The allergic march

The allergic march refers to the natural history of allergic or atopic manifestations characterised by a typical sequence of clinical symptoms and conditions appearing during childhood and persisting for a number of years.

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The allergic march is sometimes referred to as the 'atopic march'. The former term is preferred as it is easier to understand by parents and patients when used during consultations in allergy practice.

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

Several studies have demonstrated the allergic march from atopic eczema to the development of asthma and allergic rhinitis.

The allergic march refers to the natural history of allergic manifestations characterised by a typical sequence of symptoms and diseases appearing during early childhood and persisting for a number of years. Characteristically some of the clinical conditions become more prominent with time while others diminish or disappear completely.[1] In general the clinical features of atopic eczema appear first and precede the development of asthma and allergic rhinitis (Fig. 1).

Several studies have demonstrated the allergic march from atopic eczema to the development of asthma and allergic rhinitis. Rhodes *et al.*[2] studied 100 infants from atopic families over a 22-year period in the UK. The prevalence of atopic eczema reached a peak in 20% of children at 1 year of age and then declined to just below 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. The major risk factor for adult asthma was early sensitisation to foods in the first year of life or aero-allergens in the first 2 years of life.

A recent study in Germany[3] has thrown further light on the allergic march. The large Multicentre Atopy Study (MAS) demonstrated the features of the allergic 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 allergic 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 aero-allergens by the age of 5 years. The rate of aero-allergen 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.

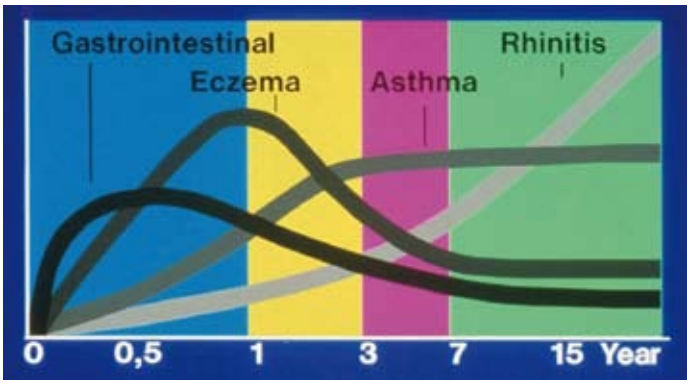

Fig 1. Progression of allergic symptoms at different ages.

Punekar *et al.*[4] followed up 24 112 children born in the UK in 1990 to the age of 18 years. The aim was to establish the sequential progression of multiple allergic diagnoses. Eczema was the most likely index condition with 60.7% of allergy sufferers being diagnosed with this condition first, followed by asthma, which in turn is followed by rhinitis.

In an interesting study Barberio *et al.*[5] followed up 692 children with asthma alone for 9 years. Some 20% of these children developed atopic eczema at 9 years. These authors propose that there may be a 'reverse' allergic march where some atopic children first present with asthma and only later on develop eczema.

A recent Australian study[6] showed that eczema in the first 2 years of life is associated with an increased risk of childhood asthma in boys, but there is no evidence of this in girls. Boys appear to be at greater risk of developing the typical progression of allergic conditions associated with the allergic march.

Relationship between atopic eczema and other allergic disorders

Atopic eczema is one of the most common skin conditions seen in children. Eczema has been proposed as an 'entry point' for subsequent allergic diseases, suggesting the possibility that effective management of eczema could prevent the development of respiratory allergy or at least reduce the severity of asthma and allergic rhinitis. Eczema and asthma share a common genetic and pathological basis. Little is known about the natural course of eczema and the potential succession of atopic phenotypes in childhood. In fact, recent genetic and epidemiological data have raised the question of whether eczema either progresses to asthma or is part of a syndrome consisting of both diseases.[7]

In non-sensitised children eczema, but not wheeze or rhinitis, is a predictor for subsequent development of sensitisation.[8] This suggests that early childhood eczema, rather than wheeze and rhinitis, may promote subsequent allergen sensitisation and again raises the possibility that early management of eczema may reduce the prevalence of sensitisation in childhood and the likelihood of developing the allergic march.

Dohi *et al.*[9] 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 nonspecific 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.

There may be a 'reverse' allergic march where some atopic children first present with asthma and only later on develop eczema.

Skin sensitisation causes a systematic 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. Spergal *et al.*[10] 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 IL-4, IL-5 and interferon gamma (IFN-y) were noted, consistent with the increase of these cytokines in 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 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 an urbanised 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.

Epidemiological trends of allergic diseases and asthma in children reveal a global rise in their prevalence over the last 50 years. Their rapid rise, especially in urban areas, suggests that recent changes in modern environments and/or lifestyles underlie these trends.[11] Naturally occurring microbial exposures in early life may have prompted early immune maturation and prevented allergic diseases and asthma from developing. Children reared in modern urban lifestyles relatively devoid of a natural microbial burden may have under-stimulated immune systems in infancy, thereby allowing for the 'allergic march'. Early life exposure to endotoxins and other microbial products in the environment, e.g. living on a farm with exposure to livestock, unpasteurised milk and manure, may reduce the risk of developing allergies in children.[12]

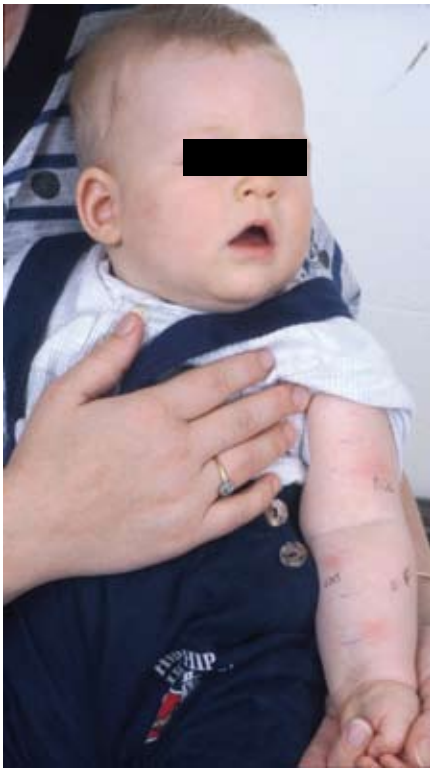

Fig. 2. Positive skin prick tests for egg in infant of 9 months.

Epidemiological studies of allergic disorders in Africa suggest another factor – that of an 'urban diet'– which may account for the rapidly increasing numbers of allergic children in African urban areas.[13]

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 to house-dust mite in the first year of life and the detection of specific IgE to common food and inhalant allergens during early infancy.[14]

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 cow's milk allergy but hypo-allergenic diets for breastfeeding mothers only seems to be of value for infants already manifesting obvious allergic symptoms.[15]

Delayed introduction (before the age of 6 months) of solid foods seems to be advisable in atopic infants. Eggs should be avoided in infants already presenting with atopic eczema.[16]

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.*[17] 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) study[18] examined the role of cetirizine in delaying the atopic march. This was a prospective study of 817 infants 1 - 2 years of age. The infants had atopic eczema and a family history of atopy. 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 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.

New insights into the use of probiotics in the prevention of the atopic march appear interesting.[19] Probiotics are cultures of beneficial bacteria that positively affect the host by enhancing the microbial balance and restore normal intestinal permeability and gut microecology. They also improve the immunological barrier function of the intestine and reduce the generation of proinflammatory cytokines characteristic of allergic inflammation. In clinical trials probiotics appear to be useful for the treatment of various clinical conditions such as food allergy, eczema and allergic rhinitis and in the primary prevention of atopy. It is postulated that in the future probiotics may be used in the primary prevention of the allergic march and asthma.

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In a nutshell

- The allergic march refers to the progression from atopic eczema to asthma in allergic children.
- Conditions may not occur simultaneously but occur and disappear with time.
- Boys are more susceptible to the allergic march than girls.
- A 'reverse' allergic march may occur, e.g. asthma appears first and eczema later on.
- The skin sensitisation occurring in eczema appears to be the trigger for the subsequent development of the other allergic conditions.
- Eczema is the most common atopic condition in children and precedes the development of asthma and rhinitis.
- The 'hygiene hypothesis' is important in explaining the rapid increase in allergic conditions in urbanised children.
- Breastfeeding may prevent or delay the occurrence of the allergic march.
- Delayed introduction of solid foods (>6 months) may help to prevent the onset of eczema.
- Probiotics appear to have promise in preventing the allergic march.

Single Suture

Benign testicular tumours and genetic disease

Genetic diseases are more common in the children of older fathers, but no-one is quite sure why. Recent research suggests that part of the answer may be that older men have more benign testicular tumours, which may give rise to sperm that contain disease-causing mutations.

Anne Goriely of the University of Oxford and her colleagues took tumour cells from men with benign testicular tumours and looked for specific mutations in the *FGFR3* and *HRAS* genes. These mutations have been linked to rare developmental diseases such as achondroplasia and Costello syndrome. They have also been linked to some stillbirths.

The team found the same mutations in tumour cells, but not in normal sperm-producing cells that were found close to the tumour cells. They concluded that the sperm made by these cells contained the disease-linked mutations and that the mutations may be driving the growth of the tumours.

Goriely A, *et al. Nature Genetics* 2009; 41: 1247-1252.