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Remodeling Phenotypes Take Center Stage in the Prediction of Preschool Wheeze Attacks

Airway inflammation and structural wall abnormalities (remodeling) are considered the two hallmark pathological features of asthma. For more than 15 years, we have known that airway remodeling is present very early, in the first 5 years of life, in preschool children with severe recurrent wheezing. There is evidence of subepithelial reticular basement membrane (RBM) thickening (1), increased bronchial smooth muscle (BSM), angiogenesis, and epithelial damage (2). However, little relationship is apparent between clinical wheeze phenotypes (viral wheezing or multiple-trigger wheezing) and remodeling (3) or between inflammation and remodeling (4) in early life. Follow-up of preschoolers with severe wheezing has shown that features of remodeling, including BSM (5) and reticular basement membrane thickness (6), rather than eosinophilic inflammation, predict progression to asthma at school age.

What has not been investigated to date is the relevance of airway remodeling in predicting shorter-term outcomes for preschool wheezers. Although unbiased analyses of lower airway inflammation have revealed distinct preschool wheeze clusters with relationships to therapeutic response (7), we did not have evidence for the role of remodeling in determining more immediate outcomes.

In this issue of the *Journal*, Fayon and colleagues (pp. 416–426) have, for the first time, demonstrated the role of a cluster of features of remodeling that predict exacerbations of severe wheeze in the year after biopsy (8). They have incorporated epithelial integrity, RBM thickness, mucus glands, fibrosis, BSM area, density of blood vessels, and RBM–BSM distance as markers of remodeling. Using latent class analyses, they identified a two-class model; the class that was characterized by increased RBM thickness, smooth muscle, and blood vessel density and reduced mucus glands, fibrosis, and RBM–BSM distance was associated with significantly more exacerbations and a shorter time to first exacerbation over the subsequent 12 months. There were no clinical features that distinguished the children in each latent class before the bronchoscopy. The mean age at bronchoscopy was 2.3 years, and, as has been shown previously for severe recurrent wheezers, only approximately one-quarter had aeroallergen sensitization, despite a median of six oral corticosteroid bursts ever for wheezing.

An important aspect of the study is the young age of the children included, highlighting that even during such early wheezing, remodeling is a complex process that involves structural modifications in virtually all components of the airway wall and that there is no single aspect of airway remodeling that appears to precede the others. The main histological changes observed in the airways of the children who went on to have wheeze attacks consisted of increased RBM thickness (due to collagen deposition in the lamina reticularis) with a concurrent increase in BSM area, thus reducing the distance between the epithelial and the smooth muscle compartments. Increased thickness of the smooth muscle layer measured on biopsy sections may result either from more muscle cells (hyperplasia), larger muscle cells (hypertrophy), and/or more extracellular matrix within the smooth muscle layer (9). Because BSM area was measured in sections stained specifically to detect smooth muscle actin, the present results would suggest a direct involvement of smooth muscle cell abnormalities. Reduced fibrosis, but increased subepithelial RBM thickness, suggests distinct mechanistic processes and types of collagen are involved in the submucosal layer compared with the subepithelial layer. An increased density of blood vessels in the airways was also observed at this early stage and was associated with exacerbations at 1-year follow-up. Changes in vascularity may be due to both dilatation and congestion of existing vessels but also to the formation of new vessels (neoangiogenesis), possibly as a response to growth factors released from other injured airway structures, such as the epithelium or the smooth muscle (10). Because increased vascularity may then contribute to the amplification of airway inflammation, it is conceivable that vascular changes associate with an exacerbation-prone phenotype.

A significant strength of the study was the inclusion of a prospective cohort of children ($n = 56$) in whom the latent

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class model was identified, with validation of the findings in a further cohort ($n = 44$). The move from simple description of remodeling to prediction of outcomes is a significant step forward, and the ability to identify a specific group with worse outcomes paves the way for mechanistic studies that might target the changes associated with frequent and severe exacerbations.

In line with previous studies of severe preschool wheeze that have related lower airway pathology to longer-term school-age outcomes, there was no evidence for inflammation in either the biopsy or BAL being a significant predictive component in the latent class model. Indeed, no clinical features, such as atopy, age, IgE, or clinical phenotype added any predictive value. Even inclusion of BAL bacterial or viral pathogens did not add to the predictive model. What remains a limitation of the study, and must be remembered before discounting the importance of inflammation, is that all children were prescribed high-dose inhaled corticosteroids, and two-thirds were also prescribed long-acting β-agonists and/or leukotriene receptor antagonists. This cannot be avoided in studies that include children with such severe symptoms but may mean the contribution of inflammation is less apparent.

An obvious consideration is the functional impact of these combined remodeling features. There were no assessments of lung function at follow-up to help understand whether any features might specifically be associated with poor lung function outcomes. Knowing the high likelihood of the children who were included in this study being set on a low lung function trajectory, it would have been helpful to know whether lung function declined over the year of follow-up and whether the remodeling phenotype associated with exacerbations was associated with worse lung function. In this context, the results from a cohort following 180 subjects from birth to the age of 36 years underscored the importance of early-life origins of asthma, indicating that lung function deficit at birth associated with high-resolution computed tomography–assessed structural airway abnormalities in adult life (11).

The other issue is the absence of any indication of mechanisms that might be driving the remodeling changes that were associated with future exacerbations. The involvement of airway smooth muscle in poor outcomes seems a consistent finding, and there is a suggestion that abnormal smooth muscle metabolism, represented by altered mitochondrial respiration, and calcium response may explain this (12). However, what is obvious is that one single feature of remodeling is not predictive of outcome; multiple parameters were in the class that had worse outcomes. Also, the spread of data when looking at the individual remodeling changes was large within each group, highlighting the heterogeneity of preschool wheeze. Even though this is a small population, the likely contribution of each parameter of remodeling in each child is different, thus making it a challenge to find a single therapeutic target that will work in all.

The need for interventions that impact multiple remodeling features is apparent. In addition, the huge challenge of finding noninvasive biomarkers that may reflect remodeling has still to be overcome. But the data from Fayon and colleagues now highlight the role of early structural airway changes in determining short-term adverse outcomes in addition to their importance in influencing long-term outcomes. This study suggests a complete re-think in our approach to the management of recurrent severe, troublesome wheezing is urgently needed, with therapeutic interventions that can target remodeling remaining a critical unmet need. ■

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