Review Article

Allergy/Atopic March and United Airway Disease: What We Know and What We Need to Know?

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Abstract

"Allergy/atopic march" refers to a typical sequence in which the allergic or atopic features appear at a certain age, and may or may not persist thereafter. In general, atopic dermatitis or atopic eczema occurs first, which progresses to immunoglobulin-E-mediated food allergy, asthma, and then allergic rhinitis (AR). However, this sequence may not be conspicuous in many cases. AR is an independent risk factor for asthma; in fact, AR often precedes that of asthma. United airway disease (allergic rhino-bronchitis) means the coexistence of AR and asthma. This has been shown in clinical and experimental studies, which suggest a similar immune pathology between the upper and lower airways in allergic subjects. In children with asthma, coexistent AR leads to an increased risk of asthma exacerbation leading to hospitalization and/or emergency visits as well as increased health-care cost. Treatment of AR in asthmatic children results in a lowered risk of asthma-related hospitalizations and emergency visits, and improved quality of life. In this article, we have discussed the current evidence for the clinically relevant effects that allergic conditions (from food allergies to atopic march, united airways disease, and AR) can have on children with asthma along with the future of allergic diagnosis (precision allergy molecular diagnosis) and allergen immunotherapy.

Keywords: *Atopic march, allergic rhino-bronchitis, children, precision allergy molecular diagnosis, component-resolved diagnostics, allergen immunotherapy*

Introduction

"Allergic/atopic march" refers to the natural progression of T-helper type 2 (Th-2) cell-mediated allergic diseases in an individual, typically starting in infancy or childhood. It often begins with atopic dermatitis (AD) or atopic eczema in infancy, which is followed by immunoglobulin-E (IgE)-mediated food allergy, and then asthma and allergic rhinitis (AR or hay fever) later in childhood or adolescence [Figure 1].[1] Recently, "eosinophilic esophagitis" has been added to the spectrum of "allergic/atopic march."[1] Although the term "march" suggests a sequential progression (where one condition leads to another over time), not all individuals with AD will develop asthma or AR (or hay fever). A recent study examining two birth cohorts in latent class analysis highlighted the heterogeneity in "allergic/atopic march" with the full phenotype of the march seen in 3.1%.[2,3] The other seven latent classes identified were: persistent eczema and wheezing (2.7%), persistent eczema with late-onset rhinitis (4.7%), persistent wheezing with late onset rhinitis (5.7%), transient wheezing (7.7%), rhinitis only (9.6%), eczema only (15.3%), and a large majority with no disease (51.3%).[2,3] The authors concluded that only a small proportion of children (around 7%) follow trajectory profiles resembling "allergic/atopic march."[3] This concept is crucial in understanding and managing allergic diseases comprehensively.

The prevalence of various allergic diseases, including AD, asthma, and AR, is constantly increasing worldwide, including India.[4,5] This is attributable to a change in lifestyle, food habits, climate, and epigenetic change. AR has been shown to be an independent risk factor for the subsequent development of asthma during the adolescent period or in adults.[6] This risk is present in atopic as well as nonatopic subjects. In fact, in subjects with AR without asthma, underlying airway hyperreactivity is present with or without altered airway smooth muscle function.[6] To better understand the impact of AR on asthma, Allergic Rhinitis and Its Impact on Asthma (ARIA)

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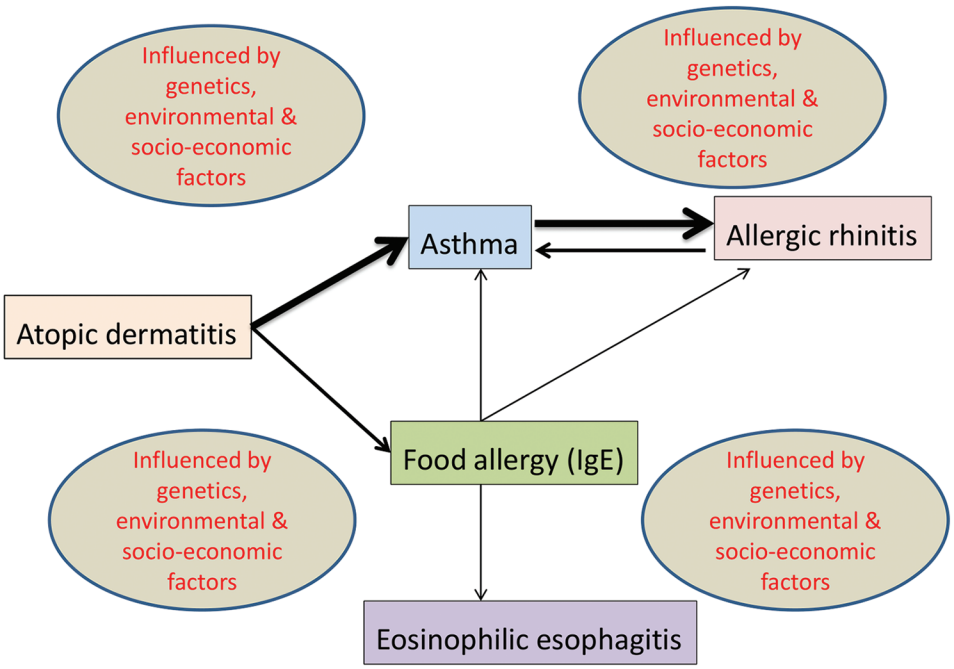

Figure 1: Allergic/atopic march trajectories.[1] The thickness of an arrow denotes the directness and strength of the association. IgE: Immunoglobulin-E

guidelines were first developed in 1999 and were updated subsequently.[7]

In the present review, we have discussed the allergic/atopic march along with united airway disease and also discussed what one needs to know for better management of children with various allergies.

Allergic or Atopic March: Relationship between Atopic Dermatitis and Airway Allergic Diseases

AD/atopic eczema is a chronic inflammatory condition characterized by dry, eczematous, and itchy skin.[8] It commonly affects infants and young children but can persist into adulthood with a global prevalence of 2.23%.[8] In 60% of cases, AD manifests during infancy (early onset), and in up to 70% of cases, the disease markedly improves or resolves until late childhood.[9] However, a prolonged course is expected in case of an early and severe onset, family history, and early allergic sensitization. Children with AD and IgE-specific antibodies to common environmental allergens present early and have a higher risk of progression to allergic/atopic march compared to those without IgE antibodies. In addition, the severity of AD also correlates with future development of asthma or AR.

AD and allergic diseases in children often share a close relationship, as they are both manifestations of an overactive immune response [Figure 2]. In AD, there is often a defect in the skin barrier, which allows allergens to penetrate more easily, leading to inflammation and allergic reactions.[9] This impaired skin barrier function can also predispose individuals to other allergic conditions. Here

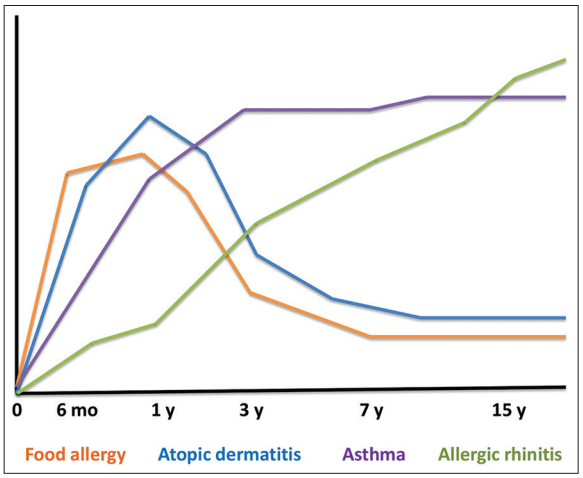

Figure 2: Timelines (age-wise) of allergic/atopic march. Each line diagram color matched with the respective disease (below the x-axis)

are some key points regarding their relationship: (a) people with AD often have a personal or family history of allergic conditions such as asthma or AR; (b) both AD and allergic diseases, such as asthma, AR (hay fever), and food allergies, are considered atopic conditions, meaning they involve an allergic response mediated by IgE antibodies; and (c) there is a significant genetic component to AD and allergic diseases. Children with a family history of either condition are at a higher risk of developing them; (d) both AD and allergic diseases can be triggered by similar environmental factors, such as pollen, dust mites, pet dander, certain foods, and irritants like harsh soaps or detergents.[2,9]

Once there is a development of asthma or AR, these diseases affect the severity and control of AD in a given

child. In a large multicenter study, out of infants who had developed AD by 3 months of age, aeroallergen sensitization was noted in 77% of the cases by 5 years of age.[10] Of these, 50% of children with a positive family history were diagnosed with asthma or AR by 5 years of age compared to 12% without AD or a family history of allergy.[10] In another study, the authors noted that 66% of children have asthma or AR by 3 years of age in those with physician-confirmed AD.[11] In a longitudinal study examining the progression of allergic/atopic march, the authors found that childhood eczema was significantly associated with asthma persisting from childhood to middle age (relative risk [RR], 1.54; 95% confidence interval [CI], 1.17-2.04).[12]

Underlying Mechanism of Allergic/Atopic March

The pathophysiology of the atopic march is complex and not fully understood, but several factors contribute to its development.[13]

(a) Genetics: Genetic predisposition plays a significant role in the atopic march. Individuals with a family history of allergic diseases are more likely to develop them. Specific genes related to immune system function, skin barrier integrity, and allergic responses have been implicated in the development of atopic conditions
(b) Immune dysregulation: At the core of the atopic march is an underlying dysregulation of the immune system. In individuals prone to allergies, the immune system overreacts to normally harmless substances (allergens) by producing IgE antibodies and releasing inflammatory chemicals such as histamine. This immune response leads to the symptoms characteristic of allergic diseases, such as itching, inflammation, and mucus production
(c) Skin barrier dysfunction: Atopic dermatitis often precedes other allergic conditions in the atopic march. Impairment of the skin barrier function allows allergens to penetrate the skin more easily, leading to sensitization and the development of allergic reactions. Genetic factors, environmental triggers, and immune dysregulation contribute to the dysfunction of the skin barrier
(d) Environmental triggers: Exposure to environmental allergens such as pollen, dust mites, pet dander, and certain foods can trigger allergic reactions in susceptible individuals. Early exposure to these allergens, especially during critical periods of immune system development, may increase the risk of developing allergic diseases later in life
(e) Microbial factors: Alterations in the composition of the microbiome, the community of microorganisms that inhabit the skin, gut, and other mucosal surfaces, may influence the development of allergic diseases. Disruption of the microbiome, such as through antibiotic use or changes in diet, can affect immune function and promote allergic responses.

Previously, a dysfunction of the adaptive immune system with an emphasis on the T-helper (Th)-1/Th2 paradigm was thought to be involved. However, recently, the focus has been shifted to a primary dysfunction in the epithelial barrier promoting an easy entry of allergens, pathogens, and other environmental triggers.[14] This leads to the development of AD with subsequent sensitization in the airways leading to the development of asthma and AR. The later results from the damage caused to the tight junctions of epithelial airways by peptidases released from the allergens. The damage to the tight junctions leads to enhanced airway epithelial permeability and increased allergen delivery. Mutations in the filaggrin (30%–50% cases) affecting the epithelial barrier function are the most well-known genetic risk factors for AD.[14] These mutations are significantly associated with IgE-mediated sensitization to inhalant and food allergens, and persistence of allergic diseases to adulthood.

Allergic/Atopic March: Role of Food Allergy

In the last few decades, there has been a dramatic increase in the incidence of food allergy-related hospitalizations for anaphylaxis, and this has led to the idea that food allergy might form a "second epidemic" of allergic diseases.[15] Here is how food allergies contribute to the atopic march:[16]

(a) Early sensitization; Food allergies often develop early in life, sometimes even during infancy. Exposure to certain allergenic foods can trigger an immune response, leading to sensitization and the production of specific IgE (sIgE) antibodies
(b) AD: Food allergies are closely linked to eczema, which is often the first manifestation of the atopic march. In infants and young children, certain foods such as cow milk, eggs, peanuts, and soy are common triggers for eczema flare-ups. The inflamed skin barrier in eczema allows allergens to penetrate more easily, leading to allergic reactions
(c) Potential for asthma and AR: While eczema is often the initial presentation, children with food allergies are at a higher risk of developing asthma and AR later in childhood. This is part of the progression of the atopic march, where allergic sensitization in one part of the body (e.g., skin) can lead to allergic reactions in other organs (e.g., lungs and nasal passages).

The most common food items responsible for "food-induced allergy" (90%) in clinical practice include egg, cow milk, wheat, peanut, nuts, fish, soy, and shellfish.[17] These are also the most common cause of asthma exacerbations in the settings of food-induced allergies.[17] In a population-based birth cohort, egg allergy increased the subsequent risk of asthma, and AR; and an IgE-mediated reaction to cow milk increased the risk of atopic diseases later on.[18-20] In a prospective study, including 118 children with cow milk allergy (CMA), those with IgE-positive CMA diagnosed at the age of 7 months

exhibited increased airway inflammation (higher fractional exhaled nitric oxide [FeNO]) and hyper-responsiveness to histamine at 9 years of age compared to those without IgE CMA.[21] However, a similar risk was observed in children with a history of recurrent wheeze during the 1st year of life and parental smoking.[21] In a cohort study of 1218 children, 2.4% had a symptomatic egg allergy, and the later was significantly associated with asthma and AR (odds ratio [OR], 5.0, 95% CI, 1.1–22.3) diagnosis at 4 years of age.[19] Egg allergy also significantly increased aeroallergen sensitization (OR 6.1, 95% CI 1.1–37.5). However, a family history of atopy did not increase the risk. Hence, it is unclear, whether the progression from food allergy to allergic/atopic march is causal or as a result of shared genetic and environmental risk factors. Hence, more prospective longitudinal studies are needed to either support or refute the role of food allergy in allergic/atopic march.

United Airway Disease/Allergic Rhino-bronchitis

Asthma and AR frequently coexist in the same individual justifying the name "united or unified airway disease." This relationship has been extensively studied in epidemiological research, and several key points have emerged.[10,22-24]

(a) Coexistence: It is estimated that up to 80% of asthmatics may have AR, depending on the population studied and the diagnostic criteria used
(b) Allergic/atopic triad: Asthma, AR, and eczema sometimes occur together in what's called the "allergic triad" or "atopic triad." This suggests a common underlying predisposition to allergic diseases. In a prospective study, around 38% of children with AR showed airway hyperreactivity to methacholine challenge, and of them, around 20% developed asthma in the next 7 years of follow-up.[25] In another large cohort study, physician-diagnosed AR increased the risk of future asthma diagnoses by almost 5-fold (HR, 4.86; 95% CI 3.5–6.73; $P < 0.001$). Of the subtypes of AR, perennial AR has a higher risk than seasonal AR[26]
(c) Shared pathophysiology: Both conditions involve inflammation of the respiratory tract. A large number of studies have shown that the inflammation of the upper (AR) and lower airways (asthma) involves similar inflammatory infiltrates (eosinophils, mast cells, T-cells, and cells of monocyte lineages). In patients with AR, the lower airway inflammation (or underlying asthma) can be demonstrated by documentation of an increased level of FeNO
(d) Allergy as a trigger: Allergic rhinitis is often triggered by exposure to airborne allergens such as pollen, dust mites, animal dander, and mold spores. In susceptible individuals, these allergens can also trigger asthma symptoms, leading to a worsening of asthma control
(e) Sequential onset: In some cases, AR precedes the onset of asthma. This sequential onset suggests that AR may be a risk factor for the development of asthma, possibly due to the "united airway disease" concept, where inflammation in the upper airways contributes to inflammation in the lower airways
(f) Impact on disease severity: The presence of AR in individuals with asthma is associated with worse asthma control, increased asthma exacerbations, and poorer quality of life. This indirectly increases the health-care cost and has a bearing on economically weaker sections of society. Addressing AR symptoms through appropriate treatment may help improve asthma outcomes
(g) Treatment implications: Because of the close relationship between asthma and AR, treating AR effectively may improve asthma control. This often involves a combination of allergen avoidance strategies, pharmacotherapy (such as antihistamines, nasal corticosteroids, and leukotriene receptor antagonists), and allergen immunotherapy (allergy shots) in some cases. Intranasal steroids for AR have been shown to reduce concomitant bronchial hyperreactivity and asthma symptoms to some extent and have additive roles to inhaled steroids used for asthma control.

Nonasthmatic subjects with AR and bronchial hyperreactivity can have mild but significant changes in their airways.

Proposed Interaction between Upper and Lower Airways

AR can affect asthma severity and control by different mechanisms. Allergen challenges to the nose can cause nonspecific bronchial hyperreactivity with or without airflow limitation. The suggested mechanisms by which interaction occurs between the upper and lower airways are as follows [Figure 3];

(a) Nasobronchial reflex: The upper and lower airways are interconnected through neural reflex pathways. Irritation or inflammation in the nasal passages can trigger reflex responses in the lower airways leading to bronchial hyperreactivity, bronchoconstriction, and increased mucus production. Similarly, bronchial inflammation can induce nasal symptoms like congestion and rhinorrhea
(b) Bone marrow-derived systemic inflammatory response: Interleukin-5 mediates eosinophilic inflammation, and during allergen exposure, its level increases in the blood leading to blood eosinophilia. Eosinophils release mediators that initiate and propagate allergic inflammation. In experimental AR models (after nasal allergen challenge), an increase in the eosinophil progenitors has been found in the bone marrow.[27] This has led to the speculation that bone marrow eosinopoesis may have a role in global airway inflammation in allergy
(c) Oral breathing: In AR, the nose is often blocked, thus promoting oral breathing. This, in turn, leads to an

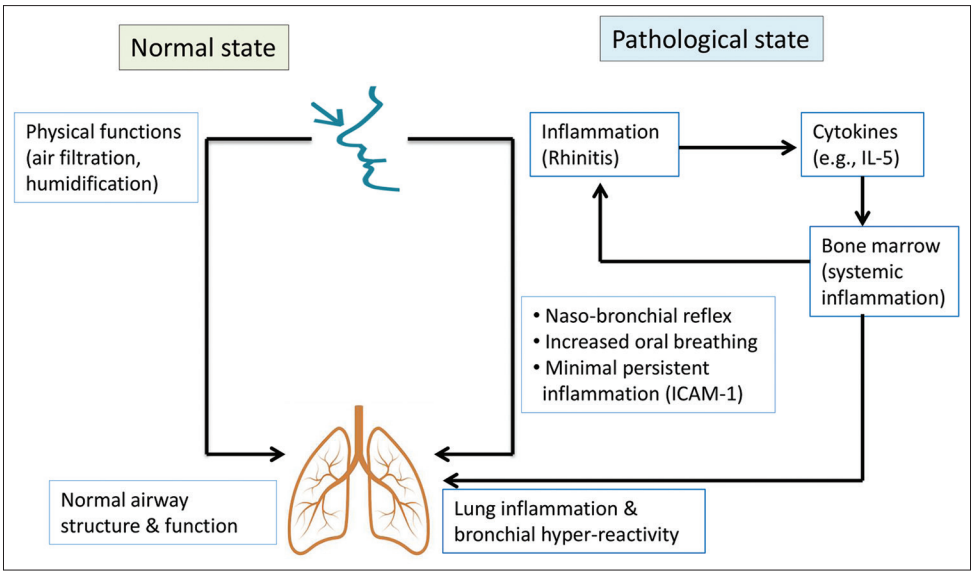

Figure 3: Proposed interaction between the upper (nose) and lower (lungs) airways. IL-5: Interleukin, ICAM-1: Intercellular adhesion molecule-1

inflammatory change in the lower airway, promoting bronchial hyperreactivity and bronchoconstriction in subjects with asthma

(d) Minimal persistent inflammation: It involves a week and persistent expression of intercellular adhesion molecule-1 in the nasal mucosa, the major receptor for human rhinoviruses (HRVs).[28] HRVs are the major viral cause of acute asthma exacerbation in the context of viral upper respiratory tract infections.[29]

What One Needs to Know?

Precision allergy molecular diagnosis in predicting atopy development

Precision allergy molecular diagnosis (PAMD) is an advanced approach to identify specific allergens that trigger allergic reactions in individuals.[30,31] Traditional allergy tests, such as skin prick tests and blood tests measuring IgE antibodies, can sometimes produce inconclusive or inaccurate results. PAMD utilizes cutting-edge technology to pinpoint allergens at the molecular level, offering more accurate and detailed information about an individual's allergic sensitivities. This diagnostic method typically involves analyzing the patient's blood sample using molecular techniques, such as microarray technology or next-generation sequencing. These techniques can identify allergenic molecules from various sources, including pollen, dust mites, pet dander, foods, and insect venoms, among others. PAMD can be of two types: "singleplex" (assess serum levels of sIgE against individual allergens) or "multiplex" (assess serum levels of sIgE against multiple allergens).[30] The first multiplex assay ImmunoCAP ISAC (semi-quantitative assay capable of analyzing sIgE against a total of 112 allergen components from 50 allergen sources, and requires only 30 µL of serum/plasma) was followed by third-generation nanotechnology applications (FABER: P-Friendly Allergy nano-Bead aRray; and ALEX2: Allergy Xplorer2).[30] FABER is now no longer produced, but ALEX2 is a quantitative assay capable of analyzing >295 allergens (extracts and molecular) in only 200–400 30 µL of blood.[30] Because of the presence of a cross-reactive carbohydrate determinant inhibitor, ALEX2 has significantly low false-positive results compared to other tests.[30]

While PAMD represents a significant advancement in allergy testing, it may not be readily available in all health-care settings and could be more costly than traditional tests. However, as technology continues to advance and become more accessible, it has the potential to revolutionize the diagnosis and management of allergies, improving the quality of life for individuals with allergic conditions.

Precision allergy molecular diagnosis in planning allergen-specific immunotherapy

Here is how precision allergy molecular diagnosis works in the context of allergen immunotherapy:

1. Identification of allergenic molecules: Instead of relying solely on skin prick tests or serum-sIgE tests, PAMD uses advanced techniques such as component-resolved diagnostics (CRD). CRD helps identify the exact allergenic molecules that a person's immune system reacts to
2. Personalized treatment plans: Once specific allergenic molecules are identified, allergists can develop personalized treatment plans tailored to the individual's allergic profile. This may involve allergen-specific immunotherapy (AIT), also known as allergy shots or sublingual immunotherapy, where the person is exposed to gradually increasing doses of the allergen to desensitize their immune system

3. Improved efficacy and safety: PAMD allows for more targeted and effective immunotherapy because it addresses the root cause of allergic reactions. By targeting the specific allergenic molecules, treatment can be more precise, potentially leading to better outcomes with fewer side effects
4. Monitoring progress: Throughout the immunotherapy process, molecular diagnosis techniques can be used to monitor the individual's response to treatment. This may involve measuring changes in allergen-sIgE levels or assessing the person's clinical symptoms over time. Adjustments to the treatment plan can be made based on these monitoring results
5. Future applications: As our understanding of allergenic molecules and immune responses continues to advance, PAMD holds promise for further innovations in AIT. This includes the development of novel therapies targeting specific molecular pathways involved in allergic reactions.

Conclusions

Allergy/atopic march" refers to a typical sequence in which the allergic or atopic features appear at a certain age, and may or may not persist thereafter. Asthma and AR are different manifestations of a single disorder of the airways. Precision allergy molecular diagnosis may help in predicting the development of atopy and plan in allergen immunotherapy to halt or alter the atopic march.

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Conflicts of interest

There are no conflicts of interest.

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