

Airway granulocytes in severe preschool wheeze: Predictive of school-age asthma attacks or disease protection

Birth cohort studies have consistently shown persistent wheezers who develop asthma have early abnormalities in lung function in the first 3–6 years that are subsequently irreversible, and sustained to adulthood.¹ Of interest, preschoolers with the most severe symptoms have the greatest loss in lung function which presents by school age.² It is, therefore, hypothesized that this early loss in lung function may occur in parallel with the key pathological abnormalities that are characteristic of allergic asthma, namely eosinophilic inflammation and structural airway changes, termed remodelling. Indeed, mechanistic data from a neonatal murine model of inhaled house dust mite exposure has shown the pathophysiological abnormalities develop in parallel.³

Several bronchoscopic studies have now demonstrated the presence of tissue eosinophilia and airway remodelling (increased thickness of the subepithelial reticular basement membrane) in endobronchial biopsies from preschool children with severe, recurrent wheeze compared to age matched nonwheezing controls.^{4,5} However, to date, only one study has followed preschoolers who were biopsied, at school age and related early pathology to later clinical status and lung function. There was no evidence that early eosinophilic inflammation or reticular basement membrane thickness predicted development of asthma by school age,⁶ but increased airway smooth muscle at preschool age was predictive.

The manuscript by Lezmi et al in the current issue of the Journal is of interest as it supports the published data that neither preschool tissue eosinophils nor reticular basement membrane thickness predict asthma at school age. Indeed, none of the pathological parameters assessed at preschool age distinguished children who did or did not develop asthma by school age. However, “asthma” in this follow-up study was defined according to GINA guidelines and included the presence of symptoms and reversible airflow obstruction, without any assessments of eosinophilia. This is of relevance since by school age the children who had severe exacerbations (at least one episode requiring a short course of oral steroids in the previous 12 months) had higher tissue eosinophils in their preschool endobronchial biopsy. The data highlight the importance of how we define “asthma” and what is meant by this term. If, in keeping with recent expert recommendation,⁷ this airway disease is defined simply by identifying treatable traits, airway eosinophilia in early life may be important because of the potential later impact on wheeze attacks.

Indeed, clinical trials of therapeutics that specifically target eosinophilic inflammation, such as the monoclonal antibody to interleukin (IL)-5, mepolizumab, have shown the biggest impact on reducing asthma attacks.⁸ It could be hypothesized that increased tissue eosinophilia in early life is associated with severe attacks of wheeze by school age. Even though “asthma” defined using reversible airflow obstruction may not be prevented by targeting eosinophils, the possibility that an exacerbating phenotype may be prevented is intriguing to consider.

Of equal interest are the findings relating tissue neutrophilic inflammation in preschool wheezers to lung function at school age. It is assumed that airway neutrophilia in the context of asthma, specifically in adults, is associated with severe and worse disease. However, in children, there has been no evidence of neutrophilia associating with severe disease.⁹ In fact, epithelial neutrophils in school-age severe asthma have been associated with better lung function.¹⁰ Intriguingly, an almost identical finding is reported by Lezmi and colleagues in this issue. Increased submucosal neutrophils in endobronchial biopsies from preschool wheezers associated with better lung function by school age. Recent data that have convincingly shown the importance of the farmyard environment in achieving protection from asthma and allergies demonstrated higher circulating neutrophils in school-age children that were protected.¹¹ The current data suggest for the first time that the presence of airway mucosal neutrophils in early life may be associated with better school-age lung function. An assessment of the airway microbiome in the children at preschool age when the biopsies were taken would have been of significant interest, as one could hypothesize that a protective microbiome may associate with neutrophilia and disease protection.

Although the numbers of patients are small, and the findings are associative, given the inherent difficulty of undertaking biopsy studies in young children, the data are of importance, suggesting airway granulocytic inflammation in early life may identify inflammatory “traits” that have an impact on school-age outcomes. Critically, these findings emphasize the need to assess mechanisms driving pathology in age-appropriate models and airway samples from children. The intriguing finding of early tissue neutrophils associating with better lung function would not have been anticipated if it was wrongly assumed that data from adult studies can be extrapolated to children.

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