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Guest Editorials

Can the atopic march be predicted?

The "atopic march" refers to the progression from inflammatory skin manifestations in early life, usually diagnosed as "atopic dermatitis," to subsequent food allergy, asthma, and allergic rhinitis. Hill and Spergel[1] note that the skin inflammation likely results from a primary skin barrier defect interacting with genetic or environmental susceptibility, which could lead to the development of inflammation mediated by T-helper cell type 2. However, up to two-thirds of children with atopic dermatitis do not have atopy as judged by skin prick test reactions or serum immunoglobulin E levels.[2] Busse[3] argues that the atopic march does not explain all development of subsequent allergic diseases, because many adults with severe asthma do not give a history, at least in retrospect, of severe skin lesions in childhood. However, he also notes that much of the evidence for the atopic march comes from cross-sectional studies rather than longitudinal follow-up of individual patients.

More than a decade ago, Flohr et al[2] called for well-conducted longitudinal studies in atopic dermatitis that compare differences in prognosis between sensitized and non-sensitized children. We addressed this in children participating in the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study. In this study, a diagnosis of atopic dermatitis but without allergic sensitization detectable at 1 year of age was not associated with an increased risk of asthma at 3 years.[4] In contrast, atopic dermatitis with allergic sensitization at 1 year detected by skin prick test reaction increased the risk of asthma at 3 years more than 7-fold. Sensitization was dominant to food allergens (egg, peanut, and milk) with less evident inhalant sensitization.

Hill and Spergel[1] point out that food sensitization can develop before the food is ingested, and that sensitization to food allergens likely occurs through the inflamed skin. Peanut allergen is found in the dust of many homes[5] and was included in some creams used to treat infantile rashes. In a previous analysis from the CHILD study, we showed that delayed introduction of milk, egg, and peanut was associated with increased risk of sensitization at 1 year.[6] This suggests that early introduction of these foods can result in tolerance to these common allergens, whereas a cutaneous route of introduction can result in sensitization.

Johansson and Hershey[7] raise an alternative hypothesis that eczema, food allergy, and airway allergy are independent manifestations of a dysfunctional immune system predisposing to an allergic reaction mediated by immunoglobulin E in response to environmental stimuli. Because only a fraction of children with early eczema go on to develop asthma and not all asthma cases are preceded by eczema, they consider it unlikely that eczema causes disease progression or the atopic march, but rather, that it is a symptom of the underlying epithelial barrier dysfunction that confers these risks. The CHILD study data showed that sensitization to allergens, predominately food allergens, at a young age was a major driver of the atopic march toward subsequent development of asthma,[4] indicating a systemic response mediated by immunoglobulin E as a significant component of this progression. Atopic dermatitis without sensitization was associated with some increased risk of allergic rhinitis and food allergy, but not of asthma. Allergic sensitization had significant interactions with atopic dermatitis on the additive and multiplicative scales in relation to asthma risk and a positive additive interaction in their effects on food allergy.

The misnomer of "atopic dermatitis" has added confusion to the concept of the atopic march. It is critical for clarity in prognosis to differentiate allergen-sensitized from non-sensitized children with dermatitis. The atopic march is much more strongly related to dermatitis accompanied by early sensitization, especially to foods, than dermatitis without sensitization.

Can the atopic march be prevented or modified? As Johansson and Hershey[7] discuss, a clearly demonstrated causal relation between early sensitization through a compromised skin barrier and the later development of asthma and allergic rhinitis might allow intervention strategies to be implemented. One such strategy is early introduction of "allergenic" foods, as shown in clinical trials[8,9] and our epidemiologic observations,[5] which promotes tolerance rather than sensitization to those foods. Ascertainment of true allergic sensitization not only helps explain the diversity of outcomes of atopic dermatitis but also identifies those at higher risk who could benefit from strategic interventions to prevent this inexorable journey.

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The atopic march: Fact or folklore?

Atopic dermatitis, allergic rhinitis, and asthma are common, frequently appear together, and usually begin in early life, thus posing lifelong burdens for many affected patients. Based on clinical observations and studies of disease prevalence, it has been proposed that the sequential development of atopic dermatitis, asthma, and allergic rhinitis is a causal relationship now known as the "atopic march"[1] (Fig 1). The concept of an atopic march has captured our interest because it earmarked an allergic harbinger of "bad things" to follow.

The atopic march has also served important and helpful aspects in patient care. First, it "alerts" the family and physician that asthma is likely to occur, an awareness that could facilitate an earlier recognition of asthma and prevent treatment delays. Second, recognizing the atopic march increases family and physician attention to look for possible precipitants of disease (eg, food allergies or wheezing with colds). Third, and perhaps most importantly, as efforts move toward disease prevention, the appearance of the atopic march had the promise of a reliable early marker to identify infants most at risk and most likely to benefit from preventative interventions.

For nearly a quarter of a century, the concept of the atopic march has been part of our specialty's beliefs. The question for today is "how well is the atopic march holding up?" The foundations for the atopic march come largely from cross-sectional studies that pointed to early life relations of atopic dermatitis, subsequent allergic sensitization, and a later expression of asthma and allergic rhinitis.[2] For patient care, this relation had considerable appeal, because it identified early life events that herald the likely progression to other allergic airway diseases. Mechanistically, the question was often asked as to whether defects in barrier protection would promote allergen entry and contribute to atopic dermatitis and then asthma.[3,4] This concept fit nicely with allergic sensitization, initially to foods and then to aeroallergens. Atopic dermatitis had become the touchstone for early sensitization and as recognition of at-risk infants who would be target candidates to interrupt the atopic march.

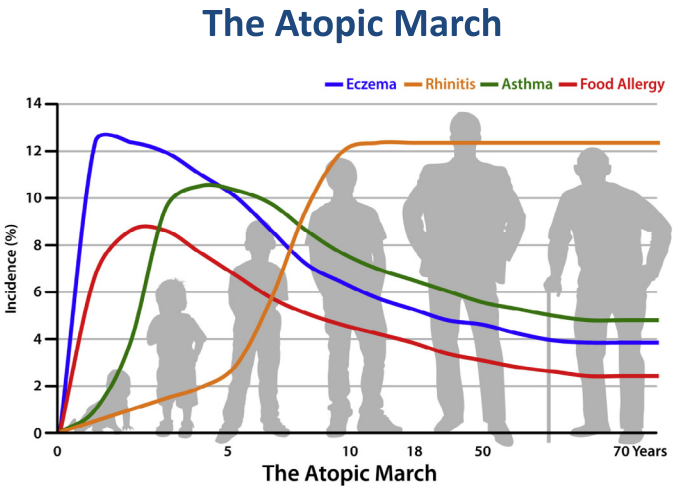

Figure 1. The atopic march. The prevalence of atopic dermatitis peaks early in infancy, opening the door to the consequent development of the atopic march. Development of food allergy, asthma, and allergic rhinitis in the young toddler group is common after cutaneous manifestations. Reprinted courtesy of Elsevier.[1]

What Concerns Exist with the Atopic March?

From my viewpoint, studies of severe asthma have not shown striking associations between early life atopic dermatitis and this aspect of asthma.[5] Although significant limitations exist in using data obtained from adults to assess early life eczema to adulthood asthma, this association has not emerged. I suspect if the atopic march were linked to later expression of asthma, then patients with severe asthma would be a key to see this relation.

More critical to concerns with this concept has been the use of epidemiologic evidence that has been based largely on cross-sectional populations and not on longitudinal development in individual patients. Moreover, the identification of allergic diseases, asthma, and atopic dermatitis, for example, is often based on a "yes" or "no" to questions. This approach fails to consider disease heterogeneity or, more importantly, variations (ie, latency) in their expression. Atopic dermatitis and asthma are "umbrella" terms for these diseases and do not recognize underlying heterogeneity that reflects variations in longitudinal expression, severity, and, importantly, underlying mechanisms.

Because asthma has been a key outcome in the atopic march, the early work of Martinez et al[6] with the Tucson Children's Respiratory Study illustrated the need to appreciate distinct patterns (ie, heterogeneity) of airway diseases rather than lumping all childhood wheezing illnesses under the asthma umbrella. Martinez et al[6] found distinct early life patterns of wheezing with differences in long-term significance to asthma: transient early wheezing, late-onset wheezing, and persistent wheezing; not all translate to later life asthma. Eczema was found to be associated with transient early and persistent wheezing but not with late-onset wheezing. If eczema was a factor for asthma in this cohort, then its impact was restricted to subpopulations, or covariants, of airway disease.

Covariant factors exist in at-risk infants, and their presumed influence on an eventual expression of allergic disease in later childhood is variable. In Childhood Origins of Asthma (COAST), 259 high-risk children were followed from birth to 6 years of age when early life events were related to the development of asthma.[7] The diagnosis of asthma in COAST was based on a documented presence of 5 potential criteria for this disease. In addition, 4 separate investigators, who had been blinded to individual subjects' antecedent histories, independently evaluated for the presence of asthma. The label of asthma needed to meet well-defined and accepted criteria for this disease. A number of key early life events in COAST emerged as being significant for the diagnosis of asthma at 6 years of age: wheezing

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