The allergies go marching on: the atopic march and the temporal relationship of allergic diseases

Atopic/allergic family of diseases affects >20% of the global population and encompasses allergic asthma, hay fever, food allergy, atopic dermatitis, and allergic rhinitis. Frequently, individuals with an allergic condition develop another allergic disease. The atopic march theory summarizes this relationship, which often starts with childhood atopic dermatitis that proceeds to allergic asthma and/or allergic rhinitis.

Allergic sensitization occurs when innocuous agents known as allergens trigger immune cells, namely helper T cells and B cells, to produce antibodies, that bind to the surface of mast cells. When next exposed to the allergen, binding to the antibodies activates mast cells to release factors that cause symptoms of allergies. This allergic response, when prolonged promotes tissue changes due to continual activation of local inflammatory cells. In the atopic march, it is postulated that changes in the skin of suspectable individuals facilitates allergen and pathogen entry, which triggers an allergic response and subsequent systemic sensitization. Murine models have shown that mice sensitized to an allergen in the skin will eventually mount a response in the airways when the same allergen is inhaled.

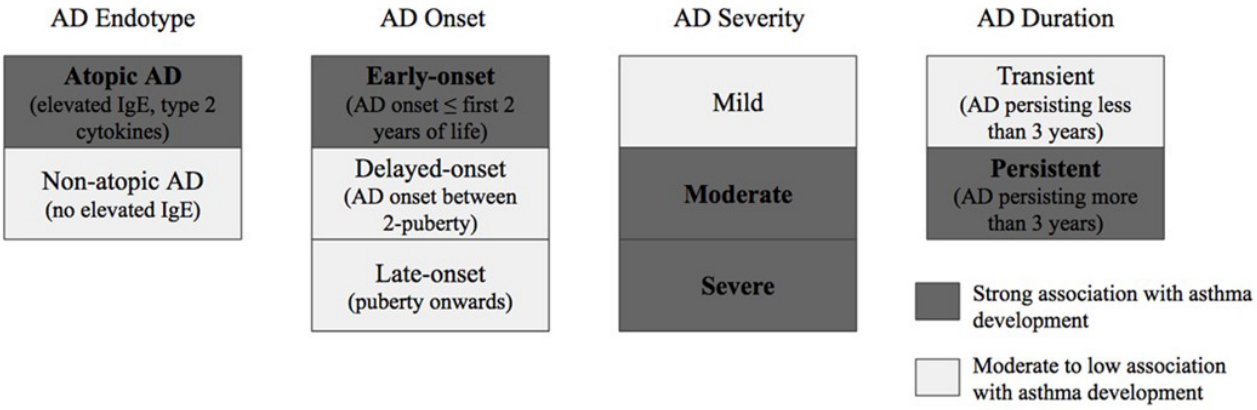

Fig. 1. Atopic Dermatitis Features Associated with Allergic Asthma Development, adapted from Aw et al, 202016. Legend: IgE – immunoglobin E, AD – Atopic Dermatitis.

Numerous epidemiologic studies demonstrate a progressive between common atopic diseases. In a population-based birth cohort, early-onset atopic dermatitis (less than 1.5 years old) was associated with persistent wheezing at age 6. Similarly, a population-based study in Tasmanian found that early-onset atopic dermatitis (onset less than 2 years old) doubled the odds of developing allergic asthma. The Dampness in Building and Health study followed 3000 children (aged 1-2) for 5 years and reported that children with atopic dermatitis had a 3-fold increased odds

ratio of developing allergic rhinitis. The German mass allergen study studied 942 infants over 17 years and reported an increased prevalence of co-morbid allergic asthma or allergic rhinits from ages 3-7 with an age dependent decrease in the atopic dermatitis prevalence.

The atopic march model may be oversimplified as only 3.1% of children follow the typical model (atopic dermatitisàallergic asthmaàallergic rhinitis); this increases to approximately 10.5% when associating atopic dermatitis with other atopic condition. Nonetheless, there are risk factors that favour atopic march progression (Fig. 1). Genetics play a major role. Children with an atopic family history are 5 times more likely to develop early persistent atopic dermatitis. There is a 0.3-0.4 phenotypic correlation with allergic asthma, of which 80% is attributable to genetics. Specifically, patients with filaggrin mutations, an integral epithelial protein, are predisposed to developing atopic dermatitis and allergic asthma. A metanalysis of 24 human studies showed that filaggrin mutations increased the odds of developing allergic asthma by 1.5 fold and 3 fold if the subjects also had atopic dermatitis. Furthermore, early onset atopic dermatitis which was persistent and severe increased the risk of developing asthma. Similarly a strong association between early-onset atopic dermatitis and asthma during a 5 year follow-up, but no association between late-onset atopic dermatitis and asthma has been reported. A prospective Canadian birth cohort study showed that the odds of developing allergic asthma or allergic rhinitis the age of 7 was significantly greater for children with early-onset persistent atopic dermtitis. Notably, only a third of patients with eczema have any allergen-specific IgE sensitization. Several longitudinal studies have found a strong relationship between IgE-associated atopic dermatitis and asthma which further implicates this phenotype.

As the global prevalence of allergic disease rises, so does its impact on population health. Epidemiological evidence supports the progression of allergic disease as seen through co-morbidity and temporal prevalence changes. Understanding the role of age, severity, family history, phenotype, and genetic traits all give a clearer picture as to how atopic dermatitis may progress into allergic airways diseases.

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