Allergy Asthma Immunol Res. 2022 Nov;14(6):585-586
https://doi.org/10.4168/aair.2022.14.6.585
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Which Subtype of Atopic Dermatitis Progresses to Asthma? A Story About Allergic March

Jinho Yu *

Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

▸ See the article "Phenotype of Atopic Dermatitis With Food Allergy Predicts Development of Childhood Asthma via Gut Wnt Signaling" in volume 14 on page 674.

Received: Oct 7, 2022
Revised: Oct 12, 2022
Accepted: Oct 18, 2022
Published online: Nov 14, 2022

Correspondence to
Jinho Yu, MD, PhD
Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3922
Fax: +82-2-3010-6978
Email: jyu3922@gmail.com

ORCID iDs
Jinho Yu
https://orcid.org/0000-0002-1226-8077

Disclosure
There are no financial or other issues that might lead to conflict of interest.

The allergic march is the progression of allergic disorders from atopic dermatitis (AD) in infancy to asthma and allergic rhinitis (AR) later. Most prospective epidemiologic studies suggest that early AD is a risk factor for the development of asthma,[1-3] whereas only a few AD subtypes with concomitant wheezing or less prevalent sensitization types in infancy are strongly associated with the risk of asthma during childhood.[4] Hence, those studies raise the question of whether the allergic march is a sequential development from AD to asthma and AR or just one of the combinations of allergic comorbidities.

Recently, Haider *et al.*[5] investigated the evolution of eczema, wheezing, and rhinitis from infancy to early adulthood using data from 4 UK population-based birth cohorts. They demonstrated that allergic diseases fit a multimorbidity framework, with no evidence for a sequential allergic march. Progression from eczema to a multimorbidity state (eczema + wheezing + rhinitis) was observed in only 1 in 5 children, and most children with eczema did not show such a progression. In this issue of *Allergy, Asthma & Immunology Research*, Lee and colleagues[6] demonstrated that the allergic march-related phenotype (food allergy [FA] + AD) had a prevalence of 2.9% in the study subjects, and 10.7% of AD phenotypes were associated with asthma. Hence, an allergic march-related phenotype accounts for a small percentage of all allergic phenotypes. However, as long as this phenotype exists, it is important to be able to predict this subtype, especially in children with AD.

FA may be involved in the progression from AD to asthma, as mentioned by Lee *et al.*[6] Before we can say that AD with FA is related to asthma, it is necessary to demonstrate the effect of FA alone on asthma development. A study of a family-based FA cohort in Chicago demonstrated an association between FA and asthma, and the association was stronger in children with multiple FA or severe FA.[7] Another birth cohort study found that eczema and FA in infancy independently increased the risk of all 4 allergic manifestations, namely asthma, AR, eczema, and FA, not just of asthma or AR at 8 years.[8] However, most studies did not confirm FA using the oral food challenge, and children with FA usually have comorbid AD in early childhood. Therefore, it is difficult to demonstrate the role of FA itself in the allergic march. The comorbidity of FA in children with AD may reflect the sensitization pattern, which may be related to the development of asthma rather than FA itself.

The Wingless/Integrase-1 (WNT) pathway is an evolutionarily conserved signaling pathway critical for embryogenesis and several biological processes. Recently, it has been reported to

be involved in inflammation, remodeling, and hyperresponsiveness of the airway, which are characteristics of asthma.[9] Of interest, WNT signaling is associated with an AD subtype (AD + FA), which had the risk of developing asthma later. However, the authors did not show the association of the WNT signal with asthma in this cohort. The WNT signal may be a secondary finding of the phenotype of AD with FA rather than mediating the development of asthma.

Unsupervised clustering techniques such as latent class analysis (LCA) can help researchers discover novel phenotypes. If a phenotype found by this method is related to other diseases, validation should be performed in the cohort using actual disease variables. Not all children with the FA + AD phenotype have both FA and AD; likewise, not all subjects with each phenotype have the same features. In addition, each variable should be evaluated using the same time periods and intervals. Some children with asthma aged 5–7 years may have an onset before the age of 3 years. If wheezing is checked annually in the first 3 years and the results are included in LCA, the phenotypic effects may be different. Therefore, children with multiple comorbidities including wheezing before 3 years of age may develop asthma at 5–7 years. Unfortunately, this aspect was not well evaluated in the current study.

Given that there is little evidence that FA is involved in the allergic march, especially as a comorbidity of AD, further studies are required to clarify the role of FA in the allergic march. Questions remain unsolved: Is the allergic march a sequential progression from AD to asthma and AR or just a combination of allergic comorbidities?

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https://doi.org/10.4168/aair.2022.14.6.585