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The Atopic March: Critical Evidence and Clinical Relevance

David A. Hill, MD, PhD^{a,b} and Jonathan M. Spergel, MD, PhD^{a,b}

^aDepartment of Pediatrics, Division of Allergy and Immunology, The Children's Hospital of Philadelphia

^bInstitute for Immunology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

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Introduction

The atopic march refers to the natural history of allergic diseases as they develop over the course of infancy and childhood. Introduced by the American allergists A.F. Coca and R.A. Cooke in 1923, the term “atopy” became closely associated with the immunoglobulin (Ig) E molecule after its identification as the carrier of hypersensitivity.¹ However, in the context of the atopic march, it is important to note that IgE is a pathophysiologic mediator of some, but not all, “atopic” diseases. As such, it is better to consider the atopic march as a progression of allergic conditions that have common genetic and environmental predisposing factors, share the immunologic feature of one or more allergen-specific T helper type 2 (T_H2) responses, and are characterized by a “type 2” effector phase that can include generation of specific IgE, activation of granulocytes, and other innate features, such as mucous production and edema. Importantly, the presence of one allergic condition increases the risk for development of others, resulting in the additive feature of the atopic march.

Classically, the atopic march begins with atopic dermatitis (AD), and progresses to IgE-mediated food allergy (FA), asthma, and allergic rhinitis (AR) (Figure 1).² Each of these are conditions carry a complex pathophysiology involving multiple facets of the immune system. For example, AD was once considered a manifestation of atopy itself, but is now thought to result from a combination of primary skin defect(s) and underlying genetic or environmental propensity to develop type 2 inflammation. While non-type 2 inflammation likely contributes to AD pathophysiology, for the purposes of this review we will focus on

Corresponding author: Jonathan M. Spergel, MD, PhD, Division of Allergy and Immunology, Children's Hospital of Philadelphia, The Wood Building, 3rd floor, 3401 Civic Center Blvd., Philadelphia, PA 19104, Phone: (215) 590-2549, Fax: (215) 590-6849, spergel@email.chop.edu.

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the role of type 2 inflammation, as it is the central tenet of the atopic march. Due to the type 2 inflammation associated with AD lesions, AD also represents an important route of allergen exposure by which systemic T_H2 responses are initiated. Once an individual has commenced on the atopic march, it is difficult to halt the progression. Here, we start with a clinical vignette and then review the epidemiologic and translational evidence supporting the concept of the atopic march. We briefly review the immunologic mechanisms that are thought to underlie the atopic march, and discuss some of the clinical interventions aimed at preventing or intervening upon the atopic march.

Clinical vignette

A 1-year-old Caucasian boy with a history of moderate AD was referred to an allergist due to concern for food allergy. The patient was exclusively breast fed until one year of age when he developed acute hives, vomiting, and respiratory distress after his first consumption of cow milk. His medical history was otherwise notable for infantile-onset AD that was poorly controlled with intermittent topical corticosteroid use. His family history included AD and asthma in his father, AD in his mother, and AD, FA, and asthma in his older sister. Skin testing confirmed the diagnosis of FA to milk, and the patient was instructed to avoid this food. An alternative AD therapeutic regimen was initiated which included more frequent and higher-dose corticosteroid use, and his skin improved over the following weeks.

The child was followed in allergy clinic and his AD significantly improved by the age of 2 years. That winter, he was admitted to the hospital for respiratory distress in the setting of a viral URI. The following spring, he developed AR and had positive skin testing to trees, grasses, and dust mite. By three years of age, he carried the diagnoses of FA, AR, and moderate persistent asthma requiring combination inhaled corticosteroid and long-acting beta agonist therapy. At four years of age, skin testing to cow milk revealed a wheel and flare of 1 and 2 mm respectively, and serum IgE to milk was 3.45 kU/L. The child subsequently passed a food challenge and introduced cow milk into his diet.

Atopic dermatitis and IgE-mediated Food Allergy: Early members of the atopic march

One of the most common pediatric conditions, AD is thought to affect between 7 and 12% of US children. AD is most commonly diagnosed in the first six months of life—prior to the development of FA, AR, and asthma.^{2, 3} AD likely results from disruption of the skin barrier due to intrinsic defects of epithelial cells in an individual with a genetic and/or environmental predisposition for type 2 inflammation. Defects in the epidermal barrier protein filaggrin, which are associated with both atopic dermatitis and allergic sensitization, are often cited as a quintessential example of such a barrier defect. However, other examples have now been identified including loss-of-function mutations in *SPINK5* and the gene encoding corneodesmosin.⁴ Importantly, loss-of-function mutations in the filaggrin gene do not increase risk of food or aeroallergen sensitivity independently of AD status.^{5, 6} Therefore, while intrinsic epithelial barrier dysfunction is central to the pathophysiology of AD, there are other important genetic and/or environmental modifiers that are required for the development of allergic skin inflammation and progression of the atopic march. For example, polymorphisms in the gene encoding thymic stromal lymphopoietin (*TSLP*) and

it's receptor influence AD risk, FA, and asthma,⁷⁻⁹ while polymorphisms in the genes encoding IL-33 and its receptor are associated with increased risk of AD and asthma.^{10, 11} Together, these studies and others support the existence of a shared set of polymorphisms which predispose to AD and promote the subsequent development of other allergic conditions.^{8, 12, 13}

Most proximally on the atopic march, the presence and severity of AD positively correlates with risk of developing FA. One recent review estimated that children with AD are as much as six times more likely to develop an FA compared to their healthy peers.¹⁴ Food-specific IgE responses can be detected in the first months of life, and peak at around 10% prevalence at 1 year of age.¹⁵ The fact that sensitization occurs prior to food ingestion in most cases suggests that sensitization to foods occurs via exposure through inflamed skin, as opposed to the gastrointestinal tract. Additionally, positive correlations have been found between the use of wheat or peanut-containing skin products and the development of wheat or peanut allergy, respectively,^{16, 17} and exposure to peanut dust in a child's home positively correlates with likelihood of developing peanut allergy.¹⁸ Finally, allergen-specific T cells isolated from peanut-allergic patients express skin-related homing molecules,^{19, 20} providing additional evidence for the skin being the site of allergen sensitization in FA. Together, these findings support the theory that there is trans-cutaneous sensitization to food allergens in susceptible individuals.

Asthma and allergic rhinitis: Late members of the atopic march

AD is also strongly associated with the development of asthma and AR.²¹ In contrast to food-specific IgE responses, IgE responses to inhalant allergens develop later in childhood providing a possible explanation for the delayed age of onset for these conditions.¹⁵ The relationship between AD and respiratory allergy is influenced by AD severity—while around 20% of children with mild atopic dermatitis develop asthma, over 60% with severe atopic dermatitis develop asthma.^{21, 22} The presence of AD is also associated with increased asthma severity, and greater asthma persistence into adulthood.^{23, 24} Similar to FA, loss-of-function mutations in the filaggrin gene correlate with asthma susceptibility and severity in patients with AD, but not in those without AD—indicating that skin inflammation is required for allergic sensitization.⁵

Despite these data, it is important to note that not every patient with AD develops asthma, and not every patient with asthma has preceding AD. A recent retrospective analysis of two birth cohorts found eight separate patterns of atopic disease progression.²⁵ Though limited by cohort size and parental survey as the reporting method, this study found that 10.5% of respondents followed the traditional pattern of the atopic march, while 15.5% had persistent AD, 5.7% had wheeze without AD, and 9.6% had rhinitis without AD. Together, these findings indicate that the atopic march is not present in all atopic individuals, and in particular those with adult-onset disease.

The presence of FA is also an independent risk factor for the development of AR and asthma. In a retrospective birth cohort study of almost 30,000 children, we found that the presence of FA was associated with development of asthma (odds ratio (OR) 2.16, 95% CI 1.94–2.40), and rhinitis (OR 2.72, 95% CI 2.45–3.03).² Of the major food allergens, FA to

peanut, milk, and egg were significantly associated with the subsequent development of asthma (OR 1.74, 1.38, and 1.60, respectively), and rhinitis (OR 2.59, 1.46, and 1.80, respectively). Additionally, there was an additive effect as patients with multiple food allergies were at increased risk of developing respiratory allergy as compared to patients with a single food allergy. A large meta-analysis of birth cohort studies recently confirmed that early life food sensitization increases risk of wheeze/asthma, eczema, and AR.²⁶ It is important to note that it is difficult to control for confounding effects in these analyses, such as personal history of AD or family history of atopy. In subsequent analysis of our study, we found that FA predisposed to AR and asthma independently of AD status—suggesting additive risk of developing new allergic conditions as one progresses on the atopic march. Additionally, the ability to more accurately predict a patient's risk of developing respiratory allergy by considering the presence of FA is of considerable clinical utility to the practicing clinician.

Finally, the clinical relationship between asthma and AR is well established, with up to three quarters of asthmatics reporting rhinitis symptoms.²⁷ This association holds after controlling for total IgE, parental history of asthma, and allergen sensitization, suggesting that the coexistence of AR and asthma is not solely due to atopic predisposition. AR is also positively correlated with asthma severity, and AR treatment improves asthma control.²⁸ Together, these observations indicate that the upper and lower airways behave as a physiological and pathophysiological unit, and have led to comprehensive recommendations from the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline panel which emphasize the importance of appropriate treatment of AR in asthmatics.²⁹

Immunologic mechanisms underlying the atopic march

As described previously, allergen exposure through inflamed skin is thought to be the primary route by which individuals initiate on the atopic march (Figure 2). This hypothesis is supported by data from animal models which indicate that trans-cutaneous allergen exposure promotes the development of specific T and B cell responses, and subsequent allergic disease. These models can take the form of genetic disruptions (as is the case with mice deficient in filaggrin), or skin irritation via mechanical or chemical means. It is worth noting that protease allergens (such as those contained in peanut, papaya, mites, insects, fungi, and some pollens) are unique in that they can induce sensitization when exposed to healthy skin, and act as an adjuvant for other allergens. For example, peanut exposure on the skin of mice increases the development of specific IgE responses to milk.³⁰ Once an allergen has entered the skin, it has the opportunity to interact with the immune system. Skin is divided into two immune compartments: the epidermis, which contains predominantly Langerhans cells and CD8⁺ cytotoxic T lymphocytes, and the dermis, which contains dermal and plasmacytoid dendritic cells (DC), macrophages, mast cells, and innate and adaptive lymphocyte subsets.³¹

The inflammation observed in AD is associated with increased production of IL-4, IL-25, IL-33, and TSLP, which recruit IL-5 and IL-13 producing type-2 innate lymphoid cells and contribute to the development of type 2 inflammation.³² DCs and other immune cells migrate from the skin to draining lymph nodes, where they stimulate naive T cells to

differentiate into allergen-specific T_H2 cells.³³ Once allergen-specific T_H2 responses are present, they can exert effects systemically. For example, in mice it is established that epicutaneous sensitization can induce allergen-specific IgE and anaphylaxis,³⁴ and allergic inflammation of the lung,³⁵ esophagus,³⁶ and GI tract.³⁷ In the case of esophageal inflammation, the mechanism is IgE-independent, implying that pathogenic T_H2 cells migrate from the skin to other tissue sites.

An additional mechanistic question related to the atopic march is whether the presence of one allergen-specific T_H2 response potentiates to the development of additional T_H2 responses. One mechanism by which this may occur is via a “bystander effect”—where existing inflammation acts as an adjuvant for the development of other T_H2 responses. Basophils are one potential contributor to the bystander effect, as they are potent sources of IL-4, are recruited to draining LNs early in the response to infectious or allergic stimuli, and can cooperate with DCs to promote T_H2 cell responses.³⁸ Critically, blood basophil numbers in the steady-state, and basophil recruitment to lymph nodes after allergen exposure, are both directly related to serum IgE levels in an antigen-independent manner.^{39, 40} Thus, elevated IgE levels may potentiate basophil-facilitated T_H2 responses both in the skin and at distant tissue sites.^{41–43} Together, these observations offer one immunologic mechanism by which the presence of a T_H2 response to one allergen could potentiate the development of additional T_H2 responses.

Clinical strategies aimed at prevention and intervention upon the atopic march

The epidemic increases in prevalence and severity of allergic conditions observed in recent decades are generally thought to have occurred too quickly to be attributed to genetic drift alone. As a result, considerable effort has been devoted to understanding the role of diet, hygiene, infections, allergens, air pollution, and other environmental factors in susceptibility to allergic disease.⁴⁴ Particular attention has been given to the influence of pathologic or commensal microbial stimuli (and in particular commensal bacteria) on the mammalian immune system.⁴⁵ Epidemiologic studies were the first to establish an increased risk for asthma and other allergic conditions with childhood antibiotic exposure.⁴⁶ These associations held after adjusting for infections, and other potential confounders, suggesting detrimental effects of antibiotic exposure on non-pathologic microbes. Subsequent studies in animal models indicated that antibiotic exposure dramatically restructures the intestinal microbiome, and skews the immune system towards type 2 inflammation.^{39, 47}

Clinical associations have also been made with childhood exposure to household pets, livestock, unpasteurized milk, and endotoxins, all of which are generally protective against allergic manifestations. Some of the most compelling recent data supporting a role for microbial exposure in atopic risk come from studies comparing geographically distinct but genetically related pediatric populations. In one study of children in Finland and Russia, a significant, dose-dependent reduction in the risk of atopy was associated with microbial exposure and prevalence of enteroviruses.⁴⁸ In another study of Amish and Hutterite farm children, prevalence of asthma and allergic sensitization was 4 and 6 times lower in the Amish (who follow more traditional farming practices). This correlated with dust in Amish homes that had 6.8 times more endotoxin, which induced MyD88 and Trif-dependent

inhibition of airway hyperreactivity and eosinophilia in a mouse asthma model.⁴⁹ Given our improved understanding of the influence of microbial factors on allergic sensitization, it is not surprising that multiple studies have now attempted to prevent progression along the atopic march through various diet or probiotic-based interventions aimed at modifying the microbiome of various mucosal sites. However, the data to date are mixed, with some positive and some negative studies.^{50, 51}

Studies have also examined the effects of optimal AD therapy, and immunotherapy, on the atopic march. One recent 3-year double-blind study examined the benefits of pimecrolimus therapy in 3 to 18-month-old patients with recent onset AD.⁵² No significant differences in the percentage of patients who developed FA, AR, or asthma were detected between the treatment and control groups, though baseline AD severity was positively correlated with development atopic comorbidities. Other small trials have shown that routine use of emollients reduces the incidence of AD by approximately half during the therapy period, though it remains to be seen if prophylactic emollients influence risk of allergic sensitization.⁵³ There is also some evidence to suggest that subcutaneous and sublingual immunotherapy may prevent the progression to asthma in high-risk atopic patients.⁵⁴ For example, one study examined the effect of receiving oral house dust mite (HDM) extract on asthma outcomes in 111 infants at high risk of atopy.⁵⁵ Oral HDM therapy was well tolerated in the treatment group, but there was no significant preventive effect observed on HDM sensitization or the development of AD, FA, or wheeze. More in-depth investigation of the role of immunotherapy in the prevention of atopic disease is warranted.

Other efforts have attempted to modify the atopic march using prophylactic antihistamines. A large trial of 817 infants with AD aged 1 to 2 years showed no significant difference between treatment with high dose cetirizine or placebo with regard to development of asthma overall.⁵⁶ However, a subgroup analysis indicated that infants sensitized to dust mite, grass, or both who were treated with cetirizine were significantly less likely to be diagnosed with asthma during the treatment period. However, a follow-up trial undertaken in children with atopic dermatitis and sensitivity to grass pollen and/or house dust mite allergens showed no benefit to levocetirizine therapy in delaying asthma diagnosis.⁵⁷

Finally, a very promising avenue for disrupting the atopic march stems from the decades of work investigating the immunologic mechanisms and clinical relevance of oral tolerance.⁵⁸ This work culminated in a randomized trial of peanut consumption in infants at risk for peanut allergy in 2015 that showed significant benefit to early peanut introduction.⁵⁹ These findings led to new recommendations from the NIAID on how to prevent FA that emphasize facilitating oral peanut exposure prior to trans-cutaneous sensitization in individuals that are at risk for developing FA.⁶⁰ However, it remains to be seen whether early introduction of peanut or other food allergens influences development of distal atopic conditions such as asthma or allergic rhinitis.

Conclusion

The pronounced global increase in the prevalence and severity of atopic diseases over recent decades is of critical relevance to our population health. The concept of the atopic march has

greatly improved our understanding of the pathophysiology of allergic conditions, and led to the development of exciting new therapeutic strategies for the prevention of atopy. Future research should be directed at better understanding environmental and genetic factors that predispose children to atopic conditions (including the role of commensal and pathologic microbes), as well as the fundamental immunologic mechanisms that lead to development of a T_H2 response upon initial allergen exposure. Finally, it is important to consider the addition of new diseases to the atopic march, as supported by rigorous epidemiologic and mechanistic evidence. In sum, the atopic march remains a fundamental and well tested concept in the field of allergy that has practical relevance to the practicing Allergist, and has led to exciting new research questions and therapeutic opportunities.

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Abbreviations

Ig	immunoglobulin
T_H2	T helper type 2
AD	atopic dermatitis
FA	food allergy
AR	allergic rhinitis
EoE	eosinophilic esophagitis
TSLP	thymic stromal lymphopoietin
DC	dendritic cell
HDM	house dust mite

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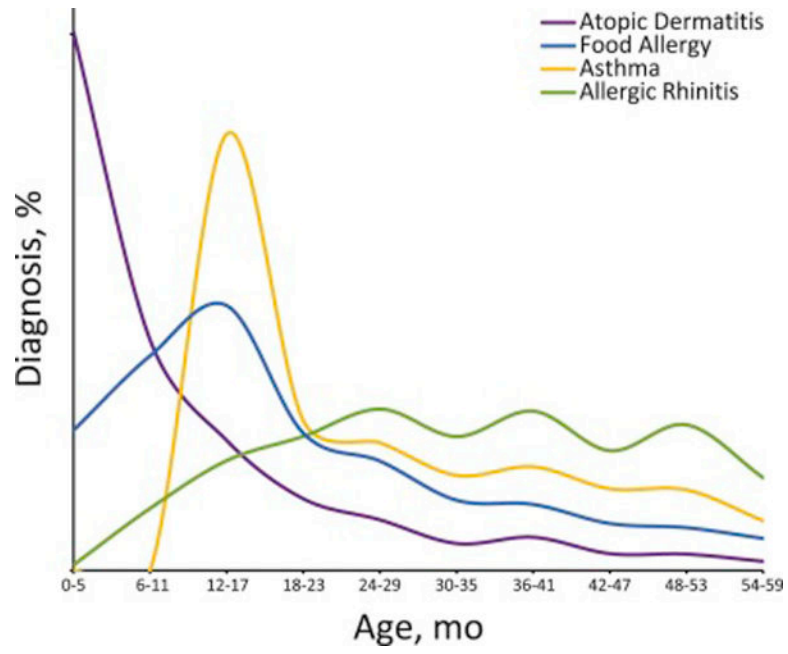


Figure 1.
Age at diagnosis of common allergic conditions.

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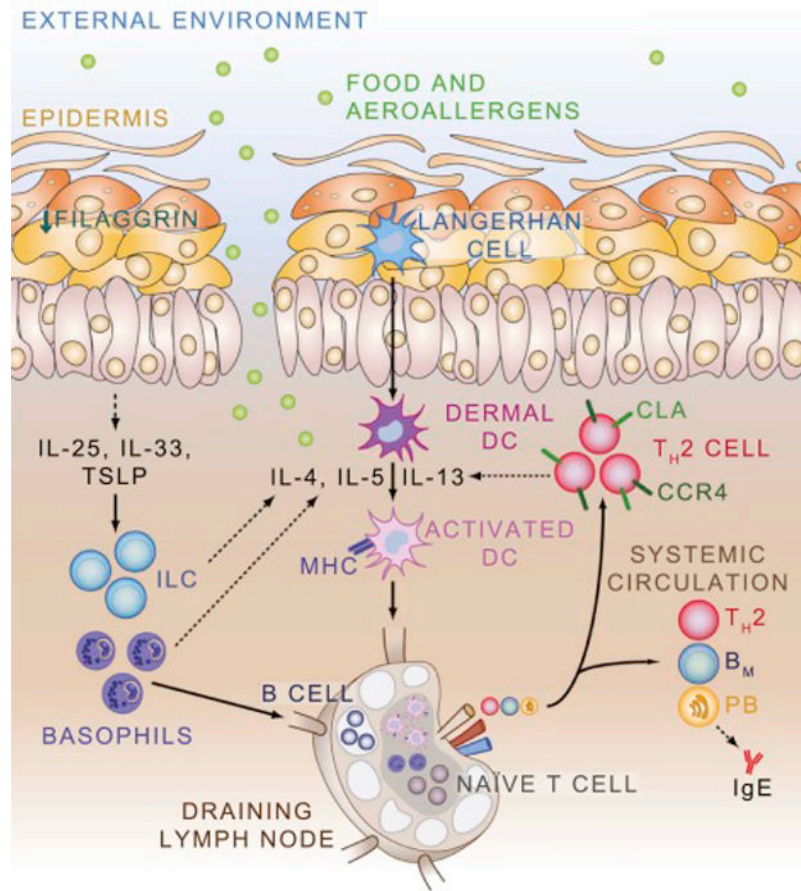


Figure 2.

Model of the Atopic March. Deficiencies in epithelial proteins such as filaggrin, in conjunction with atopic predisposition, result in skin inflammation. Epithelial-derived cytokines such as IL-25, IL-33, and TSLP recruit and activate innate cell types including innate lymphoid cells (ILC) and basophils which produce cytokines that promote the activation of dendritic cells. Activated dendritic cells process allergen, upregulate MHC, and circulate to draining lymph nodes where they can interact with naïve T and B cells to promote the development of allergen-specific T and B cell responses. Allergen-specific T helper type 2 (T_H2) cells home back to the skin through expression of C-C chemokine receptor type 4 (CCR4), cutaneous lymphocyte antigen (CLA), and other molecules. T_H2 cells also enter the systemic circulation where they can exert effector response at distant tissue sites. Memory B cells (B_M) recirculate in the blood and lymph, while plasmablasts (PB) home to the bone marrow where they differentiate in to plasma cells and produce allergen-specific IgE.