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Wheezing phenotypes

Louis I Landau

There are increasing reports of excellent data on wheezing phenotypes in early childhood.¹ Despite some contradictory findings, generally based on differences in definitions used or ages studied, the findings are gradually providing valuable perspectives towards understanding this very common symptom. It is clear that much of respiratory disease throughout life is programmed during fetal life and the early years after birth. The patterns differ between developing and developed countries, apparently related to differences in microbial exposure, diet and exposure to cigarette smoke.^{2,3} The outcomes are probably mediated through the effects of these agents, timing of these exposures being critical, on airway development and maturation of the immune system.⁴ The airways may be structurally smaller due to abnormalities of the wall size, function of the smooth muscle or increased thickness of the mucosa. Abnormal maturation of the immune

system influences the response to both allergens and microbes promoting either hypersensitivity or tolerance.⁵

Cough and wheeze are very common symptoms in the early years of life with more than 60% coughing and more than 30% wheezing in the first year.⁶ Wheeze is a cardinal symptom of asthma but, in the first year of life, more than half is likely to be due to causes other than asthma such as congenitally small airways, bronchiolitis, cystic fibrosis, congenital heart disease, aspiration syndromes, social disadvantage and chronic neonatal lung disease.

A predisposition to wheeze is seen with small airways related to factors such as male gender and exposure to maternal smoking.⁷ It is more likely at this age due to a lack of collateral ventilation, a weak chest wall with reduced tethering of the airways, increased smooth muscle in the peripheral airways (particularly in pre-term infants) and an immature immune system.

There have been many genes associated with asthma prevalence, severity or response to drugs, although no single

gene accounts for more than 10% of the asthma phenotype.⁸ Those identified generally relate to β_2 receptor activity, immune maturation or function and leucotriene metabolism.

Prospective longitudinal studies commencing before birth such as those from Tucson,⁹ Melbourne,¹⁰ Perth¹¹ and Bristol¹² have been reported; a follow-up from this last study by Henderson and colleagues is included in this issue of *Thorax* (see page 974). They have defined four or more patterns of preschool wheezing: early transient (first year only), late transient (second or third year), persistent (from first year to beyond 6 years) and late onset (commencing after 3 years). Better information on these phenotypes has been obtained with measurements of lung function in this age group by forced expiratory flows using the rapid thoracic compression technique,¹³ tidal breath analysis,¹⁴ interrupter resistance measurements,¹⁵ multiple breath gas washout and lung volumes,¹⁶ exhaled nitric oxide,¹⁷ analysis of induced sputum¹⁸ and airway hyper-responsiveness.¹⁹

Those with early transient wheezing have been found to have low flow rates and airway hyper-responsiveness before the onset of symptoms associated with male gender and maternal smoking. Other triggers are being sought. One manifestation of this pattern is bronchiolitis in the

Correspondence to: Dr L I Landau, The University of Western Australia, Crawley, WA 6009, Australia; llandau@meddent.uwa.edu.au

first year where those who develop the clinical syndrome on exposure to the respiratory syncytial virus are more likely to have low lung function present before the onset of the acute illness. Those who develop bronchiolitis in the second year are more likely to be atopic, with more having positive skin prick tests (57% vs 22%) and to subsequently be diagnosed with asthma (71% vs 22%).^{20–22} Similarly, those with late transient wheezing have abnormally low maximum expiratory flow but variously reported atopy. Those reported in the paper by Henderson *et al*¹² do have increased prevalence of atopy. These inconsistencies probably highlight the problem of categorising continuous variables by age at 1, 2, 3, 4 and 6 years.

Persistent wheeze has been associated with low flows in some prospective studies but not in others.^{9–22} Low airway responsiveness at both 1 month and 6 years is associated with above average lung function and little probability of asthma, while high airway responsiveness at both 1 month and 6 years is associated with a 50% chance of developing asthma and below average lung function. Those with low airway responsiveness at 1 month which is high at 6 years have an average risk of developing asthma and average lung function probably reflecting the evolving disease in those with late onset asthma, while those with high airway responsiveness at 1 month which is low at 6 years have an intermediate risk of developing asthma and average lung function.²² These observations provide insight into possible processes but are not sufficiently predictive in individuals.

The risk of developing asthma increases with the presence of atopy, parental asthma and increasing number of episodes of preschool wheeze.²¹ It is also increased in those hospitalised with bronchiolitis,²⁴ those with recurrent croup²⁵ and those with croup and wheeze.²³

Transient wheeze is more common in children not breast fed, with a greater number of siblings and day care, consistent with increased infections in those

with small airways. Persistent wheeze is more common with persistent breast feeding (cause or reverse causation), fewer siblings and no day care.^{26–27}

What have we learnt? Preschool wheeze is the result of a complex interaction of genetic and environmental factors starting during fetal life and manifests in the early years of life. The predictors of the causes and the outcomes will vary when assessed clinically, epidemiologically or when researched with multiple objective measurements. We are increasingly recognising an evolving syndrome with better information to inform parents and to seek mechanisms which should lead to opportunities for prevention and/or reversibility. Unfortunately, early steroid therapy—most effective as a preventer of symptoms in established asthma—has been shown not to be effective for this purpose.²⁸ Although none of the cohorts has yet been followed through to old age, low lung function does track below average and this group may be at risk for chronic obstructive airway disease much later in life.²⁹

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