Asthma: early predisposing factors

Iolo J M Doull* and Stephen T Holgate†

*Paediatric Intensive Care Unit, Hospital for Sick Children, London, UK; †University School of Medicine, Southampton General Hospital, Southampton, UK

The significance of factors affecting the development of asthma and atopy in children must be judged against their ability to contribute to the increase in childhood asthma. Although genetic factors are clearly important to the development of asthma and atopy, they can not explain the increased prevalence of these conditions.

Atopy is characterised by a genetic predisposition for generating IgE against common environmental allergens, expressed clinically as asthma, eczema and rhino-conjunctivitis. Cross sectional and longitudinal studies indicate that serum total IgE is one of the greatest risk factors for the development of asthma. Over 90% of childhood asthmatics demonstrate evidence of allergic sensitisation.

A characteristic feature of asthma is enhanced responsiveness of the airways to a wide variety of specific and non-specific stimuli. This bronchial hyperresponsiveness (BHR), when quantified by histamine or methacholine challenge, has been used in epidemiological studies as an objective measure which greatly strengthens the diagnosis of asthma. While the factors that contribute to BHR are multiple and complex, in adult asthma the degree of BHR broadly reflects the level of airway inflammation and subsequent epithelial damage characteristic of the disease. Asthma is a clinical diagnosis lacking a clearly defined phenotype or ‘gold standard’ diagnostic investigation. Consequently, serum IgE and BHR are used as easily measured and reproducible surrogate markers of asthma.

Serial prevalence studies performed in the same population with the same methodology demonstrate that the prevalence of asthma is increasing. This is unlikely to be due solely to changes in diagnostic criteria, changes in diagnostic coding rules or changes in clinical management. The increased prevalence is reflected in increased rates of hospital admission for asthma in children.
Genetics of atopy, asthma and BHR

The prevalence of atopic disease increases with the number of atopic relatives, and is higher in monozygotic twins than dizygotic twins. Family studies have proposed varying models for the inheritance of atopy including recessive, dominant, codominant, polygenic and exclusively through the maternal line (reviewed in 5). Similarly, the prevalence of BHR is increased in asymptomatic relatives of subjects with BHR, and is higher in monozygotic twins than dizygotic twins. Evidence for atopy and BHR candidate genes have been reported on chromosomes 5, 6, 11 and 14.

Chromosome 5

Two populations of CD4+ T helper cells, Th1 and Th2, have been identified in the mouse based on differential cytokine expression. Th1 cells are characterised by relative increased production of interferon gamma (INFγ), interleukin-2 (IL2) and tumour necrosis factor beta (TNFβ), while Th2 like cells demonstrate relative increased production of IL4, IL5, IL10 and IL13. Both Th1 and Th2 like cells also produce IL-3, IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF). Th2 derived cytokines appear crucial to an allergic response by regulating the isotype switch of B cells from IgM to IgE synthesis (IL4, IL13), the growth, maturation of mast cells and basophils (IL3, IL9, IL10) and eosinophils (IL3, IL5, GM-CSF) and the upregulation of vascular cell adhesion molecule-1 (VCAM-1) on the endothelium responsible for VLA-4 mediated recruitment of eosinophils and T cells.

Although the Th1/Th2 subdivision is simplistic in humans, atopic adults demonstrate evidence of increased Th2 like activity. T cell clones from atopic peripheral blood produce IL4 and IL5 on antigen stimulation. Lymphocytes in nasal biopsies following allergen provocation show increased expression of mRNA for IL3, IL4 and IL5. Similar findings are seen in lymphocytes recovered from broncho-alveolar lavage fluid following airway allergen challenge, and in bronchial biopsies from atopic asthmatics (reviewed in 7).

The gene cluster on chromosome 5q31-33, containing loci for IL3, IL4, IL5, IL6, IL9, IL13 and GM-CSF, is therefore a strong candidate region for a gene with a general effect on atopy. Two groups have reported linkage between markers in this region and total IgE. In 11 large Amish families, Marsh et al reported linkage of total IgE to 5q31.1, with the greatest evidence of linkage to IL4. In 92 Dutch families selected on the basis of a parent with asthma and BHR to histamine,
Meyers et al reported linkage of total IgE to 5q, although the evidence appeared strongest for loci distal to IL4. The same group have reported that IgE is co-inherited with BHR, and that a gene governing BHR is located near a major IgE regulating locus on chromosome 5q. We also have demonstrated allelic association between IL9 and serum total IgE in a random sample of 131 Southampton families. The 7-transmembrane β2-adrenoceptor gene lies in close proximity, and polymorphisms within it have been associated with asthma severity, although a direct effect of the β2-adrenoceptor on IgE seems unlikely. The abundance of candidate loci in 5q31 is likely to complicate the resolution of the true effect from linkage disequilibrium.

Chromosome 6

Although polymorphisms of the human leucocyte antigen (HLA) genes encoded on chromosome 6p are important in allergen specific IgE responses, their exact role remains uncertain. Total serum IgE, however, shows no evidence of linkage to chromosome 6p. It is possible that the HLA haplotype may influence the T cell receptor repertoire during thymic development, so skewing the TcR repertoire within CD4 and CD8 subsets (reviewed in).

Chromosome 11

Atopy, transmitted exclusively through the maternal line, has been mapped to chromosome 11q13 by linkage and sib pair analysis, with the β chain of the high affinity IgE receptor (FcεRIβ) being selected as the candidate locus. These findings have been extended by describing an association for a broad definition of atopy and a single base pair substitution of a leucine for an isoleucine residue at position 181 in the first of four transmembrane domains of the β subunit of FcεRI. In each family, Leu181 was maternally inherited, and strongly associated with atopy. The same group have reported that 4% of cases from random population in Busselton, Western Australia, tested positive for a Leu181/Leu183 variant, while no cases tested positive for the Leu181 variant. All 13 children who inherited the Leu181/Leu183 variant maternally were atopic, while none of the 8 children who inherited the variant paternally were atopic. Other studies give contradictory results with some investigators reporting evidence for linkage with others unable to replicate linkage, or to detect either Leu181 or leu181/Leu183 variants (reviewed in). We also have failed to confirm linkage between IgE and 3.
markers distal to FcεRIβ on chromosome 11q in our 131 families\textsuperscript{16}, although there was evidence of allelic association between markers at 11q13 distant from FcεRIβ and both serum total IgE and BHR.

**Chromosome 14**

The interaction between the HLA class II molecules and the T-cell receptor (TCR) is crucial to specific IgE production. The TCR comprises alpha and beta chains whose genes are encoded on chromosome 14 and 7, respectively. Using sib-pair analysis, Moffatt\textsuperscript{17} demonstrated significant linkage between specific IgE reactions to highly purified major allergens and the TCR alpha gene, with no evidence of linkage to the TCR beta gene.

**Preferential inheritance of atopy through the maternal line**

Bray first described a preferential inheritance through the maternal line in 1931. Fifty years later Happle and Schnyder reported similar findings and interpreted this as evidence that atopy is a polygenic disease. The more predisposing genes an individual possesses, the more likely they are to develop the condition — the ‘Carter effect’. As the threshold for atopy is greater for females than in males, so a female must possess more predisposing genes for disease expression. Consequently, the male offspring of atopic mothers will have higher rates of atopy.

Since these early reports, a number of other authors have reported similar findings (reviewed in\textsuperscript{18}), and a putative mechanism has been proposed via the gene encoding the β subunit of FcεRIβ located on chromosome 11q13\textsuperscript{14}. However, there are major difficulties in the interpretation of such reports, centring primarily on proband ascertainment and phenotype definition. Many studies are conducted through antenatal clinics, with a likely excess of atopic mothers compared to fathers. Ascertainment of the father’s atopic status is frequently via the mother. Even random samples may be liable to this bias as mothers are the principal carers.

Cord total IgE in newborn infants of atopic mothers are higher compared to newborn infants of non-atopic mothers, and atopic dermatitis in the first year of life may be commoner in the offspring of atopic mothers. However, there is no evidence in older children for increased risk of atopic dermatitis through the maternal line, and for asthma there is evidence of preferential inheritance through the paternal
Asthma: early predisposing factors

line. In the largest reported study of over 6000 randomly selected children, the risk of asthma was increased in those children whose father had asthma, but not if their mother had asthma, or if either parent had atopic dermatitis or hayfever alone (reviewed in\textsuperscript{18}).

Thus the strongest evidence for preferential inheritance of atopy through the maternal line applies to cord IgE and atopic dermatitis in early life. Possible explanations include paternal genomic imprinting, although non genetic factors such as programming of the fetus or trans-placental passage of maternally derived cytokines seem more likely. Godfrey \textit{et al}\textsuperscript{19} have demonstrated a positive correlation between specific anthropometric measurements at birth and serum total IgE at 50 years of age. The highest IgE levels occurred in those infants with a large head circumference but a disproportionately small crown heel length at birth. In a prospective study of over 200 Southampton school children, we have demonstrated that children with a positive skin prick test at (mean age) 12 years had larger head circumference at birth, and a positive correlation between head circumference at birth and IgE measured at (mean) 12 years of age (A. Gregory, personal communication).

The effect of maternal smoking on infant lung function and respiratory symptoms

There is a substantial body of evidence that maternal smoking during pregnancy results in small for gestational age offspring, with the infants born to mothers who smoke being on average 220 g lighter than infants of non-smokers\textsuperscript{20}, and the greatest effect occurring during the third trimester\textsuperscript{21}. Mothers who smoke have in addition a greater risk of delivering very small preterm infants, and their infants have higher perinatal mortality at every relative birth weight\textsuperscript{20}.

In a rat model maternal smoking during pregnancy resulted in decreased fetal weight and decreased lung weight and nucleic acid content\textsuperscript{22}. Longitudinal prospective birth cohort studies demonstrate maternal smoking as a significant risk factor for impaired postnatal respiratory function. Investigators have measured forced expiration in infants by means of a rapid thoracic compression utilising an inflatable thoraco-abdominal jacket — the 'squeeze technique'. The infant is tested while asleep wearing a facemask with pneumotachograph and encased in the inflatable thoraco-abdominal jacket. The jacket is rapidly inflated at the end of inspiration, causing a passive partial forced expiration. The jacket pressure is increased during successive measurements until the maximum flow is produced, and maximal flow calculated with reference
to functional residual capacity ($V_{\text{max}\text{FRC}}$). Provided flow limitation is achieved, $V_{\text{max}\text{FRC}}$ is a measure of intrathoracic airway function. Compared to the infants of non-smokers, infants whose mothers smoked during pregnancy demonstrated significantly decreased forced expiratory flow rates and $V_{\text{max}\text{FRC}}$, even after controlling for post-natal passive environmental tobacco smoke exposure\textsuperscript{23}. After correction for prenatal tobacco exposure there were no significant differences in pulmonary function between infants exposed and unexposed to postnatal environmental tobacco. Similarly, Martinez\textsuperscript{24} demonstrated that children who wheezed in the first 3 years of age had significantly lower $V_{\text{max}\text{FRC}}$ at 1 year and 6 years of age, and were more likely to have mothers who smoked. Airway responsiveness to inhaled nebulised histamine quantified by a decrease in the $V_{\text{max}\text{FRC}}$ can be detected as early as 4 weeks of age. Using this method Young et al\textsuperscript{25} demonstrated significantly increased airway responsiveness in infants with a family history of asthma or parental smoking.

Post natal tobacco smoke exposure increases the incidence of respiratory illness (bronchitis and pneumonia) in children aged less than 18 months in a dose dependent manner\textsuperscript{26}, and in older children increases the probability of persistent wheezing\textsuperscript{27}, and the probability of being diagnosed asthmatic and results in decreased lung function\textsuperscript{28}. Long term follow up of large birth cohorts demonstrate increased respiratory morbidity in childhood, with in utero tobacco smoke exposure having greater effect than ex utero. Follow up of a UK national birth cohort of over 12,000 children demonstrated that maternal smoking, but not paternal smoking, had a significant influence on the reported incidence of bronchitis and admission to hospital for lower respiratory tract illness during the first 5 years of life\textsuperscript{29} and on wheezing during the first 5 years of life\textsuperscript{30}. Smoking during pregnancy exerted a greater influence on the reported incidence of bronchitis than did postnatal smoking\textsuperscript{29}. It is noteworthy that 85% of children with wheezing during the first 5 years of life were asymptomatic by 16 years of age\textsuperscript{30}.

It has been speculated that part of the increase in the prevalence of asthma in childhood may have resulted from the increased prevalence of smoking amongst women of child bearing age\textsuperscript{28}, but this is as yet unsubstantiated.

**Viral infections and the development of atopy**

There is strong epidemiological (reviewed in\textsuperscript{31}) and pathophysiological (reviewed in\textsuperscript{32}) evidence to link viral infection to exacerbations in childhood wheezing and asthma. There is much less evidence, however,
that viruses can alter the allergic phenotype and, indeed, it is proposed that viral infections early in life may be protective against the development of allergic disease\textsuperscript{33}.

The evidence that viral infections may increase the susceptibility to atopic disease derives mostly from animal experiments, with little direct evidence in humans. In a prospective study, 13 infants born to allergic parents were compared to 28 infants born to non-allergic parents. Over the 4 years of the study, all 13 index infants developed some evidence of allergic sensitisation compared with only 7 of 28 controls. The authors noted that 11 of the 13 infants had a documented URTI 1–2 months prior to sensitisation. From this temporal coincidence of URTI and allergic sensitisation, the authors concluded that, in atopically susceptible children, viral infection could alter IgE immunomodulation with resultant allergic disease, and supplied further evidence in a dog model of pollen allergy. Pups from pollen sensitive bitches injected with pollen extracts produced higher pollen specific IgE when inoculated with either live attenuated distemper hepatitis virus or canine parainfluenza virus, than when inoculated with placebo\textsuperscript{34}.

There is circumstantial evidence to support a potentially protective role of viruses in atopy and asthma, reviewed by Martinez\textsuperscript{33}. Isolated island populations such as those on Tristan da Cuhna and the Western Carolina islands, with little host immunity to common virus infections such as influenza, have a much higher prevalence of respiratory disease and BHR than less isolated communities. However, genetic inbreeding is likely to have a major influence in such isolated communities.

A striking feature of the worldwide increase in the prevalence of childhood asthma is the higher prevalence in developed, ‘westernised’ societies. First generation immigrants from developing countries to developed countries have a much lower prevalence of asthma than does the indigenous population. Second generation immigrants have asthma prevalence similar to the indigenous. Studies in Zimbabwe\textsuperscript{35} and in South East Asia\textsuperscript{36} demonstrate that within the same ethnic group, prevalence of asthma is higher in an urban ‘westernised’ environment. Following the re-unification of Germany, West German children had a higher prevalence of asthma, BHR and allergic sensitisation compared to East German children, despite the level of heavy industry airborne pollutants being considerably higher in the old East Germany\textsuperscript{37}.

Strachan\textsuperscript{38} observed a decreased risk of allergic rhinitis with increasing birth order in children, i.e. the greater the number of older siblings, the lower the risk of a child developing atopic rhinitis. Similar findings were observed in a cross-sectional study of German school children\textsuperscript{39}. The prevalence of atopy (defined as at least one positive skin prick test) decreased with increasing birth order. The authors proposed that higher birth order children are exposed to a greater frequency of viral infections
passed on from their older siblings in the first years of life, and so viral infections early in life may be protective against the development of atopy. Decreased risk of positive skin prick test with increasing birth order have since been reported by Strachan for the 1958 UK birth cohort, and a decreased risk of seasonal rhinitis with increasing birth order by Jarvis in a survey of over 700 young adults in East Anglia. Of note, however, in neither of these surveys was birth order associated with either wheeze or asthma.

Central to this paradigm is the belief that children in westernised communities have fewer viral infections, or at least fewer viral infections in the first few months or years of life, compared with children in less developed communities. The first direct evidence for a protective role for viruses in atopy derives from a historical cohort study following a measles epidemic in Guinea-Bissau 15 years earlier. The prevalence of atopy (defined on skin prick weal) was lower in subjects with a history of previous measles infection (12.8%) compared to those who had not had measles and had been vaccinated (25.6%). Of note is that the mean age of the subjects during the epidemic was over 2 years of age, and that all children without a history of measles were vaccinated shortly afterwards. Nevertheless, it suggests that, in West Africa, measles infection (as compared to measles vaccination) may protect against the development of atopy, and with the increasing uptake of immunisation, forward a possible explanation for the increase in atopic diseases in westernised countries over the last few decades, and thus a mechanism for the increase in childhood asthma.

References

5. Wilkinson J, Holgate ST. Candidate gene loci in asthmatic and allergic inflammation. Thorax 1996; 51: 3-8
Asthma: early predisposing factors


Fetal and early childhood environment: long-term health implications