

Infant lung function, bronchial responsiveness and the development of asthma

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For many years, clinical observation has suggested that asthma in early life is a different disease from asthma in later childhood. Infants and younger children who wheeze appear to do so more exclusively in relation to viral illnesses than older children (1), are less responsive to bronchodilator treatment (2) and many improve by the time school age is reached. For the individual infant, determining whether or not they have asthma that is likely to persist into later childhood is not easy, as there is considerable overlap between clinical features of early onset viral-associated wheeze and early onset atopic asthma. Some authorities have suggested that viral-associated wheeze in infants is not asthma (1). This concept has the problems that there is no clear definition of asthma and viral infections usually exacerbate asthma at any age, so that attempting to differentiate asthma from non-asthma on clinical grounds is risky.

More recently, data from longitudinal studies beginning at or before birth have allowed a better understanding of the differences between asthma in infants and older children. These physiological, immunological and genetic data show that

asthma in infants and young children has major aetiological differences from asthma in children aged over about 5 years of age. The aim of this paper is to briefly review the physiological data and relevant genetic information.

Data from longitudinal studies beginning in infancy

Physiological data

Over the last decade, physiological data have become available from longitudinal studies beginning in infancy. Advances in the measurement of respiratory function in infants have allowed these studies to make more accurate and relevant measurements of physiological status soon after birth (3). The main methodological area of progress has been in measurements of forced expiration. Initially, these used rapid thoracic compression over the tidal volume range, but in more recent years these measurements have been made over a raised lung volume (3). However, only a few studies have included physiological assessment of respiratory function in early infancy. The main advantage in these

assessments is that they were performed at a time in life when environmental influences could be expected to have been minimal and the level of function could, therefore, be expected to be more of a reflection of genetic and *in utero* environmental effects. The interest in the measurements is that they have been found to be predictive of the development of asthma in the first decade of life. They are also predictive of several aspects of respiratory status and physiological function during this time. The physiological assessments can be divided into those of infant lung function and those of infant airway responsiveness.

Infant lung function

The level of infant lung function measured soon after birth correlates with clinical outcome in early childhood and some aspects of respiratory function in childhood, but not with the development of asthma in later childhood. The most important parameter in these studies has been maximal forced expiratory flow at functional residual capacity ($V'_{max}FRC$) generated using an inflatable jacket and performed within the tidal volume range (3). In the Tucson study, infants who wheezed in the first 3 years of life, but not between 3 and 6 years of age, had lower levels of $V'_{max}FRC$ than those who did not wheeze or those that wheezed either throughout the first 6 years of life or only between 3 and 6 years of age (4). Similar findings have been made in the Perth infant respiratory longitudinal study (5). $V'_{max}FRC$ at 1 month of age correlated with asthma symptoms and the diagnosis of asthma in the second and third years of life, but not in the fourth, fifth or sixth years. In a study in London, $V'_{max}FRC$ did not correlate with wheeze in the first year of life, although there was a trend for lower levels in boys who wheezed compared with boys who did not wheeze (6).

Maternal smoking

Airway function in early life is likely to be determined largely by genetic factors, but maternal smoking is an important *in utero* determinant. An effect of maternal smoking has been shown within days of birth in a study comparing infants of smoking mothers with those of non-smoking mothers; the former had a tidal breathing consistent with airways obstruction (7). In a study from Boston, $V'_{max}FRC$ was inversely correlated with the level of maternal cotinine, which is an objective assessment of maternal smoking level (8). Insight into how maternal smoking affects the infant's airway has come from a recent study in which airway geometry was assessed in 19 infants

who had died from sudden infant death syndrome (SIDS) (9). These infants had thickening of the inner airway wall compared with 19 infants who died from SIDS, but whose mothers did not smoke. Thickening of this part of the airway would not necessarily lead to SIDS, but would predispose to airway narrowing and amplify the effect of any other cause of airway narrowing.

Infant airway responsiveness

This can be measured in infants using a 30 or 40% fall in $V'_{max}FRC$ in response to an inhaled agonist (PC30 or PC40, respectively) as the main outcome variable (10). Only two studies have measured the level of airway responsiveness in early life and followed the population longitudinally. The largest study measured the level of airway responsiveness in 171 infants, 90 of whom were males, at 1 month of age (11) and follow-up of this cohort to 6 years of age has recently been completed. The initial level of airway responsiveness was related to the presence or absence of a history of parental asthma, but not to the initial level of lung function (11). The level of infant airway responsiveness was the best predictor of respiratory outcome at 6 years of age correlating with both FEV1.0 and airway responsiveness at 6 years, and was the only parameter measured in infancy that correlated with the presence of a diagnosis of asthma at 6 years (5). With regard to symptoms experienced by children during the third to the sixth years of life, the level of infant airway responsiveness did not show correlations until the fifth and sixth years of age (5). The only other data on infant airway responsiveness come from the London cohort, but the assessment was only made in 62 infants and follow-up was limited to 12 months. They found that PC30 was associated with increased wheezing in the first year of life, but only in females (6).

Immunoglobulin E

Cord immunoglobulin E (IgE) levels did not predict outcome in either the Tucson or the Perth cohorts. In the former, serum total IgE at 9 months of age was increased in the group of infants with persistent wheezing through the first 6 years of life (4). IgE level at 6 years also correlated with persistent wheeze (4). In the Perth cohort, in a preliminary analysis, cord IgE level did not correlate with any outcome at age 6 years, but the level of total serum IgE at 6 years did correlate with several aspects of respiratory status at that age (12).

Summarising the data from infant longitudinal respiratory studies

Combining the observations from these studies suggests that asthma in the first 3 years of life is mainly due to airways that either are narrow or have increased airway wall compliance, and that asthma between 3 and 6 years is due to both increased airway responsiveness and the development of atopy. The latter risk factors also predispose to asthma in childhood and during adult life. However, in reality, the picture is not nearly as clear-cut as this and there are likely to be wide overlaps between the ages at which particular risk factors are important in individuals. Furthermore, the data that have been collected in this age group are few and caution is needed in making generalizations outside these populations.

Genetic data

Genetic origins of asthma in early life

To date, little is known about the genes that are involved in producing a genetic predisposition to asthma in infancy and early childhood. This situation is not likely to be easy to resolve, due to the limited number of studies at this age. In addition, many of the genes that produce a predisposition to asthma in early life are not known and are likely to be different from those relevant to asthma in older populations, so that a genome-wide screen would be needed to find them. This represents a considerable problem, as very large numbers would be needed and getting accurate phenotype information soon after birth in siblings would require much time, funding and organization. For candidate gene or association studies, cross-sectional studies may be of some use, but longitudinal data sets are theoretically much more likely to yield worthwhile results (13).

Genes involved in infant lung function

The level of infant lung function, as assessed by the forced expiration technique, is likely to be determined by several geometric factors including relatively small airways, increased airway wall thickness and increased airway wall compliance. To detect the genetic basis of this predisposition using a candidate gene approach, a wide range of possible genes would need to be considered. These would include genes that set the level of tissue elasticity, genes associated with growth of the airways and lung parenchyma and genes associated with all the individual components of the airway, its smooth muscle and its supporting tissue.

Molecular genetic evidence

Associations between known DNA variations and phenotype have been examined in the Perth cohort. The most interesting association noted was with polymorphisms in the gene for the Clara cell 16 kDa protein (CC16). CC16 is an anti-inflammatory protein that is secreted only in the airway epithelium and in the urogenital system (2). The CC16 gene lies in the region of chromosome 11 that has been linked to atopy and airway hyper-responsiveness in children from Perth (14) and is near the gene for the beta chain of the high affinity receptor for IgE (*FcεR1-B*) (15). Until recently, CC16 was known as CC10, based on incorrect evidence that the gene produced a 10 kDa protein (16). There has been considerable recent interest in the role of the CC16 gene in respiratory disease, as a growing body of evidence suggests that CC16 plays a major role in inhibiting airway inflammation (17). We recently discovered a polymorphism, A38G, in exon one of the CC16 gene (18) within a region thought to have promoter-like activity (17). We found that 38A homozygotes had a seven-fold increased risk for asthma (18). In a preliminary analysis, we later found that the 38A allele was associated with increased airway responsiveness at 1 month of age and increased risk of asthma at 6 years of age (19). In a further clinical study, the 38A allele was found to be associated with decreased serum levels of CC16, as would be expected from an anti-inflammatory protein (20). Serum CC16 levels were also reduced in the presence of current asthma (20). These findings are unique, as, to our knowledge, they are the only data on DNA variations that both predispose to asthma and show altered *in vivo* protein levels. Associations were also seen between polymorphisms in the beta-two adrenoreceptor and airway responsiveness (21). No other polymorphisms have been associated with asthma phenotype in this age range.

Summary

Infants who wheeze are likely to have narrowed or overly compliant airways rather than atopy. After around 3 years of age, airway responsiveness and atopy are associated with the development of wheeze and the diagnosis of asthma. Anti- or pro-inflammatory genes are likely to be responsible for at least part of the predisposition to wheeze seen in older children, but further studies are needed to clarify this situation.

References

- MARTINEZ FD. The relationship between impaired lung growth and the onset of bronchial asthma in early life. *Pediatr Pulmonol* 1997; 16: 84–85.
- TURNER DJ, LANDAU LI, LE SOUËF PN. The effect of age on bronchodilator responsiveness. *Pediatr Pulmonol* 1993; 15: 98–104.
- LE SOUËF PN, CASTILE R, TURNER DJ, MOTOYAMA E, MORGAN WJ. Forced expiratory maneuvers. In: STOCKS J, SLY P, TEPPER R, MORGAN W, eds. *Infant Pulmonary Function – A Practical Guide*. New York: Wiley-Liss, 1996: 379–410.
- MARTINEZ FD, WRIGHT AL, TAUSSIG LI, et al. Asthma and wheezing in the first six years of life. *New Engl J Med* 1995; 332: 133–138.
- RYE PJ, PALMER LJ, YOUNG S, et al. The association between lung function and respiratory symptoms during the first 6 years of life (abstract). *Am J Respir Crit Care Med* 1997; 155: A77.
- CLARKE JR, SALMON B, SILVERMAN M. Bronchial responsiveness in the neonatal period as a risk factor for wheezing in infancy. *Am J Respir Crit Care Med* 1995; 151: 1434–1440.
- STICK SM, BURTON PR, GURRIN L, SLY PD, LE SOUËF PN. Respiratory function in newborn infants: effects of maternal smoking during pregnancy and a family history of asthma. *Lancet* 1996; 348: 1060–1064.
- HANRAHAN JP, TAGER IB, SEGAL MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992; 145: 1129–1135.
- ELLIOT J, VULLERMIN P, ROBINSON P. Maternal cigarette smoking is associated with increased inner airway wall thickness in children who die from sudden infant death syndrome. *Am J Respir Crit Care Med* 1998; 158: 802–806.
- LE SOUËF PN, GEELHOED GC, TURNER DJ, MORGAN SEG, LANDAU LI. Response of normal infants to inhaled histamine. *Am Rev Respir Dis* 1989; 139: 62–66.
- YOUNG S, LE SOUËF PN, GEELHOED GC, STICK SM, TURNER KJ, LANDAU LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *New Engl J Med* 1991; 324: 1168–1173.
- JUDGE PK, PALMER LJ, LAING IA, et al. Serum IgE levels and the prediction of respiratory outcome: a 6 year follow-up (abstract). *Am J Respir Crit Care Med* 1998; 157: A47.
- LE SOUËF PN. Use of cohorts with extensive longitudinal data in investigating the molecular genetics of asthma. *Clin Exp Allergy* 1998; 28 (suppl 1): 46–50.
- PALMER LJ, DANIELS SE, GIBSON NA, et al. Linkage of chromosome 5q and 11q markers to asthma-associated quantitative traits in Australian children. *Am J Respir Crit Care Med* 1998; 158: 1825–1830.
- COOKSON WOCM, SHARP PA, FAUX JA, HOPKIN JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; i: 1292–1295.
- DIERYNCK I, BERNARD A, ROELS H, DE LEY M. Potent inhibition of both human interferon-alpha production and biologic activity by the Clara cell protein CC16. *Am J Respir Cell Mol Biol* 1995; 12: 205–210.
- HAY JG, DANIEL C, CHU C-S, CRYSTAL RG. Human CC-10 gene expression in airway epithelium and subchromosomal locus suggest linkage to airway disease. *Am J Physiol* 1995; 268 (Lung Cell Mol Physiol 12): L565–L567.
- LAING IA, GOLDBLATT J, EBER E, et al. A polymorphism of the CC16 gene is associated with increased risk of asthma. *J Med Genet* 1998; 35: 463–467.
- LAING IA, EBER E, HAYDEN CM, et al. CC16: the A38G polymorphism is associated with airway responsiveness at one month and asthma at 6 years in children unselected for asthma (abstract). *Am J Respir Crit Care Med* 1998; 157: A857.
- LAING IA, HERMANS C, BERNARD A, BURTON PR, GOLDBLATT J, LE SOUËF PN. Plasma CC16 levels are associated with the A38G polymorphism and asthma. *Am J Respir Crit Care Med* 2000; 161: 124–127.
- RAMSAY CE, HAYDEN CM, TILLER KJ, BURTON PR, GOLDBLATT J, LE SOUËF PN. Polymorphisms in the beta-2-adrenoreceptor gene are associated with decreased airway responsiveness. *Clin Exp Allergy* 1999; 29: 1195–1203.