

Toward a definition of asthma phenotypes in childhood: Making a long way shorter?

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Asthma is a global health problem that imposes a burden on the family, the health care system, and society as a whole and results in massive social and economic costs to the community.¹ In most cases asthma has its origins in early childhood, when the interaction of genetic and environmental factors shape airways development in a healthy or pathologic direction.² Many attempts have been made to stop asthma in its early stages in childhood. Unfortunately, long-term pharmacologic treatment, allergen avoidance, or other strategies can hardly modify the natural course of the disease.³

Guidelines have been based on a uniform therapeutic approach, as if asthma were rather homogeneous. However, early childhood asthma has highly heterogeneous phenotypes, and a mismatch between heterogeneous phenotypes and homogeneous therapy contributes to treatment failure.⁴ For a few years, it has been debated whether asthma should be seen as a single disease or rather a “syndrome” including multiple, separate, and overlapping “asthma-like” mild and severe diseases differing in risk factors, triggers, mechanisms, pathophysiology, and natural course and therefore requiring tailored diagnostic and therapeutic approaches.⁴⁻⁶ Hence not only standard diagnostic or therapeutic approaches⁷ but also standard predictive and preventive strategies can be nonspecific in most patients because the strategies do not suit the wide heterogeneity of asthma phenotypes.^{8,9} Therefore it is essential that we learn to identify in early life the different asthma phenotypes and their risk factors, profiles, and pathophysiologic mechanisms.

In this issue of the *Journal*, Just et al¹⁰ use cluster analysis for 551 wheezing 3-year-old infants to characterize the heterogeneity of wheeze in early childhood. On the basis of 19 variables, they describe 3 independent groups of wheezing children: early viral wheezers, multitrigger wheezers (MTWs), and nonatopic uncontrolled wheezers (NAUWs). The first category might correspond to the “early wheezers” described almost 2 decades ago by Martinez et al.¹¹ The remaining 2 clusters describe infants with more severe wheezing and quite polarized characteristics: MTW

children are typically atopic boys with higher total IgE levels whose relatively well-controlled wheezing is triggered by multiple factors in supposedly highly allergenic environments. In contrast, NAUW children are more frequently nonatopic girls with uncontrolled wheezing often associated with infectious agents. This observation might have been hampered by some limitations. First, the 2 categories of wheezing children overlap because some boys belonging to the MTW cluster are nonatopic and some girls belonging to the NAUW cluster are atopic. Second, atopy has been defined not by frequently observed clinical comorbidity (atopic dermatitis and food allergy in infancy and allergic rhinitis or a positive family history for atopic diseases) but on the basis of total and airborne specific IgE in the serum. Third, the expression of clinical phenotypes might have been biased by antiasthma pharmacotherapy.

In any case, the authors conclude that they have identified 2 novel phenotypes of severe wheezing in early childhood. Interestingly, the categories of MTW and NAUW children described by Just et al¹⁰ echo the traditional definitions of “extrinsic” and “intrinsic” asthma, respectively, in adults. Therefore the logical question is whether these 2 categories of wheezing children are stable or whether their combinations of sex, symptoms, and triggers are bound to be dissolved and later in life reaggregated with other symptoms and risk factors in different combinations and shapes. Unfortunately, the purely cross-sectional nature of the study by Just et al does not allow an answer to this crucial question. Nevertheless, many of the 19 parameters investigated in the study have also been included in serial birth cohort studies on allergy and asthma that have been performed in the last 2 decades. Therefore this study could inspire new statistical analyses of those birth cohorts to test the hypothesis that MTWs and NAUWs are the antecedents in early life of “extrinsic” and “intrinsic” asthma phenotypes.

We clearly need to make progress in early phenotypic characterization of asthma to move toward improved control, prediction, and prevention. For example, patients in the category of atopic male MTWs might wheeze because of allergic inflammation and catarrh in the lower airways, which are still small for age, in the absence of bronchospasm or bronchoconstriction. Then this “wheezing” would, in most cases, naturally disappear with age as soon as the bronchial lumen grows large enough. Hence MTW children might be affected by “allergic bronchitis” rather than “asthma.” Allergic bronchitis would be the disease of those atopic children, mostly boys, with allergic rhinoconjunctivitis and wheezing at preschool age whose “asthma” (but not hay fever) goes into remission before puberty.¹² We would need a specific diagnostic and predictive algorithm for “allergic bronchitis” in addition to those used to diagnose and predict “asthma.”

While analyzing the natural course of wheezing disorders in the Multicenter Allergy Study birth cohort, we chanced on the observation that the pattern of risk factors useful to predict the

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long-term outcomes of wheezing changes according to the age of the onset of wheezing.⁸ From this, we hypothesize that multiple algorithms are necessary to predict with confidence the different phenotypes of asthma in childhood.¹³ Notwithstanding the limitations of their study, Just et al¹⁰ have helped to move knowledge in this same direction. The way is quite long, but every step forward makes it shorter.

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