



Editorial

The atopic march

Where we are going? Can we change it?



The atopic march is classically thought to be the progression of atopic dermatitis (AD) to other atopic conditions (asthma, allergic rhinitis [AR], food allergy, and eosinophilic esophagitis). The 4 articles^{1–4} published in this edition of the *Annals of Allergy, Asthma & Immunology* highlight the risk factors, mechanisms, and heterogeneity in this progression.

The question of whether all patients must progress from AD to food allergy and then asthma and AR or can a patient skip around has been raised.^{5,6} Gabryszewski and Hill² described the possibility of multiple different pathways on which individuals may progress. In their review of epidemiologic literature and their own data from the Children's Hospital of Philadelphia, they have identified multiple paths of the atopic march, including the newest type 2 inflammation disease, eosinophilic esophagitis. They found that although AD → asthma → AR might be the most common pathway, only a small number of patients follow this classic pathway and multiple pathways exist in which one atopic disease follows another starting with either AD or immunoglobulin E–mediated food allergy. It is also important to note that the atopic march is important in pediatric development of atopic disease, but less important for the adult-onset atopic disease.

Hossenbaccus et al³ reviewed risks identified from birth cohorts for the progression of the atopic march. In their review of birth cohorts from published data from 2014 to 2021, a few key important risk factors and protective factors were identified. Genetics plays an important role because parental atopy increases the risk of progression of the atopic march by approximately 2-fold. Infant microbiome probably plays a key role because cesarean delivery, early antibiotic use, and viral infections have been identified as risk factors. Exposure to cigarette smoke is a risk factor whether in perinatal or prenatal period, particularly in the second or third trimester. Although breastfeeding is probably protective, it is controversial, given that the findings are inconsistent in studies; moreover, the protective effects of breastfeeding may be lost in children with AD. Another key protective effect is diet diversity in newborn period. An interesting protective effect is early exposure to allergens, including pets, fungal diversity, and dust mites.

In these studies, severity and persistence of AD were key risk factors for the development and progression of the atopic march. Therefore, it is a complex interplay of genetics, microbiome, environmental factors, and epidermal factors that play a role in the development of the atopic march.

Ziegler⁴ evaluated the potential mechanism of the atopic march focusing on skin barrier dysfunction and type 2 inflammation

pathway. In his review, defects in the epithelial barrier were identified, which were found to contribute to the development of atopic march in particular defects in filaggrin, corneodesmosin, and serine peptidase inhibitor Kazal serine (SPINK5) on the basis of both genetic studies and the role of skin sensitization and exposure to food antigens. The associated alarmins (thymic stromal lymphopoietin, interleukin [IL]-33) of the epidermal barrier and their receptors have also been identified as risk factors in the atopic development. It is these alarmins that play a key role in the development of type 2 inflammation (IL-4, IL-5, and IL-13). These alarmins can be induced by damage to the epithelial surface from scratching or microbiome indicating a pathway consistent from the data from the birth cohorts.

The goal of preventing progression of the atopic march is one of the holy grails of allergy, preventing atopic disease.¹ Jimenez and Paller¹ evaluate the most recent published studies and possible ways to prevent the atopic march, including the skin.⁷ Nevertheless, the 2 prevention trials on improving skin barrier (Barrier Enhancement for Eczema Prevention and Preventing Atopic Dermatitis and Allergies) failed to reveal clinical benefit, indicating a complex interplay and potential need for a different approach to prevent the atopic march. They suggest the use of biologics instead to prevent the atopic march.

These series of articles highlight the complexity of the atopic march, which is not a simple progression and in which multiple pathways exist with multiple starting points. Various risk factors have been clearly identified from birth cohort studies including lack of diet diversity and perinatal smoking, whereas pet exposure and other early allergen exposure may be protective. Additional approaches are needed to prevent or change the progression of the atopic march because simple approaches of improving the skin barrier function have failed.^{5,7–9}

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