

Childhood asthma: what is it and where is it going?

Increases in childhood asthma have become a major public health concern. The last 20 years have seen significant rises in the prevalence of wheezing,¹ exercise-induced peak flow variability,² and asthma diagnosis³ in several western countries.^{4,5} Many studies have shown lower respiratory symptoms, principally wheeze and cough, to be common throughout childhood, from infancy⁶ through school age¹ to adolescence.^{7,8} Better understanding of the aetiology of childhood lower respiratory illness will have important consequences for the response to these changes. Despite its high prevalence it is still not possible to define "childhood asthma" satisfactorily,⁹ and there is some danger that asthma may become a generic term for the majority of recurrent lower respiratory illnesses of children which could hinder further understanding of the underlying causes and consequences of this common problem.

Wheezing illness in infancy and early childhood

Although it is widely assumed that atopy explains the majority of lower respiratory illness (LRI) in childhood there is a growing body of evidence that such illness, particularly in infancy and early childhood, represents a heterogeneous group of syndromes.¹⁰ Several studies have failed to demonstrate a positive association between markers of atopy in the first two years of life and wheezing illness. A large community based prospective study in Tucson, Arizona, USA has shown an inverse relationship between IgE levels in cord blood and wheezing illness in the first two years of life, although this relationship was reversed in the third year of life.¹¹ Further follow up of this group has shown no association between transient early wheezing before the age of three and family history of atopy, increased serum total IgE, or skin test positivity at age six. In contrast, persistent wheezing or wheezing developing after the age of three were significantly associated with a personal or family history of atopy.¹² Similar outcomes have been demonstrated using other features characteristic of atopy. No relationship between wheezing illness and atopy assessed by skin prick testing or clinical history was demonstrated in two groups of infants and young children identified following hospital admission for wheezing illness.^{13,14} Follow up to age 11 of a birth cohort with at least one atopic parent showed a significantly lower prevalence of continuing symptoms or positive skin tests in children with onset of wheezing before the age of two than those with onset thereafter.¹⁵

Quite apart from the relationship between atopy and wheezing illness, it has been suggested that genetic or intrauterine environmental determinants of airway size and function may influence the later development of wheezing illness.¹⁰ Prospective studies have suggested that wheezing illness in early infancy is related to indices of tidal airflow reflecting reduced airway calibre,¹⁶ and low maximal flow at functional residual capacity (\dot{V}_{maxFRC}),^{12,17,18} a marker of impaired small airway function. Reduced \dot{V}_{maxFRC} has also been found in recurrently wheezy infants.¹⁹ Airways hyperresponsiveness to methacholine, as measured by reduction in \dot{V}_{maxFRC} , is common in infancy and is unrelated to wheezing symptoms.^{14,19} These findings point to significant differences between virus-associated wheeze in infancy, in which small but significant impairment of airway

function appears to be a major determinant, and asthma in later childhood where atopy and airways hyper-responsiveness are common features. Neither atopy, assessed by any one of several markers, nor airways hyper-responsiveness appears to be a significant determinant of wheezing illness in infancy; indeed, it has been argued that wheezing illness in this group represents a disease distinct from asthma.²⁰ Such distinctions would be valuable if they carried clear therapeutic, prognostic, or aetiological implications. There is some evidence to suggest that attempting to identify separate childhood "asthma" syndromes may meet these criteria.

Outcomes of viral wheezing illness in infancy

There is obvious scope for diagnostic and functional overlap between children with virus-associated wheeze and asthma, and follow up studies have not clearly distinguished between these broad groups although there is a trend towards better prognosis with earlier onset of wheeze in some, but not all, studies.²¹⁻²⁴ A follow up study to early middle age has shown a better prognosis for those children with a clinical diagnosis of "wheezy bronchitis" than those with asthma,²⁵ although none of the existing long term follow up studies recruited children sufficiently young to provide unambiguous identification of asthma and virus-associated wheeze. Other evidence is available from studies of long term outcome in viral-induced bronchiolitis, a common clinical syndrome in infancy usually caused by the respiratory syncytial virus (RSV). Over 95% of children are infected with RSV before the age of two, usually during the winter, although only 40% suffer lower respiratory infection and less than 1% require admission to hospital.²⁶ Follow up at age 10 of children admitted with proven RSV infection before the age of two has shown continuing symptoms and an excess of exercise- or histamine-induced airway hyperresponsiveness, but no excess of atopy, compared with controls.²⁷ Children infected in infancy with RSV had poorer baseline lung function at age 10, even amongst those without continuing symptoms. Recent work has confirmed bronchiolitis as a risk factor for continuing respiratory morbidity and airways hyperresponsiveness independent of atopy.²⁸

The degree to which outcome in bronchiolitis reflects outcome after other viral infections in infancy is unclear.²⁹ Martinez *et al* have shown lower levels of \dot{V}_{maxFRC} at age six in children with a history of transient early wheezing, independent of atopy.¹² Significantly lower levels of small airways function have also been demonstrated in non-atopic school age boys with a history of recurrent wheezing lower respiratory infection.³⁰ In addition, hyper-responsiveness to cold air challenge in school age children with a history of lower respiratory infection has been shown to be independent of atopy.³¹ This suggests persisting abnormalities of lung function, unrelated to atopy, in a wider group of children with viral infection in infancy, as well as the few who require admission to hospital for bronchiolitis. Although the relationship between viral infection and abnormal lung function is not clear, prospective studies in infancy suggest that poor lung function may be an aetiological factor in the genesis of recurrent lower

respiratory tract symptoms,^{12 16 18} possibly modified further by viral infection.

Furthermore, the evidence suggests that virus-associated wheeze in infancy is associated with continuing symptoms and lung function abnormalities well into mid childhood, and that this syndrome is unrelated to atopy. Although these children show reversible airways obstruction and airways hyperresponsiveness to non-specific stimuli, the lack of association with atopy suggests differences from classical atopic asthma in which allergic airway inflammation is a cardinal feature.³² Distinctions between asthma and "wheezy bronchitis" have previously been regarded with caution as liable to result in underdiagnosis and undertreatment of asthma in childhood.^{33 34} Nevertheless, the evidence for heterogeneity in wheezing illness in infancy and early childhood is strong and calls for a reappraisal of early childhood "asthma" and the long term consequences of different wheezing syndromes.

Lower respiratory illness in later childhood

Recurrent wheeze is common in older children^{35 36} and, together with diagnosed asthma and airways hyperresponsiveness, is strongly associated with atopy.^{37 38} The prevalence of airways hyperresponsiveness declines between the ages of seven and 12,^{39 40} whilst the association between more severe atopy, wheeze, and airways hyperresponsiveness strengthens.^{39 41} The presence of wheeze, airways hyperresponsiveness, and atopy in effect describes a group with "classical" atopic asthma.^{42 43} Studies in Melbourne have shown atopy to be an important determinant of outcome of childhood asthma into early adult life,^{44 45} while a family history of atopic disease was associated with poorer outcome in some,^{46 47} but not all,⁴⁸ follow up studies into middle age.

The significance of other lower respiratory symptoms and isolated airways hyperresponsiveness in childhood is less clear cut. Cough without wheeze is a common finding in epidemiological studies in childhood and appears to decrease with age.⁴⁹ Recurrent dry cough without wheeze was found in 11.5% of the 813 nine year old New Zealand children studied by Sears *et al.*⁵⁰ Frequent non-wheezy cough was reported by 4.5% of eight year olds and 2.3% of 12 year olds in Queensland,⁵¹ whilst Holgate and colleagues have shown high levels of cough without wheeze in Southampton.^{52 53} Although cough alone has been described as a feature of asthma and has been shown to be responsive to antiasthma treatment in several small, highly selected groups,^{54 56} it is not clear whether these symptoms in the community form part of the same syndrome.^{54 57} Airways hyperresponsiveness has been advanced as an important feature of "cough variant asthma",⁵⁸ although only 24% of the subjects with cough alone studied by Sears *et al.* had airways hyperresponsiveness.⁵⁰ No association between cough and atopy or airways hyperresponsiveness was observed by Holgate and colleagues after correcting for wheeze, an observation which led them to question the epidemiological relevance of cough as a diagnostic feature of asthma.⁴⁹ The same group has shown wheeze to be associated with increased levels of airways hyperresponsiveness, greater variability in peak expiratory flow rate (PEFR), and greater chronicity of symptoms compared with cough in a selected group of 7–8 year olds followed intensively over one year.⁵³ Atopy was associated with increased airways hyperresponsiveness and PEFR variability in this group, but had no effect on the frequency, duration, or magnitude of episodes of respiratory morbidity assessed by falls in PEFR, many of which appeared to be of viral aetiology.⁵⁹ The epidemiological evidence, which also shows approximately equal sex ratios for cough, in

contrast to the male preponderance of wheeze, suggests that there are important differences in the determinants of recurrent cough alone and wheeze in this age group.

"Lumping" and "splitting"

The lack of association between cough without wheeze and atopy or airways hyperresponsiveness raises questions as to whether this group should be considered alongside those children with wheeze, atopy, and airways hyperresponsiveness. There is evidence that maternal history of bronchitis is a more significant risk factor for non-wheezy cough than parental history of asthma.⁵¹ Persistent cough may reflect an increased susceptibility to viral respiratory infection, which may have a heritable component. It is intriguing to speculate whether this susceptibility involves mechanisms related to those involved in virus-associated wheeze in infancy, and to what extent the two groups of children with virus-associated wheeze in infancy and cough in later childhood may be linked, or even the same. Although the short to medium term prognosis for those with cough alone appears to be good,⁶⁰ the longer term implications of this pattern of lower respiratory illness (which may previously have been described as "bronchitis" or "pneumonia") for the development of adult obstructive lung disease may be less favourable.^{61 62} Such children may be at increased risk not only from viral infection but also from other environmental factors such as passive smoking⁶³ or air pollution.

The decline in airways hyperresponsiveness may indicate a subgroup of children in which airways hyperresponsiveness associated with lung function abnormalities and sensitivity to viral infection rather than atopy becomes less obvious as the lung matures. Indeed, airways hyperresponsiveness unrelated to symptoms or atopy is common among 7–9 year olds,³⁷ while mild degrees of airways hyperresponsiveness have been shown to be unrelated to persisting symptoms or atopy over the age range 8–14.³⁹ Slower rates of growth of forced expiratory flow between 25% and 75% of vital capacity (FEF_{25–75}) and forced expiratory volume in one second (FEV₁) have also been observed in inconsistent responders to cold air challenge compared with controls over a similar age span.⁶⁴ Lung function has also been shown to be an independent predictor of airways hyperresponsiveness in both children^{41 65} and adults.⁶⁶ Others have found a high degree of tracking in the development of lung function in low birth weight children from ages one to nine.⁶⁷ Given the importance of airway function in predisposing infants to wheezing illness, it may be that reduced airway calibre and viral infection interact to produce continuing susceptibility to respiratory symptoms and airways hyperresponsiveness which is independent of atopy and which gradually resolves with lung growth and maturation.

Causes and consequences

If abnormalities of lung function are major determinants of significant childhood respiratory morbidity, what factors may influence this? Maternal smoking, particularly in pregnancy, has been shown to be related to decreased lung function in children⁶⁸ and increased frequency of lower respiratory infection in the first year of life,⁶⁹ and much attention has focused on this as a modifiable risk factor. There is also evidence that other environmental effects may have significant effects on lung growth and development.⁷⁰ Genetic effects may also be important. There is some evidence that a parental history of cough predisposes to frequent cough in children.^{51 71} Major genetic effects on lung function have been identified⁷² although the mech-

anisms are unclear. If poor small airway function and, potentially, abnormal viral responsiveness are important determinants of a significant proportion of childhood respiratory morbidity, it may well be possible to identify genetic and environmental factors that contribute to these effects. The emergence of several loci linked to atopy,⁷³ total serum IgE levels,^{74,75} specific IgE responses⁷⁶ and, perhaps, airways hyperresponsiveness⁷⁵ promises to increase our understanding of the genetic determinants of atopy and its role in respiratory disease. Further prospective studies of well characterised families are likely to help in the identification of heritable and environmental influences on other childhood lower respiratory illness and adult obstructive lung disease.

Increased understanding of the natural history of lower respiratory illness, particularly in childhood, will be of great importance for health services planning. If the significantly increased burden of childhood respiratory illness continues into adulthood in the same, or higher, proportion as has occurred in the past, this will present a major additional burden on resources in a manner similar to that represented by the ever increasing numbers of adults with cystic fibrosis.⁷⁷ Increases in the prevalence of childhood wheeze¹³ and exercise-induced PEFR variability,² together with smaller increases in hayfever symptoms,¹ possible increases in childhood eczema,⁷⁸ and limited evidence for an increase in the prevalence of atopy,^{79,80} raise the possibility that a significant increase in atopic disease is occurring.⁸¹ The association between atopy and more severe, persistent asthma⁴⁵ suggests that, if atopy is increasing, there will be a major additional burden of adult disease in the near future.

Nevertheless, the evidence for an increase in atopy is less convincing than that for recurrent lower respiratory tract symptoms. Other factors including small airway function and viral infection, together with poorly understood genetic and environmental interactions, may have contributed significantly to the increase in childhood lower respiratory morbidity. The interaction between these effects and atopy is likely to be complex but, given the present state of knowledge, the assumption that the present epidemic of lower respiratory tract symptoms in childhood is due entirely to atopic asthma is unsustainable. There is clearly an urgent need to increase our understanding of the determinants of childhood respiratory morbidity in order to facilitate both longer term intervention to reduce morbidity and to anticipate the magnitude of the problems that may affect the adult population in the near future.

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