PAEDIATRIC RESPIRATORY REVIEWS (2006) **7S**, S251–S254

ELSEVIER

Paediatric Respiratory Reviews

Paediatric basis of adult lung disease

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KEYWORDS
fetal origins;
environment;
genetics;
infant lung function;
maturation

Summary Most lung disease throughout life is programmed in utero or early post-natal life. Factors in the fetal environment such as maternal smoking and diet can lead to reduced lung function, immunological modification or symptoms from birth. There are clear genetic components documented for cystic fibrosis, alpha1 anti-trypsin deficiency and asthma. In early life, the outcomes for those predisposed to asthma or allergy appear to be dependant on the relative timing of exposure to infective agents, allergens or helminths. Abnormal airway structure is present in both transient and persistent wheezers. New drugs and environmental manipulations will need to be developed with an understanding of the mechanisms associated with this early programming.

INTRODUCTION

Studies are increasingly reporting that a tendency to respiratory disease through out life is programmed during fetal life and the early years after birth. Considerable differences in disease patterns persist between developing and developed countries. The cycle of poor housing, poor sanitation, malnutrition and infections continue to underlie the major causes of death and disability in developing countries. The changes in the environment in developed countries with improved socio-economic status, have led to both a reduction in microbes in the home, change to a high carbohydrate and fat diet and, in many societies, an increase in exposure to pollutants such as tobacco smoke, pesticides, preservatives and other chemicals. These independently or together are associated with new morbidity, particularly atopic and other inflammatory disorders.

The characterization of the human genome is leading to the promise of a better understanding of the genetic and molecular basis for most diseases. However, the substantial variation in the phenotypic expression for single gene disorders, the important contributions of multiple genes to common disorders, the recognition of epigenetic influence of modifier genes and the impact of environmental factors such as diet on gene expression are highlighting the important role of environment – gene interactions in the disease spectra in both the developing and developed worlds.

Environmental factors may impact on the outcomes in genetically pre-disposed individuals in-utero, peri-natally, during infancy and later childhood. The outcome will depend on the timing and sequence of environmental insults during development from conception to maturity. Exposure to an infection at one stage in development may lead to a reduction in atopy while, at another stage, may potentiate the emergence of atopic features. Good fetal weight gain during pregnancy may be beneficial for prevention of the metabolic syndrome, but excessive weight gain after birth, especially if born small, may be associated with more severe manifestations of the metabolic syndrome and the development of asthma. Xu *et al.*[1] reported that at age 31 years, those born small, with rapid postnatal weight gain and BMI above the 95th percentile had the highest risk for asthma (OR 3.27: 1.32–8.11).

Chronic lung disease in adulthood has been associated with lower respiratory illness in childhood. The question arises as to whether the symptoms in early life identify the 'at-risk' individual who continues to have problems in adult life or whether illness in early life causes lung damage that predisposes to progressive lung disease. There are studies which support each hypothesis.

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doi:10.1016/j.prrv.2006.04.186

GENETICS

Numerous candidate genes have been identified which impact on atopic status and airway function. Asthma appears to be a manifestation of a number of these genes which are influenced by environmental factors. No single genomic region has been linked in all studies and no individual genetic marker has been found to account for more than 10% of the asthma phenotype. Studies in twins suggest that over 50% of variance for all cytokines is genetically determined, being particularly high for IL1beta and IL10. Some of the potentially relevant genes identified include those for atopy, such as CD14(159T) and GM-CSF(117T); for asthma, CC16(A38G), TNF alpha(308G), LTC4 synthase (A444C), and IL10(−571C); and for asthma severity, Beta2R(A16,Gly17) and IL4(−589T).

The gene for cystic fibrosis – the cystic fibrosis transmembrane conductance regulator (CFTR) – was identified 16 years ago. Since then over 1,000 mutations of this gene have been identified with varying phenotypic expression and disease manifestations. Substantial variation of the disease have been noted within the same CFTR genotype suggesting modification by factors that could be related to diet and the environment or to modifier genes co-inherited with the CFTR polymorphism. However, definitive modifier genes for cystic fibrosis remain to be identified.

Severe alpha-1 antitrypsin deficiency is one proven genetic risk factor for chronic obstructive pulmonary disease in adult life. Apart from presenting as liver disease in early life, most patients are not detected until the individual is at an age at which they may have commenced smoking and rapidly develop lung disease.

Towards the end of gestation, the fetal lung prepares for the transition to air breathing at birth. Respiratory epithelial cells synthesize lipids and surfactant proteins that are necessary for alveolar stability with air breathing. Numerous, usually isolated, genetic disorders have beeen reported in these processes leading to perinatal morbidity and death related to respiratory distress syndromes, as well as later alveolar proteinosis and familial lung fibrosing disorders.

PRENATAL ENVIRONMENT

Maternal age and age of menarche of the mother may influence fetal development and maturation, possibly associated with variance in hormonal levels. Later age of menarche has been reported to be associated with lower rates of atopy but not asthma.[2]

In fetal life there is a skew to a TH2 immune response to prevent maternal rejection of the foreign placenta and fetus. Those primed to develop asthma and/or atopy have evidence of immaturity of both their TH1 and TH2 immune systems at birth with a propensity to TH2 as reflected by cytokine levels (high IL4/IFNgamma ratios) and cord blood mononuclear cell proliferation studies.[3] Low IFNgamma levels are associated with increased infections in early life and with increased atopy in later life. These may both be direct consequences of priming during fetal life or a result of the sequence of postnatal exposures in genetically predisposed infants. Infection and the development of tolerance to potential allergens may result in reduced airway reactivity, while sensitisation before infection and development of tolerance in those with immaturity of T cell maturation may lead to increased airway reactivity.

Lung function measured soon after birth suggest that airway structure and function has also been affected in association with these immunological changes or other stimuli such as exposure to maternal cigarette smoking before birth predisposing to the development of 10w flow rates and respiratory symptoms.

Many authors have reported lower prevalences of atopy with increasing birth order. Turner *et al.*[4] have found that the lower prevalence in those not first born is only transient and delayed to around 11 years. The effect of birth order on immunological development may be related to different hormonal levels, reduced levels of transplacental IgE, variation in nutritional status during subsequent pregnancies or to the different microbial exposures after birth due to contact with other young children in the house.

Maternal smoking is associated with elevated cord blood IL4, altered responses of IL5, IL9 and IL13 production to stimulation of cord blood cells and abnormal lung function soon after birth. Nicotine causes growth dysfunction of the airways with increased airway branching and increased airway wall thickness and reduced alveolar elastin in animal models.[5] Humans demonstrate an association of prenatal smoking with transient wheezing during infancy, increased sudden infant death syndrome and continuing reduced lung function but the associations with asthma, atopy and persistent wheezing are less consistent.

High vitamin E in the maternal diet is associated with changes in cord blood macrophage proliferation, but this is not related to blood levels of Vitamin E suggesting that the dietary intake may be a marker of some other factor that influences immunological development and atopic priming.[6] A potential reduction in subsequent infant allergy has been seen with maternal supplementation with polyunsaturated fatty acids. Lower levels of vitamin E in the maternal diet have been reported to be associated with increased wheeze and elevated exhaled nitric oxide measured at 5 years. Similar findings are suggested for Vitamin C.

POSTNATAL ENVIRONMENT

Postnatally, commensal gut flora appear to be a strong stimulus for maturation of the immune status, particularly the TH1 response. There are over 400 species of bacteria in the human gastro-intestinal tract and these compete for adhesion receptors, produce antimicrobials and stimulate gut associated lymphoid tissue. Kalliomaki *et al.*[7] reported that probiotics (lactobacillus) given to the mother and infant was associated with a 23% prevalence rate of eczema