Revisiting the Atopic March Current Evidence

The concept of the atopic march was originally proposed to describe the typical sequence of progression of childhood allergic disorders, with atopic dermatitis predating the development of asthma and allergic rhinitis (1). Data from cohort studies conducted over the past 2 decades has greatly improved our understanding of the natural history of allergic diseases, and there is now a large body of evidence revealing that applying a strict interpretation of the atopic march as initially described does not accurately reflect the wide heterogeneity of the natural history across diverse patient populations. For example, allergic conditions may not necessarily evolve in the order as described, and the "march" of conditions may span across many decades, with asthma developing in adulthood, years after childhood atopic dermatitis (2). Moreover, it remains unclear whether the interrelationships between allergic conditions are causal or related to confounding by shared genetics and/or shared environment. There is convincing evidence that the allergic conditions share a common genetic origin (3), and there is also compelling data from twin and sibling studies that controlled for shared genetics and shared environment, which suggests the associations between conditions could be causal (4, 5). Confirming the existence of causal relationships would have substantial implications in an era marked by soaring prevalence of allergic disease and asthma and few effective prevention strategies.

Interest in the atopic march has increased substantially in the past decade. On PubMed, journal publications related to the topic have increased from five articles between 1990 and 1999 to 45 articles annually between 2019 and 2021. Of note, the definition of "atopic march" applied by authors across these studies has varied widely, with some studies adhering to the narrow definition as originally described and others applying a broader interpretation to acknowledge the diversity of disease natural history that has been reported. Furthermore, authors have variably assumed a causal relationship between atopic dermatitis and later allergic airway disease. These inconsistencies have caused much confusion, with the same findings often being used to both support and reject the atopic march concept. For example, the observation that eczema and asthma may coexist in early childhood has been used to support the atopic march; conversely, the atopic march has been challenged based on the argument that where eczema and wheeze occur together in early life, it is wheeze rather than eczema that is associated with subsequent asthma (6). Nevertheless, some cohort studies have demonstrated persistence of the association between eczema and subsequent asthma even after excluding wheezers from the analysis (7).

In this issue of the *Journal*, Haider and colleagues (pp. 950–960) aimed to evaluate the validity of the atopic march hypothesis using data from four birth cohort studies in the United Kingdom (8). They investigated the onset, progression, and resolution of eczema, wheeze, and rhinitis using sequence mining and Latent Markov modeling. Strengths of the study are its birth cohort design, prospectively collected data, and state-of-the-art statistical methodology. Findings showed that one in four children with eczema transitioned to at least one allergic phenotype, and one in five transitioned to multimorbidity (having all three conditions). As only a small subset of children with eczema progressed to other allergic conditions, the authors concluded that there is no typical sequence of disease development that characterizes atopic multimorbidity. Although the authors can be commended for undertaking this elegant study, which contributes substantially to the ongoing debate about the atopic march, the conclusions are perhaps premature.

The broad definition of eczema as an itchy rash applied by Haider and colleagues (8) requires further scrutiny. Eczema encompasses a range of phenotypes, including both atopic and nonatopic dermatitis. It is well-established that selected eczema phenotypes, specifically atopic dermatitis that is associated with positive allergen-specific IgE, early-onset eczema that starts within the first 6 months of life, and severe eczema, are strongly associated with food allergy and allergic airway disease, which is in line with the atopic march concept. Although it is a valid approach to apply the broad eczema definition in population-based studies, this would have resulted in substantial misclassification for evaluating the atopic march, and it is not surprising that only one in five children with eczema in the study were significantly more likely to transition to allergic disease multimorbidity. It is likely that limiting the definition of atopic dermatitis to atopic eczema or very early life eczema would have produced a stronger association. Furthermore, there is increasing evidence of the role of food allergy in this march (9) and factoring this into the equation could produce more nuanced findings.

On the basis of the study findings, the authors recommend that clinicians withhold advice to parents of children with eczema regarding the potential future risk of asthma. In an era of prioritizing precision prevention and management, it is perhaps hasty to dismiss the importance of risk communication in clinical settings. Understanding the likelihood of developing asthma or allergic rhinitis can benefit patients by increasing awareness and enabling timely diagnosis and management. An alternate approach could be to better define the characteristics that identify the 25% of children with "itchy rash" (defined as eczema) who are at risk.

We propose that the findings of the current study, taken together with previous studies, provide strong evidence for the validity of the atopic march, when this is interpreted to broadly describe the temporal associations between allergic phenotypes that may evolve along multiple pathways, incorporating the progression from

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sensitization to overt clinical allergic disease or from one allergic condition to others (10). In this wider context, the original description of atopic dermatitis preceding allergic airway disease represents the most observed pathway. We support an expanded interpretation of the atopic march that includes the various transitions in atopic conditions as it expedites the advancement of precision practice by offering an approach to early identification of patient subgroups at risk of marching toward other allergic conditions.

There is great potential to conduct in-depth investigations of multiple phenotypes of allergic disease using the rich birth cohort data sets as presented in the current manuscript (8) with the aim of better understanding risk trajectories for the development of allergic diseases. Such information will benefit efforts toward personalized patient care and may facilitate the development of novel tailored strategies to arrest an individual's march toward further disease. Let's not "throw the atopic baby out with the bathwater" just yet. ■

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References

1. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(6, Suppl):S118–S127.
2. Burgess JA, Dharmage SC, Byrnes GB, Matheson MC, Gurrin LC, Wharton CL, *et al.* Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol* 2008;122:280–285.
3. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, *et al.*; 23andMe Research Team; AAGC collaborators; BIOS consortium; LifeLines Cohort Study. Shared genetic origin of asthma, hay fever, and eczema elucidates allergic disease biology. *Nat Genet* 2017;49:1752–1757.
4. Khan SJ, Dharmage SC, Matheson MC, Gurrin LC. Is the atopic march related to confounding by genetics and early-life environment? A systematic review of sibship and twin data. *Allergy* 2018;73:17–28.
5. Hopper JL, Bui QM, Erbas B, Matheson MC, Gurrin LC, Burgess JA, *et al.* Does eczema in infancy cause hay fever, asthma, or both in childhood? Insights from a novel regression model of sibling data. *J Allergy Clin Immunol* 2012;130:1117–1122.e1.
6. Shen CY, Lin MC, Lin HK, Lin CH, Fu LS, Fu YC. The natural course of eczema from birth to age 7 years and the association with asthma and allergic rhinitis: a population-based birth cohort study. *Allergy Asthma Proc* 2013;34:78–83.
7. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ, *et al.* Do boys do the atopic march while girls dawdle? *J Allergy Clin Immunol* 2008;121:1190–1195.
8. Haider S, Fontanella S, Ullah A, Turner S, Simpson A, Roberts G, Murrary CS, *et al.*; STELAR/UNICORN11 investigators. Evolution of eczema, wheeze, and rhinitis from infancy to early adulthood: four birth cohort studies. *Am J Respir Crit Care Med* 2022;206: 950–960.
9. Alduraywish SA, Standl M, Lodge CJ, Abramson MJ, Allen KJ, Erbas B, *et al.* Is there a march from early food sensitization to later childhood allergic airway disease? Results from two prospective birth cohort studies. *Pediatr Allergy Immunol* 2017;28: 30–37.
10. Lowe AJ, Abramson MJ, Hosking CS, Carlin JB, Bennett CM, Dharmage SC, *et al.* The temporal sequence of allergic sensitization and onset of infantile eczema. *Clin Exp Allergy* 2007;37:536–542.

Insights into Endotheliopathy in COVID-19

Severe coronavirus disease (COVID-19) is characterized by a disruption of barrier function between the pulmonary circulation and alveoli, leading to characteristic alveolar infiltrates, hypoxemia, and in the worst case acute respiratory distress syndrome (ARDS) (1). Endothelial integrity plays an important role in maintaining the pulmonary capillary–alveolar barrier. Autopsy studies have shown that severe COVID-19 is associated with endothelial cell damage, perivascular inflammatory cell infiltration, with interstitial edema and alveolar space fluid consolidation (2). Clinical studies measuring circulating endothelial biomarkers support the hypothesis that endothelial dysfunction is an underlying factor in COVID-19 pathogenesis and a harbinger of poor outcome (3). Despite evidence that lung endothelial injury plays a key role in severe COVID-19, there has been relatively little translational investigation focusing on pulmonary vascular endothelium and its response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

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