The Atopic March. A Literature Review

Juan F. Salazar-Espinosa.[1]

Abstract

The atopic march is defined as the progression of atopic diseases, generally during childhood, such as atopic dermatitis, asthma, allergic rhinitis and food allergies. The main risk factors for developing these atopic diseases include genetics, aeroallergens, food allergens, late food introduction to the infant, and living in developing countries. The immunologic contributors to this problem include the Th2 response, epigenetics, and lack of certain factors like thymic stromal lymphopoietin (TSLP) and filaggrin. As a whole, the therapeutic approach has been changing during recent years because of the discovery of new factors involved in this problem. This article explains the definition of atopic march, the immunological pathway, clinical features, epidemiology and therapeutic approaches to create a context for the broader understanding of this important condition.

Keywords: Atopic dermatitis; asthma; allergy; atopy; Th2 response; atopic march (Source: MeSH, NLM)

Introduction

Atopic march is an epidemiological phenomenon involving atopic diseases and describes the process by which some atopic diseases interrelate through a patient's life. These atopic diseases include asthma, atopic dermatitis (AD), allergic rhinitis, and food allergies. The common progression of these diseases is from atopic dermatitis to asthma and then allergic rhinitis; this is not, however, the only way that this condition progresses. The atopic march has some associated risk factors that have been described in epidemiological studies from different countries. There exist, however, some differences in the disease epidemiology depending on the socioeconomic status of the country studied.[1]

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The pathogenesis of the atopic processes share a common systemic Th2 response and epigenetic factors. Related to Th2 response are other immunological factors like filaggrin deficiency and thymic stromal lymphopoietin (TSLP) overexpression which have been demonstrated in mouse models and serve as therapeutic targets.[2] These exist in addition to the ratio between histone acetyl transferase (HAT) and histone deactetylase (HDAC) as the most important epigenetic factors involved in allergies.[3] The therapeutic approach has multiple pharmacological options, including subcutaneous and sublingual immunotherapy, prebiotics, probiotics and, most recently, anti-IgE monoclonal antibodies. The multitude of therapeutic approaches seen in atopic march may be explained by the observation that there are different preferences for various treatments among different medical specialties.[4]

Search Strategy and Selection Criteria

A literature search was performed using MEDLINE MeSH terms "eczema", "asthma", "food allergy" and "allergic rhinitis" where each term was combined with "atopic march" using the PubMed search builder. A total of 177 articles were found. Following filtering by author criteria (publication within last 20 years, English language, and the existence of a relation between at least two atopic diseases), 32 articles remained and an additional 22 articles were retrieved from references. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[5]

Immunological Pathway

The first step in atopic march pathogenesis is allergen exposure or the first sensitization episode in a patient's life, leading to the activation of the epithelial cell triggers and the release of TSLP and tumor necrosis factor alpha (TNF-α). These are chemotactic factors for dendritic cells, which induce the expression of adhesion molecules at the endothelium.[6] Dendritic cells internalize the allergen through their high affinity IgE receptors (FcεRI) and migrate and mediate the naïve T cell activation in Th1 cells, which releases interleukin-2 (IL-2) and interferon-gamma (IFN-γ), and Th2 cells, which releases IL-4, in the lymph nodes. Following this is a process called scratch-rubbing cycle where a skin barrier dysfunction (filaggrin mutations) leads to a decrease in Th1 response and an increase in Th2 response with the release of IL-5 and IL-13. This triggers the increase in eosinophilic infiltration with an immunoglobulin E (IgE) hyperproduction. The Th2 response enhances the allergen response in the nasal and bronchial mucosa, leading to eosinophil infiltration and IgE hypersecretion in addition to the mast cell proliferation, epithelial cell activation, mucus hypersecretion, and smooth muscle proliferation observed in asthma.[7,8]

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Filaggrin is a protein produced in the stratum corneum of the epidermis that plays an essential role in the formation of the protective skin barrier by the prevention of water loss and entry of microbes into the inner layers of the skin. The main mechanism that involves filaggrin in the allergic disease pathogenesis is the enhancement of the Th2 systemic response, which leads to the susceptibility of skin, bronchial, nasal, and gastrointestinal epithelia to the development of atopic diseases, especially atopic dermatitis and asthma.[9] Importantly, it has been discovered that the maintenance and repair of the epidermal barrier in infants with AD may prevent the subsequent development of asthma.[10]

The TSLP is an IL-7-like interleukin which is produced in the skin, gut, lungs and thymus and contributes to the activation of dendritic cells without the allergen molecule, the predomination of Th2 differentiation, and the upregulation of this response by the mast cells in the nasal epithelium, leading to the development of allergic rhinitis.[11] *Figure 1* shows the process involved in the generation of atopic march and some of the factors that may contribute to the development of atopic diseases.

Takai et al., suggested that environment, infection, and/or self-derived toll-like receptor ligands contribute to the initiation and/or amplification of Th2-type skin inflammation, including atopic dermatitis, through the induction of TSLP expression in keratinocytes. This finding is helpful for understanding the role of the gene–environment interaction relevant to allergic diseases.[12]

One of the main factors in the epigenetics of the atopic march is GATA-3, which is activated by T-cell receptor (TCR) and IL-4 receptor activation and maintains its own expression through positive feedback. GATA-3 induces permissive histone and chromatin changes at the Th2 Locus Control Region (LCR) which enhances the Th2 response and suppresses the Th1 response against the allergens. Another important factor is FFOXP3, which regulates the T regulator cell action by promotiing the binding of demethylation factors and the consequent lack of toleration to self and exogenous antigens.[3]

Mouse Models in Atopic March
Zhang et al., carried out investigations in which they injected

mice with intra-peritoneal ovalbumin and measured the TSLP produced by keratinocytes. TSLP is the mediator of the skin inflammation triggered by an allergen and consequent sensitization. Additionally, another mouse model demonstrates a relation between high skin keratinocyte-derived TSLP, high TSLP serum levels and the upregulated epicutaneous sensitization, and aggravated allergic asthma generated upon allergen challenge in airways.[13,14] However, Demrhi et al., demonstrated that during the first 3 years of life, the plasma circulating TSLP of children with eczema, allergen sensitization, or wheezing was not statistically associated with the manifestation of these symptoms.[2] The TSLP is implicated in mouse models for the development of atopic diseases. This supports the utilization of TSLP inhibition as a proposed therapeutic option to prevent or limit allergen sensitization and thus halt the progress of the atopic march.[15]

Clinical Features
Atopic Dermatitis
There are three established phases in the progression of AD: an infantile phase (from birth to 2 years of age), a childhood phase (2 years to puberty) and the adult phase (from puberty to the adulthood). The first manifestations correspond to erythematous papules and vesicles that typically begin on the face and are intensely pruritic. There is also edema of affected areas, leading to oozing and crusting. The childhood phase of AD additionally presents with lichenified papules and plaques, representing a more chronic disease. Lymphadenopathy might be a prominent feature in affected children. Although the disease sometimes tends to self-resolve, there is an adult phase of AD which predominantly involves the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. Weeping, crusting, and exudation might occur, usually as a result of superimposed Staphylococcal infection.[10]

Asthma, Allergic Rhinitis and Food Allergy
A wide array of risk and protective factors including hygiene, infections, outdoor and indoor air pollution, allergen exposure, breast-feeding practices, genetic factors, nutrition, and obesity play a multifaceted role in shaping the observed worldwide trends of respiratory allergies.[16] Some of these patients never present with any clinical symptoms throughout their lives, although airway hyperresponsiveness, shortness of

Figure 1. A proposed pathway to explain the atopic march from childhood eczema to the development of asthma and allergic rhinitis.[4]
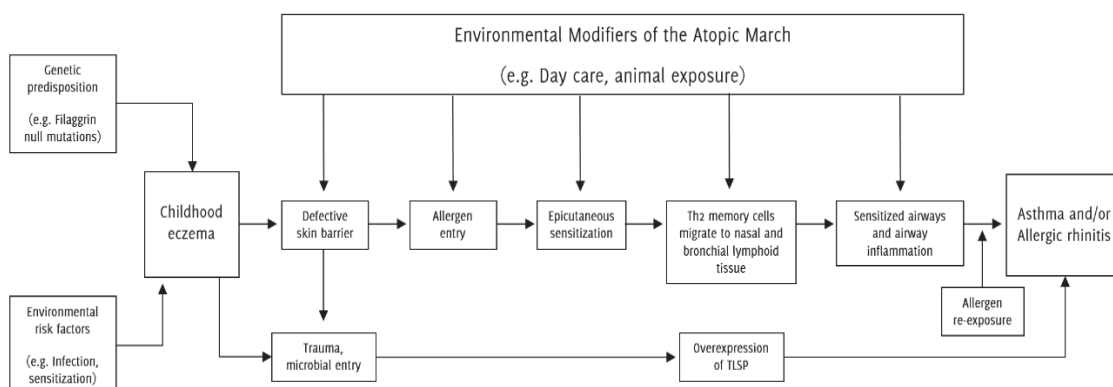
breath, wheezing which causes chronic airflow limitation, and decreased lung function are common. Examinations of these patients reveal low forced expiratory volume in 1 second (FEV1) together with an increased eosinophil and Th2 infiltration in bronchial tissue. An Indian study shows that fractional exhaled nitric oxide (FeNO) is a marker of lower airway inflammation; therefore, significantly higher FeNO levels in atopic allergic rhinitis patients may predict the onset of asthma.[17] For allergic rhinitis, there are four main symptoms: watery rhinorrhea, nasal obstruction, nasal itching, and sneezing.[18] Like asthma, allergic rhinitis could be classified as mild or moderate-severe based on severity.[19-21]

Food allergy is known to be one part of this atopic process and its incidence tends to be higher at 2 years of life.[22] A clinically relevant event is cow milk allergy, which is proposed as a risk factor for the development of asthma, rhinoconjuctivitis and eczema.[23] Food allergy is clinically well characterized by urticaria, angioedema, vomiting or anaphylaxis. These clinical manifestations are present within two hours following the food ingestion. There are some foods that mediate this disease like peanuts, cow milk, and eggs. Besides these symptoms other clinical manifestations include a scratchy throat, hives anywhere on the body, swelling of the eyelids, face, or tongue, nausea, cramps, vomiting, diarrhea, nasal congestion, and shortness of breath or wheezing due to the exposure to a hapten of the food.[24] A controversial dilemma, which began in the 1970s and remains unresolved, includes whether the introduction of food antigens into the diet either early or later in life has any effect on the development of food allergy, atopy or allergic asthma. This is explained by the antigens present in the food (cow milk) which are captured by the Peyer patches and generate a Th1 response in healthy children.[25,26] Some studies concluded that the early food introduction and six months breastfeeding after birth are poor prognostic factors and predispose the infants to the development of food allergy.[27] However, a population-based prospective cohort study using 3781 children performed in 2013 established that long term breastfeeding and the early introduction (with specific timing) of wheat, rye, oats, barley cereals, fish, and eggs is preferred in that it protects against the development of asthma and allergic rhinitis from a few months following birth to the age of five. This finding suggests a potential conflicting effect of breastfeeding on different asthma phenotypes.[28]

Epidemiology

There are three established progressive pathways in this process: (1) atopic dermatitis to asthma and allergic rhinitis, (2) asthma to atopic dermatitis, and (3) asthma to rhinitis without the presence of atopic dermatitis. Food allergy is an associated risk factor in the development of these three conditions, and for this reason it can be found in any phase of the atopic march. However, a reverse atopic march has been proposed, with patients developing asthma first with the later appearance of atopic dermatitis. This is demonstrated in a prospective study that followed nearly 700 children aged six to nine years with asthma alone for nine years. Twenty percent of the children developed atopic dermatitis at the end of nine years.[29]

Atopic dermatitis has a prevalence that ranges from 7% to 30% in children and from 2% to 10% in adults.[30] AD and food aller-

gies have the highest incidence in the first two years of life. Sensitization to inhalant allergens is rare at that time of life. In later childhood, the prevalence of AD and food allergies decreases while the prevalence of asthma, allergic rhinitis, and sensitization to inhalant allergens rises.[31] Shen et al., followed a birth cohort for seven years and classified the eczema into preschool and late-onset and examined the correlation between the development of asthma and allergic rhinitis. Results showed that the 36 month old group (late-onset group) had the highest risk for developing asthma or allergic rhinitis five years later. This indicates that it is necessary to evaluate the associated risk factors at the first presentation of atopic disease in order to predict its progression in subsequent years.[32]

A longitudinal study of a prospective birth cohort of 620 children described a higher prevalence of atopic march in boys than girls by a mechanism that remains unknown.[33] Higher body mass index (BMI) is a risk factor for atopy, wheezing, and cough in girls only.[34] However, higher BMI is not a risk factor for asthma or airway hyperresponsiveness in either boys or girls. As the atopic march is a disease of interrelation, the etiology is not the same for all components. In fact, it is described that parents with asthma give birth to children with four times the odds of developing food allergy.[35] The food allergy is associated with six times the odds of developing asthma compared to patients without any food allergy.[36,37]

It is believed that developed countries have reached a plateau in the incidence of asthma while in developing countries the incidence of these diseases is still increasing.[16] Van der Hulst et al., conducted a systematic review which assessed the risk of developing asthma in children with atopic eczema during the first four years of life and found that the prevalence of asthma at the age of six years in eczema cohort studies was 35.8% for inpatients and 29.5% for a combined group of inpatients and outpatients.[38] A Norway study, with 4780 children divided into two groups depending on whether they were followed from two years old to six years old (n=2192) or not followed (n=2588). Among children with follow-up data at six years, the prevalence of eczema, asthma, and wheezing at two years was 17.8%, 6.5% and 25.3%, respectively. Among children with follow-up data at six years, the odds ratio between eczema at two years and current asthma at six years was 1.95. When the age of onset for eczema was included in the model, an onset before four months of age was significantly associated with asthma at six years (OR= 4.51).[39]

Meanwhile, in middle-income countries, a study conducted during the 2009-2010 period in Colombia collected information from 5,978 patients and analyzed three principal atopic diseases: allergic rhinitis, atopic eczema and asthma. It was discovered that 12% of the patients had asthma, 32% had allergic rhinitis and 14% had atopic eczema and demonstrated an increased presentation of symptoms characteristic of these conditions.[40] In Taiwan, Hwang CY et al., collected longitudinal cohort information through the medical institution databases that followed patients for eight years. Overall, 66,446 patients were diagnosed with atopic dermatitis and 49.8% of them had concomitant allergic rhinitis and/or asthma. The overall 8-year prevalence of atopic dermatitis, allergic rhinitis, and asthma was 6.7%, 26.3% and 11.9%, respectively.[41] In addition, Waked

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et al., administered standardized written questionnaires to 5- to 12-year-old students at 22 schools. In total, 3,909 individuals were analyzed. The prevalence of diagnosed asthma (4.8%) was low, while the prevalence of allergic rhinitis was 21.2% and that of eczema was 11.8%. Marked variations and differences were found across the governorates in Lebanon, with the lowest prevalence of diagnosed asthma found in Bekaa (1.8%) and the highest prevalence in Beirut (11.6%).[42] The differences in the prevalence of atopic diseases between developing and developed countries likely reflect the differences in the extent of urbanization, industrialization, life style, latitude, and disease severity. Other possible factors, such as socioeconomic status or ethnic group, may also contribute to this variation.

Therapeutic Approaches

Gordon BR et al., suggested that it is possible to interrupt the atopic march to prevent allergy, especially asthma, with three possible interventions: (1) supplements of dietary probiotics, (2) exclusive breast feeding during the first few months of life, which provides protection from the development of allergies through the high transforming growth factor beta (TGF-ß) levels in breast milk, and (3) treatment with inhalant allergen immunotherapy by either subcutaneous or sublingual immunotherapy, both of which decrease the risk of progression to asthma and allergic rhinitis. From current data, if these strategies were widely employed, there would likely be a substantial reduction in future asthma cases.[43] This is supported by the 2013 PRACTALL trial, which has established a subcutaneous immunotherapy and a sublingual immunotherapy for allergic asthma and rhinitis based on scores given for symptom reduction, improvement in quality of life, and the induction of favorable changes in specific immunologic markers.[44] In a randomized controlled trial, Passalacqua et al., found immunotherapy for allergic rhinitis to be a preventive factor for asthma development due to the impairment of new sensitizations.[21]

Anti-IgE treatment with omalizumab is another therapeutic option used for rhinitis where its mechanism of action is by specifically binding to IgE with the consequent interruption in the allergic response. New information suggests that the combination of immunotherapy with omalizumab is a good strategy to treat allergic rhinitis.[45] However, when the monoclonal antibody XmAb7195, human leukocyte-engrafted mouse like omalizumab, was administered, it selectively reduced serum human IgE levels and was much more effective than omalizumab in suppressing IgE levels by dual pathways involving IgE neutralization and a CD32b-dependent inhibition of the formation of IgE-secreting plasma cells. This demonstrates new advances in therapeutic approaches by inhibiting one of the main factors in the development of atopic diseases (i.e. IgE).[46]

Prebiotics, probiotics and breast feeding balance the "Th2 bias", thus improving intestinal processing of antigens ingested in the diet and reducing intestinal inflammation and IgE production by increasing the uptake of antigens by Peyer's patches. This prevents the development of a Th2-exaggerated immune response which would lead to the systemic sensitization and major enhancement and distribution to tissues like bronchial tissue.[47] Breastfeeding is recommended to be complemented with probiotics because it increases the number of of immunoglobulin secretor cells, which is one of the main factors involved in protection against atopic problems.[48] It is theorized that probiotics act at the Clostridium/Bifidobacterium ratio by increasing the Bifidobacterium populations.[49] Moreover, according to Vitaliti et al., the use of probiotics induces the enhancement of regulatory cell responses to produce more anti-inflammatory cytokines which may decrease the likelihood of the development of allergies.[50] In 62 mother–infant pairs, *Lactobacillus rhamnosus GG* administered during the four weeks before the infant's birth and during breast feeding (first three months) increased the immuno-protective potential of breast milk, as assessed by the enhancement of anti-inflammatory TGF-ß2 in the milk of the mothers receiving probiotics vs. placebo.[51] Furthermore, the probiotics are considered to be the main factors involved in the prevention of atopic march.[52] Prebiotics are nondigestible food products (most commonly oligosaccharides) that stimulate the growth or activity of Bifidobacteria and other "friendly" bacteria in the colon. However, further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula fed infants. It is unclear whether the use of prebiotic should be restricted to infants at high risk of allergy or whether they may have an effect in low risk populations or on other allergic diseases including asthma.[53]

Conclusion

New information constantly expands our understanding of allergen-induced diseases; this information is reflected in epidemiological studies which demonstrate a non-linear development and relationship of the various components of the atopic march. The atopic march should be understood as an immunological imbalance in Th2 responses together with factors like the TSLP, lack of filaggrin, and epigenetics (FOXP3 and GATA-3). The epidemiologic data tends to be in accordance with data obtained using mouse models, which provide insights to the development of additional epidemiologic studies. In regard to the therapeutic approach, atopic march should always be understood as a multiple-disease problem and not simply as a single atopic disease. The monoclonal antibodies, sublingual therapy, immunotherapy, prebiotics and probiotics are proving to be promising therapies which need further investigation to demonstrate their action against the immunological factors involved in this disease.

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