Prospects for preventing asthma

There is substantial evidence from epidemiological surveys that asthma prevalence has increased significantly in the school age population over the past 30 years. In children in one community, doctor diagnosed asthma increased from 4.1% in 1964 to 10.2% in 1989 and to 19.6% in 1994. In part these results may reflect increased awareness of symptoms and diagnostic transfer, although these effects are unlikely to explain the magnitude of the changes. Increases in the prevalence of bronchial hyperresponsiveness (BHR), such as induced falls in peak expiratory flow on exercise or methacholine bronchial challenge testing have also been reported, supporting a true increase in the prevalence of asthma. It is also becoming apparent that this increase is mainly in children from “low risk” families; those with no strong family history of atopic disease. Assuming that the reported increase in asthma is real, are there opportunities to reduce the prevalence and turn the clock back to an earlier time when asthma was less common?

Which population?
If an intervention is to be assessed an important question must be what is the appropriate population for such an intervention? There is no doubt that allergen sensitisation and atopic disorders are more prevalent in high risk children; those with one or both parents with an atopic history. However, the environmental contribution is arguably greater than the genetic contribution, as shown by the relatively low concordance of atopic sensitisation and atopic symptoms in identical twins: as low as 20% in a large twin study. The significant increase in asthma and wheezing illness in the UK and other industrialised countries over the past 30 years also points to a significant environmental contribution. Although there is evidence from a birth cohort and cross sectional studies that the large increase in symptomatic wheezing and atopic children in the past two to three decades is occurring in what have in the past been considered to be low risk families (children of parents with no atopic history), it is likely that the level of exposure required for sensitisation may be significantly lower for high risk individuals. Hence more rigorous and possibly unsustainable measures may have to be required for those at high risk in contrast to a more modest reduction in exposure required for a measurable effect in the whole population.

Infection, immunisation, and lifestyle
Several studies, which have shown striking contrasts in respiratory symptom prevalence and atopy in genetically similar populations between European countries on opposite sides of the former Iron Curtain, support the contribution of environmental exposures in atopic sensitisation and in the cause of childhood respiratory disease. Studies of 8–11 year old children in Munich (former West Germany) and Leipzig (former East Germany) showed no difference in the prevalence of wheezing, diagnosed asthma or BHR, although hay fever was significantly more common in Munich and diagnosed bronchitis significantly more common in Leipzig. Subsequent studies showed a higher prevalence of asthma and atopic sensitisation among children in the former West Germany than in the former East Germany, while upper respiratory symptoms in the former East Germany were associated with high levels of sulphur dioxide (SO2), oxides of nitrogen, and particulate air pollutants. Studies in Estonia, a relatively unpolluted area, have also shown low prevalences of respiratory symptoms, asthma, and atopic sensitisation.

In terms of an intervention aimed at prevention, what can we learn from these studies? One could conclude that a return to a less affluent lifestyle, which attempts to reproduce the internal (home) and external environment in these previous Soviet block countries, may reduce the prevalence of atopy and asthma, although at the cost of increasing bronchitis and respiratory infections. This would clearly not be acceptable for most people who have become attached to a postindustrial consumer led lifestyle. The apparent association between less notable infectious diseases and more prevalent atopic disease has, with the development of the T helper (TH)1 and 2 subtype hypothesis, led to the suggestion that interference with allergen specific immunological memory may become a feasible approach in primary prevention. In the proposed TH1/TH2 mechanism, antigen presentation to T lymphocytes results in the selection of TH2 clones, which enhance IgE production by B lymphocytes and ultimately eosinophil recruitment. Most viral and bacterial antigens stimulate TH1 lymphocytes, which tend to downregulate TH2 (allergic) inflammation. This mechanism may in part explain the observation that large family size and presumed “sharing” of common childhood infections is associated with a reduced prevalence of the related atopic illness hay fever.
Environmental tobacco smoke
Maternal smoking in pregnancy is an established risk factor for wheezy illness and impaired lung function in infancy, although not in later childhood. The hazards of passive environmental tobacco smoke exposure in children have been reviewed. In a multivariate analysis of the Tucson birth cohort at age 6 years, only maternal smoking was significantly associated with transient wheezing illness, whereas maternal asthma, hay fever, and eczema were associated with persistent wheezing. It is therefore possible that the adverse effects of maternal smoking are, in part, mediated by adverse effects on lung growth reflected in impaired function. Reduction in exposure would undoubtedly improve the health of the whole population and reduce wheezing illness in the very young and the adult population, although with less impact on classic asthmatic asthma in mid-childhood and adolescence.

Respiratory syncytial virus
Although every clinician (and asthma sufferer) knows that viral infections can precipitate wheezing episodes, the evidence for their role in causation is far from clear. An increased prevalence of coughing and wheezing has been shown 5 to 10 years after bronchiolitis diagnosed either clinically, by viral isolation, or a combination of the two. In the affected population, wheezing and other respiratory symptoms tend to decrease with time, an improvement that the subsequent development of atopy does not appear to influence. Taken together, cross sectional and limited longitudinal data suggest that there may be a group of children characterised by impaired lung function in infancy who experience wheezing, lower respiratory illness associated with viral infection, independent of atopy and who then experience recurrent, although declining, symptoms in later childhood associated with decreased lung function and evidence of BHR. An effective immunisation programme for respiratory syncytial virus, although reducing morbidity in infancy and early childhood, would be unlikely to have an impact on persistent asthma in later childhood.

Immune modulation
The observation that family size appears to be inversely related to the risk of the related atopic disease hay fever has, with other supportive evidence, suggested a possible intervention in the form of infant BCG immunisation. However, as pointed out in a recent review, immune modulation by stimulating TH1 responses and other techniques such as allergen specific immunoprophylaxis both have potential dangers and will require rigorous testing in animal models. Just as there is strong evidence for lifelong “imprinting” of T cell selection, powerful immunological interventions may have undesired long term effects, including delayed-type hypersensitivity and autoimmunity.

Dietary intervention
Interest in possible dietary factors has increased in recent years and a number of possible targets have been identified. These include associations among dietary fatty acid composition, dietary antioxidant intake, and asthma. However, the studies to date only show associations and have either been cross sectional or ecological in design. High ω-3:ω-6 fatty acid ratios in the diet may help reduce the development of airways inflammation, and a very good source is fish oil. An association between reduced risk of childhood asthma and consumption of oily fish has been demonstrated and has biological plausibility as ω-6 fatty acids such as linoleic acid, which are low in fish oils, are metabolised to arachidonic acid and then to prostaglandin E2, which in turn reduce lymphocyte production of interferon γ and result in upregulation of the TH2 allergic inflammatory profile. Eicosapentaenoic acid, an ω-3 fatty acid found in significant amounts in oily fish, competes with arachidonic acid and inhibits prostaglandin E2 production. As yet there are no studies examining the role of maternal dietary modification of either or both of these constituents in the subsequent development of childhood asthma. There is some experimental and circumstantial evidence that poor antioxidant intake (including vitamin C and selenium), mainly provided as fresh fruit and vegetables, may be associated with increased bronchial responsiveness and asthma. Avoidance of dietary allergens during pregnancy, another potential approach, has been largely disappointing. Although significant reduction in eczema has been achieved, no impact on later expression of asthma and wheezing illness has been established.

Reducing allergen exposure
The observation that in inland areas (where mites are less common) levels of atopic sensitisation and asthma prevalence are lower suggests an association between atopic sensitisation and asthma. A slight but significant correlation between house dust mites in samples from bedding and BHR in school age children has also been noted, as has a dose relation between exposure in the first year of life and wheezing at age 11 years. However, in areas of high mite exposure (at low altitude) and low mite exposure (at high altitude) there do not appear to be any significant differences in the prevalence of respiratory symptoms or asthma. In a high altitude arid environment with virtually no house dust mites, current respiratory symptoms, reported asthma, and BHR were similar to those reported in children of similar age at sea level. High levels of atopic sensitisation were also observed in both symptomatic and asymptomatic children. Only sensitisation to cats was significantly higher in symptomatic children, and no clear relation was found between allergen levels and sensitisation.

Despite these apparent contradictions, the large population studies of Peat and colleagues in New South Wales, Australia provide the most convincing evidence for differences in disease prevalence associated with different levels of atopic sensitisation. However, even in areas of low atopic sensitisation, the prevalence of current asthma (defined as wheeze in the previous 12 months and BHR) was 7–10% compared with 12–13% in areas of higher atopic sensitisation. The high levels of atopic sensitisation noted in asymptomatic individuals indicate the importance of other factors in the cause of asthma and suggest that atopy is only one aspect of a complex multifactorial process.

Allergen avoidance in intrauterine and early life may only delay rather than prevent sensitisation and development of disease. This can be inferred from occupational allergy, where exposure to novel allergens occurs in adult life, and sensitisation occurs in a significant proportion of individuals over the first few months of exposure, which subsequently diminishes in frequency. Thus it could be argued that whenever the exposure occurs, a proportion will be sensitised and subsequently develop symptoms. Set against this concept are data for sensitisation to cat and dog dander in the first year producing the greater probability of asthma and allergy to animal danders than for sensitisation after the first year of life. Population research also supports the importance of early sensitisation. Migration after the first year of life results in an asthma prevalence characteristic of the community from which the child originated, whereas migration before birth results in the prevalence of asthma characteristic of the community into which the child was born. Furthermore, early onset atopy...
has a different prognosis to late onset atopy with a far greater probability of persistence of wheezing and BHR than in late onset disease. The observations from stable populations in the former East and West Germany also point to a strong and recent environmental drive to airway sensitisation and asthma. It is only in the population born since the separation and before the reunification of the two communities that asthma is higher in the western population. With the evidence from twin studies that indoor allergens are a major risk factor, the relevance of early sensitisation is strong and offers a target for intervention.

Pharmacological intervention

While no one would support using a pharmacological intervention in the whole population, the early and prolonged use of inhaled corticosteroids as a tertiary method of prevention is already being tested in an uncontrolled experiment as a consequence of the widespread dissemination and adherence to national guidelines of asthma management. The evidence from adult studies that chronic airway inflammation and submucosal airway fibrosis is a common feature of persistent asthma, and that these changes can be reversed by inhaled corticosteroids, has led to an even earlier use of this class of drug. The continuing concerns about their long term use in children has been balanced by the observation that long term outcome appears to be better the earlier inhaled corticosteroids are introduced.

Other approaches that have been suggested in symptomatic and atopic infants and preschool age children include the early introduction of cromones, which have been shown to reduce IgE production from B cells (at least in vitro). The use of the related but orally administered compound ketotifen and third generation antihistamines such as citerazine have also been advocated. However, clinical trial data for cromoglicate are not encouraging. Ketotifen awaits confirmation in an adequately powered study and the early results from a recently reported large citerazine trial show some benefit but only in a highly selected strongly atopic group. The problem of identifying confidently infants and very young children with early atopic asthma from the larger group with transient wheezing is an as yet unresolved issue.

Which intervention?

Apart from reverting to housing conditions and general lifestyles operating more than 30 years ago, what opportunities are there for preventing asthma? Government policies and supportive legislation have a role to play—for example, in the further discouragement of smoking and in the control of environmental air pollution, although both these measures would have their greatest impact in reducing exacerbations rather than in primary prevention. Immunological manipulation to stimulate TH1 immunity has considerable risks and requires further development in animal models. Some modification of current immunisation policy might be worth considering, such as re-introduction of the infant BCG immunisation, but only after adequate trials. Dietary change to increase antioxidant intake may be beneficial in several other contexts such as ischaemic heart disease and bowel cancer, and this general advice has already been given to the population. Prospective trials with dietary or vitamin supplementation in pregnancy and early childhood could be mounted, but there are many concerns surrounding dietary manipulation during such a vulnerable period. Increasing physical activity, particularly outdoors, would be of benefit not only in removing the individual from the indoor environment but also because of concerns about the relative “unfitness” of today’s child and young adult populations. Reduction in exposure to the prevailing inhaled allergens, particularly indoors, could be mounted, and the best candidate in western Europe would be the use of effective interventions that reduce exposure to mites and their faecal particles are available, such as comfortable breathable bedding materials and a reduction in carpets and heavy furnishings, particularly in the bedroom and main living areas. Indeed, such an early intervention has shown some promise despite the difficulties in pursuing this line of research. The relevance ofmite avoidance in individuals with established asthma has recently been the subject of a narrative review and a meta-analysis.

The contribution of all the factors outlined, and no doubt others as yet unidentified, are all likely to be relevant to the recent asthma “epidemic”. From what is already known a number of whole population interventions could be conducted to establish their potential in reducing the development of what has become the most common chronic illness of childhood.

PETER J HELMS

GORDON CHRISTIE

Department of Child Health, University of Aberdeen Medical School, Foresterhill, Aberdeen AB25 2ZD, UK

email: p.j.helms@abdn.ac.uk


3 Osman M, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. BMJ 1996;312:34.


15 Strachan DP, Butland BR, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national cohort. BMJ 1993;306:149.


26 Hodge L, Peat JK, Salome C. Increased consumption of polyunsaturated oils may be a cause of increased prevalence of childhood asthma. Aust NZ J Med 1994;24:727.
Glutaric aciduria and suspected child abuse

Subdural and retinal haemorrhages in young children without an appropriate history of trauma strongly suggest non-accidental injury. Similar features are occasionally found in patients with glutaric aciduria type 1 (GA1), a rare inborn error of metabolism, and have led to the mis-diagnosis of non-accidental injury.\(^1\)\(^2\)\(^3\) When and how should this condition be sought in cases of suspected child abuse?

GA1 is an autosomal recessive disorder caused by deficiency of the enzyme glutaryl-CoA dehydrogenase. Commonly it presents before age 18 months with a sudden onset of encephalopathy, following which the child has a severe and persistent movement disorder. Before this there may have been episodes of irritability or mild encephalopathy with no sequelae. Clinical examination at this stage often shows macrocephaly, and cerebral imaging may show bilateral frontotemporal atrophy or widening of the Sylvian fissures, with or without subdural effusions (fig 1). Following the catastrophic encephalopathic episodes, magnetic resonance imaging usually shows changes in the basal ganglia. Other patients present with a less acute deterioration and an unknown number remain asymptomatic.\(^4\)\(^5\)\(^6\)

Subdural haematomas have been found in symptomatic and asymptomatic patients, even in the immediate post-natal period.\(^1\)\(^2\)\(^5\)\(^6\) They can occur with minimal trauma, sometimes repeatedly, presumably because the bridging veins are elongated in the presence of cerebral atrophy and are easily ruptured. Retinal haemorrhages have also been reported.\(^1\)\(^2\)

Investigation for GA1 is not entirely straightforward. Urine organic acid analysis by gas chromatography–mass spectrometry usually reveals glutaric and 3-hydroxyglutaric acids. Glutaric acid can, however, be...
found in other conditions and abnormalities are not always present in patients with GA1, particularly when the patient is clinically stable. In the presence of normal total and free plasma carnitine concentrations, GA1 can be detected by measuring glutaryl-carnitine in fresh blood spots, preferably using electrospray ionisation tandem mass spectrometry. Unfortunately, at the time of diagnosis, patients with GA1 usually have low plasma carnitine concentrations and glutaryl-carnitine is then a less reliable diagnostic marker. The definitive test for GA1 is measurement of glutaryl-CoA dehydrogenase activity in leukocytes or cultured fibroblasts but this is expensive and may introduce a delay.

GA1 does not cause skeletal abnormalities. In particular, it does not predispose patients to fractures; if a subdural haematoma is accompanied by a fracture, exclusion of GA1 is probably unnecessary. Subdural haemorrhages have not been reported in cases of GA1 without frontotemporal atrophy and, given the proposed mechanism, they would not be expected. It is, therefore, not appropriate to look for GA1 if cerebral imaging shows subdural haematomas without any frontotemporal atrophy or widening of the Sylvian fissure. On the other hand, in the presence of bilateral frontotemporal atrophy, investigation for GA1 is essential. Under these circumstances, we recommend urinary organic acid analysis and the measurement of blood spot glutaryl-carnitine, combined with total and free plasma carnitine concentrations. If the results suggest GA1, the diagnosis should be confirmed by measuring glutaryl-CoA dehydrogenase activity. The enzyme assay should also be undertaken if the initial tests show low plasma carnitine concentrations (free carnitine < 15 mmol/l) or equivocal findings (such as borderline blood spot glutaryl-carnitine concentrations or raised urinary glutaric acid without 3-hydroxyglutarate).

All guidelines need to be interpreted in the light of individual circumstances. Even without the characteristic neuroimaging findings, biochemical investigations, including enzymology, should be considered if the history or examination reveals features typical of GA1, such as macrocephaly or an extrapyramidal movement disorder following an encephalopathic illness. It should also be remembered that the diagnosis of GA1 does not exclude non-accidental injury. Patients with GA1 tend to be irritable and many have severe problems, such as feeding difficulties that can cause parental frustration. We recommend performing a skeletal survey on all infants with unexplained subdural haematomas, even if they are known to have GA1.

Obviously, it is very important that potentially treatable metabolic defects should be detected and that parents should not be accused wrongly of injuring their children. It is equally important for children to receive protection when necessary. These recommendations should enable children with GA1 to be identified, without the need for extensive biochemical investigations in every patient with a subdural haematoma in whom non-accidental injury is suspected.

A A M MORRIS
Department of Child Health,
Royal Victoria Infirmary,
Newcastle upon Tyne, UK

G F HOFFMANN
Department of Neuropediatrics and Metabolic Diseases,
University of Marburg, Germany

E R NAUGHTEN
A A MONAVARI
The Children’s Hospital,
Temple Street, Dublin, Republic of Ireland

J E COLLINS
J V LEONARD
Metabolic Unit, Great Ormond Street Hospital,
London, UK

Correspondence to: Dr A A M Morris, Department of Child Health, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK