectious contacts and the early use of antibiotics) can more easily lead to this situation. This is the so-called 'hygiene hypothesis' which is the subject of much current interest.

EARLY MARKERS OF INCREASED RISK FOR ALLERGIC DISEASE

A number of early markers for atopy indicating an increased risk for the development of subsequent allergy have been identified. These include an elevated cord-blood IgE level (high specificity but low sensitivity), a positive skin-prick test to egg (Fig. 2) or house - dust mite in the first year of life and the detection of specific IgE to common foods and inhalant allergens during early infancy.⁶



Fig. 2. Positive skin-prick test to egg.

PREVENTION OF ATOPY

Primary prevention measures for atopic diseases involve the avoidance of early allergen exposure to certain foods and inhalants. These measures must be introduced from birth to be successful. Breastfeeding is recommended in spite of evidence that allergenic food fractions such as eggs and peanut will appear in breast milk if consumed by the mother. Breastfeeding appears to delay or prevent the occurrence of cows' milk allergy but hypo-allergenic diets for breastfeeding mothers only seem to be of value for infants already manifesting obvious allergic symptoms.⁷

Delayed introduction (>age of 6 months) of solid foods seems to be advisable in atopic infants and eggs should be avoided in infants already presenting with atopic eczema.⁸

Infants with atopic dermatitis should be a target group for the prevention of asthma. Several studies have

involved the early use of antihistamines in children with atopic eczema as a measure to reduce the risk of developing asthma and allergic rhinitis.

In the first of these trials Iikura *et al.*⁹ treated 121 children with atopic eczema (aged 1-36 months) with either ketotifen or placebo before the onset of asthma. After 1 year of study significantly fewer patients in the ketotifen group had developed asthma compared with the placebo group.

The ETAC (Early Treatment of the Atopic Child) study¹⁰ examined the role of cetirizine in delaying the atopic march. This was a prospective, randomised, double-blind parallel group and placebo-controlled study of 817 infants of 1-2 years of age. The infants had atopic eczema and a family history of atopy. The treatment duration was 2 years and total and specific IgE were measured at baseline and at regular intervals throughout the study period. The infants were treated with high-dose cetirizine or placebo. At the end of the study 40% of the infants had developed asthma. Children with early sensitisation to egg, milk, cat, grass or house dust had an increased risk for asthma. The study showed no significant difference between the cetirizine and the placebo-treated groups for the development of asthma.

However, the number of patients with house-dust mite sensitisation who developed asthma dropped from 51% in the placebo group to 28.6% in the cetirizine group.

Also 58% of children with grass sensitisation in the placebo group developed asthma while only 27.8% of the cetirizine group developed asthma. Although this study appears promising, more long-term information is required focusing specifically on allergic children. A second large (ETAC) study using cetirizine is currently under way and the results should be most informative.

In the future it is anticipated that therapies that modify the severity of atopic eczema in infants and young children will decrease the risk for the eventual development of asthma and thus prevent the consequences of the atopic march.

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