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THE ATOPIC MARCH

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ABSTRACT

The progression of atopic diseases, such as atopic dermatitis, asthma, allergic rhinitis and food allergies are generally seen during childhood and they are known as 'the atopic march'. There are various risk factors for developing atopic diseases including genetics, food allergens, late food introduction to the infant, life style and hygiene. There are some immunologic contributors to this disease. Different therapeutic procedures and newer methods have been introduced.
In this article, the author explains the definition of atopic march, pathophysiology, clinical features, epidemiology and therapeutic approaches.

Keywords: Dermatitis, atopic, asthma, hypersensitivity

INTRODUCTION

Ulrich Wahn explains the term "atopic march" as "the natural history of atopic manifestations, which is characterized by a typical sequence of immunoglobulin E (IgE) antibody responses' and clinical symptoms that appear early in life, persist over years or decades and often remit spontaneously with age" (1). Asthma, atopic dermatitis (AD), allergic rhinitis and food allergies are the atopic diseases (2). These diseases affect nearly 20% of the population in the developed countries (3). These diseases commonly progress first from atopic dermatitis to asthma, then to allergic rhinitis. But this is not always the way of progression (2). Atopy can be defined as the natural tendency (personal/familial) to develop IgE antibodies and subsequent sensitization in response to environmental stimuli (4). It is considered that underlying atopy is critical in asthma, AD and allergic rhinitis (4, 5).Both genetic and environmental factors are responsible for development of these diseases. These diseases may develop sequentially along a common atopic pathway. There may be a relationship between eczema and atopic respiratory disorders. Different cross sectional and longitudinal studies support the atopic march. Experimental findings of mouse models also support the evidence of atopic march (3).

EPIDEMIOLOGY

Normally there are three proposed pathways of atopic march. Firstly atopic dermatitis can lead to asthma and allergic rhinitis. Secondly, asthma can lead to atopic dermatitis. Thirdly, asthma can lead to rhinitis without atopic dermatitis. Food allergy is also associated with these disorders (2). However in 2008 Barberio et al. reported a possibility of a reverse atopic march. In this proposal asthma develops first and atopic dermatitis follows (7).

Atopic Dermatitis is associated with increased total IgE serum levels in 70-80% of patients (8).Its prevalence is 7% to 30% in children and 2% to 10% in adults (9). The highest level of sensitization in Atopic Dermatitis and asthma occurs in first two years of life and in late childhood the prevalence of these diseases decrease. On the other hand, the prevalence of asthma and allergic rhinitis increases with time. Sensitization to inhalant allergens rises with age (10).

Kulig et al. reported that half of the children with atopic dermatitis developed allergic respiratory diseases at the age of five (11). Shen et al. (12) classified the eczema into preschool and late-onset.While following a birth cohort for seven years, they reported that late-onset group had higher risk of developing asthma or allergic rhinitis five years later. Ricci et al. (13) found that the

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severity and good control of AD can be predicted for the onset of asthma.

Ohshima et al. conducted a follow up study on 169 Japanese children. They found that 35% of children developed asthma (14). More than half of the children with AD develop asthma and more than three-fourth of them develop allergic rhinitis during the first six years of life, as reported by Spergel JM (9).

Lowe AJ et al. in 2008 reported that eczema in early life in boys is associated with an increased risk of childhood asthma. In girls, the association was weak (15). Meanwhile other studies also reported that boys have great risk of asthma during childhood (16, 17).

The association between a higher BMI and symptoms of wheeze and cough in children has been observed in different studies (18-20).

There are six times the odds of developing asthma associated with food allergy than patients without any food allergy (21, 22). Patients with positive family history of food allergy have a high risk of developing food allergy in subsequent period (23).Monozygotic twins have higher risk of developing peanut allergy than dizygotic twins. The sibling of an affected person of allergy has ten times more risk to develop allergy (24).

While studying about the worldwide incidence of atopic diseases, we found that developed countries have reached a plateau, while in the developing countries the incidence is increasing (2, 25).However a study found that in Australian school children, the prevalence of asthma increased from 12.9% to 38.6% from 1982 to 1997 (26).The prevalence of AD in children increased from 17.3% to 27.3% from 1986 to 2001 and from 5.3% to 12.0% from 1964 to 1986 in Denmark and Scotland respectively (27, 28).

In developing counties, there are also similar studies. In Colombia, a study on 5.978 patients found that, 12% of the patients had asthma, 32% had allergic rhinitis and 14% had atopic eczema (29). In a longitudinal cohort study in Taiwan, the 8-year-prevalence of atopic dermatitis, allergic rhinitis and asthma was 6.7%, 26.3% and 11.9%, respectively (30). A study conducted among North Indian population discovered that atopic was the commonest dermatitis (28.46%) in children in a pediatric dermatology clinic (31). In 1999, a study in Bangladesh showed 5.2% of the country's population is suffering from asthma (32).

These differences may be due to differences in extent of some factors like urbanization, industrialization, life style, latitude, disease severity, socioeconomic status and ethnicity (2).

PATHOPHYSIOLOGY

At first there is initial sensitization to the allergens in the patient's life. This triggers the activation of the epithelial cells, which as result release chemotactic factors for dendritic cells thymic stromal lymphopoietin (TSLP) and tumor necrosis factor alpha (TNF-alpha), that induce the expression of adhesion molecules at the endothelium (2, 33). Dendritic cells have high affinity IgE receptors (FcERI) by which they internalize the allergen, which lead the naive T cell activation in Th1 (by IL-2 and IFN-alpha), and Th2 (by IL-4) cells in the lymph nodes. Then filaggrin mutations lead to a decrease in Th1 response and an increase in Th2 response and release of IL-5 and IL-13 which trigger eosinophilic infiltration and hyperproduction of IgE. In the nasal and bronchial mucosa, the Th2 response stimulates the allergen response. This leads to eosinophil infiltration, IgE hypersecretion, mast cell proliferation, epithelial cell activation, mucus hypersecretion and smooth muscle spasm(5, 34).

Harskamp et al. describe the immune response in atopic dermatitis skin. Infiltration of T cells in the skin due to microbial toxins, allergens, and mechanical trauma leads to IgE production (induced by IL-13), IL-4 production. On the other hand, IFN-gamma decreases production of IgE (35).

Dharmage SC et al. (36) proposed the mechanism of atopic march. According to them, genetic predisposition like filaggarin null mutation and environmental risk factors like infection leads to childhood eczema. Due to trauma and defective skin barrier there is microbial and allergen entry , which lead to epicutaneous sensitization. Th2 memory cells migrate into the nasal and bronchial lymphoid tissue and causes airway inflammation. Allergen re-entry and over expression of TLSP this lead to bronchial asthma and allergic rhinitis.

According to the "Hygiene Hypothesis" proposed by David Strachan in 1989, cleaner environment decreasing infections and in developed countries over the last few years have led to a higher prevalence of atopic diseases (28).

CLINICAL FEATURES

a) Atopic Dermatitis:

The first manifestations are intensely pruritic erythematous papules and vesicles on the face. There is widespread cutaneous dryness. Edema of affected areas leads to oozing and crusting. There might be lymphadenopathy in affected children. The disease is sometimes self resolving. Atopic dermatitis in adults predominantly involves the flexural folds, the face and neck, the upper arms and back and the dorsum of the hands, feet, fingers and toes. As a result of superimposed Staphylococcal infection there is crusting and exudation (2, 3, 37).

b) Asthma:

Common features of asthma are cough, chest tightness, breathlessness and wheeze. It may have diurnal variations and the symptoms are worse at early morning although there is a variety named nocturnal asthma (38). In some patients there is low forced expiratory volume in 1 second (FEV1) along with eosinophil and Th2 infiltration in bronchial tissue (2).Kumar R et al. have shown that fractional exhaled nitric oxide (FeNO) is marker of lower airway inflammation and higher level of FeNO in allergic rhinitis patients can be used as a predictor of the onset of asthma (39).

c) Allergic Rhinitis:

Watery rhinorrhea, nasal obstruction, nasal itching and sneezing are the main symptoms of allergic rhinitis (40).

d) Food Allergy:

Incidence of food allergy is higher at first 2 years of life (41). Also it has a wide variety of signs and symptoms. Skin reactions are the most common which include acute urticaria, angioedema and erythema. Laryngeal edema, rhinorrhea and bronchospasm are the symptoms of respiratory tract involvement and nausea, vomiting, abdominal pain and diarrhea are the symptoms of gastro-intestinal system. Anaphylaxis is the most serious condition. It could trigger peanuts, tree nuts and shellfish are the most common reason of anaphylaxis (42).

Development of asthma, rhinoconjuctivitis and eczema are triggered by cow milk allergy (43).

THERAPEUTIC APPROACHES:

Gordon BR et al. (44), proposed that supplementation of dietary probiotics, exclusive breast feeding and inhalant allergen immunotherapy (Subcutaneous/Sublingual) are the ways of preventing allergy. It has been shown that high TGF-b levels in breast milk protect the child from development of allergies .For allergic asthma and rhinitis 2013 PRACTALL has confirmed subcutaneous and sublingual immunotherapy (45). Matricardi PM et al. in their meta analysis have shown that in controlling seasonal allergic rhinitis subcutaneous immunotherapy is at least as potent as pharmacotherapy (46).

In 2006, the PRACTALL consensus paper proposed step-based algorithm for eczema therapy (depending on severity) (47) (Table 1).

Omalizumab, which acts by binding with free IgE and preventing free IgE from attaching to high-affinity IgE receptor, effectively reduces exacerbation rates of asthma. This drug is indicated for patients who are 6 years and older, with moderate to severe asthma (48). It can be used in allergic rhinitis also although its high cost may lower its compliance (49).

Leukotriene receptor antagonists (montelukast) are recommended for the treatment of asthma. In an open randomized clinical trial in Bangladesh, it has been showed it can be used in atopic dermatitis (50).

Prebiotics, probiotics and breast-feeding balance improve intestinal processing of antigens ingested in the diet. By increasing the uptake of antigens by Peyer's patches, they also reduce intestinal inflammation and IgE production. This prevents developing an exaggerated Th2 immune response. Otherwise like bronchial tissue, there would be systemic sensitization and major enhancement and distribution to tissues (51).Breastfeeding increases the number of immunoglobulin secretor cells and thus protects against atopic diseases (52). By increasing the Bifidobacterium populations, probiotic controls Clostridium/Bifidobacterium ratio. Probiotics decreases the risk of development of allergies by producing anti-inflammatory cytokines and inducing the regulatory cell responses (53).

Table 1: Proposed eczema therapy by PRACTALL (PRACTical ALLergy) consensus paper (47)

Sl No	Type of Eczema	Proposed Treatment
1	Dry skin	Hydration
2	Mild eczema	Low potency topical corticosteroids
3	Moderate eczema	Mid potency topical corticosteroids
4	Severe eczema	High potency topical corticosteroids
5	Resistant eczema	Systemic Therapy

RESULTS

The beauty of science is that it has no boundary. Medical science cannot be an exception for this. We are getting new information constantly which enlightens us about atopic diseases. Atopic march is a combination of multiple diseases and it needs multimodal therapeutic approaches. In spite of having promising therapies like monoclonal antibodies, sublingual therapy, immunotherapy, prebiotics and probiotics, more studies should be done to find out the exact "magic bullet" to fight against this atopic march.

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