

The chicken or the egg: allergy or asthma?

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

Jinho Yu

Introduction

Allergy is not the same as asthma. If you define allergy as atopy, a positive response to at least one allergen in the skin prick test, allergic sensitization precedes the development of asthma. However, if you define allergy as allergic diseases including atopic dermatitis, food allergy, asthma, and allergic rhinitis, allergic diseases share common allergic immune response. Although the association of allergy with asthma can be different by the definition, asthma has heterogeneous phenotypes and endotypes including allergic phenotype, and allergy is still a strong risk factor for the other allergic diseases. However, the association of allergy with asthma is still not simple beside the issue of definition.

Asthma include different phenotypes underpinned by different pathophysiology

Recent academic trend is to try to divide asthma into diverse subgroups (phenotypes/endotypes) according to the clinical and pathophysiologic characteristics, although the majority of asthma cases are still being treated with the one-size-fits-all management.

Th2 endotype is a most common endotype both in children and adults with asthma. This endotype is strongly linked to atopy, and usually starts during childhood. Several subendotypes might exist within this endotype, such as the IL-5-high, IL-13-high, or IgE-high. Biologic therapy for Th2 asthma, omalizumab, an anti-IgE molecule is commonly used recently, IL-4/13 blockade or Anti-IL-5 treatment is reported to be effective in some patients with Th2-related asthma.

Non-Th2 endotype is much less known in terms of the mechanism. This endotype was associated with Th17 endotype or neutrophilic endotype, and was found in both adults with asthma and recurrent wheezers

during early childhood. This phenotype is mostly non-atopic in adults, but non-atopic asthma phenotype during childhood is not similar with this phenotype.

There is no study showing the clinical characteristics and natural course of childhood asthma according to the phenotype in Korea. We have established a pediatric nationwide asthma cohort (Korean childhood Asthma Study, KAS) from 20 hospitals since July 2016, and total of 830 children with asthma were recruited and are currently being traced. Cluster analysis showed four clusters (cluster 1: male-dominant atopic asthma, cluster 2: highly atopic asthma with atopic dermatitis, cluster 3: female-dominant, puberty-onset, atopic asthma, cluster 4: relatively non-atopic asthma). The cluster of childhood asthma was determined by the presence of atopy, sex, puberty and allergic comorbidities. Most of our clusters are atopic, but cluster 4 was non-atopic. It still remains to be elucidated whether this non-atopic asthma is underpinned by several endotypes or a single endotype.

I prefer the old concept that both viral airway infection during early childhood and atopy are required to develop childhood asthma, and the persistence of asthma was dependent on the atopy and airway hyperresponsiveness during childhood. Lower respiratory tract infection during early childhood leads to the change of airway tone, and even its structure, resulting in airway lability and airway hyperresponsiveness. Our non-atopic asthma may reflect the airway change after injury by virus, air pollution or other environment factors during early childhood or even during pregnancy, and the limitation of airway growth and development without atopy. I think this concept of the development and the growth of airway should be added to childhood asthma phenotypes.

Conclusion

Asthma has heterogeneous groups with various pathophysiology, and the course and the prognosis may be different depending on its phenotype, wherein atopy is one of them, strongly linking to asthma. Recently, the cluster of Korean childhood asthma was determined by the presence of atopy, sex, puberty and allergic comorbidities. It is necessary to clarify the mechanism of each cluster, and which cluster has more exacerbation or progresses into uncontrolled asthma through long-term follow up study.

References

1. Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol.* 2014;133:1289-300.
2. Just J, Saint-Pierre P, Gouvis-Echraghi R, Laoudi Y, Roufai L, Momas I, et al. Childhood allergic asthma is not a single phenotype. *J Pediatr.* 2014;164:815-20.
3. Simpson JL, Grissell T V., Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in

- neutrophilic asthma and bronchiectasis. *Thorax*. 2007;62:211-8.
4. Von Mutius E, Vercelli D. Farm living: Effects on childhood asthma and allergy. *Nat Rev Immunol*. 2010;10:861-8.
 5. Bousquet J, Anto J, Sunyer J, Nieuwenhuijsen M, Vrijheid M, Keil T, et al. Pooling birth cohorts in allergy and asthma: European union-funded initiatives-a MeDALL, CHICOS, ENRIECO, and GA2LEN joint paper. *Int Arch Allergy Immunol*. 2013;161:1-10.
 6. Smits HH, van der Vlugt LEPM, von Mutius E, Hiemstra PS. Childhood allergies and asthma: New insights on environmental exposures and local immunity at the lung barrier. *Curr Opin Immunol*. 2016;42:41-7.
 7. Taylor SL, Leong LEX, Choo JM, Wesselingh S, Yang IA, Upham JW, et al. Inflammatory phenotypes in patients with severe asthma are associated with distinct airway microbiology. *J Allergy Clin Immunol*. 2018;141:94-103.
 8. Turner S. Gene-Environment Interactions—What can these tell us about the relationship between asthma and allergy? *Front Pediatr*. 2017;5:8-14.
 9. Guibas G V., Mathioudakis AG, Tsoumani M, Tsaouri S. Relationship of allergy with asthma: There are more than the allergy “eggs” in the asthma “basket.” *Front Pediatr*. 2017;5:1-7.
 10. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. *J Allergy Clin Immunol*. 2017;140:1-12.
 11. von Mutius E. Biodiversity: The new kid on the block? *J Allergy Clin Immunol*. 2018;141:1215-6.
 12. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: Implications for development of asthma prevention strategies. *J Allergy Clin Immunol*. 2005;116:16-25.