Environmental factors and gene-environment interactions in the aetiology of asthma

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Summary

1. The importance of early life environmental influences on the aetiology of asthma is implied by the observed geographic and temporal variation in the prevalence of the disease among children.

2. There is evidence pointing to the role of exposure to allergen, various aspects of diet and hygiene-related factors in the aetiology of asthma.

3. There is also evidence that heritable factors influence the impact of hygiene-related exposures on the risk of having asthma. Polymorphism within genes coding for the TLR-LPS signalling pathway may underlie variation in effects of hygiene-related exposures, including specifically endotoxin, on the risk of developing allergic sensitisation and allergic disease.

4. At present there is no unifying theory to explain the childhood origins of asthma and hence no solid basis for developing preventative interventions. Progress towards this goal requires better understanding of the heterogeneous nature of the disease in early childhood, improved characterisation of relevant environmental exposures, and long-term follow-up of birth cohorts with reliable and valid measures of allergy and asthma outcomes.

Introduction

Asthma is a complex, heterogeneous disorder that has proved difficult to define and classify. Descriptions of the disorder focus on characteristic symptoms of wheeze, chest tightness, shortness of breath and sometimes cough, accompanied by evidence of reversible, variable or inducible obstruction to airflow in the presence of underlying airway inflammation.[1]

There is a substantial burden of illness attributable to asthma[2,3] and evidence of a rising trend during the 1980s and 1990s led to widespread concern.[4,5] Among primary school children in Belmont, New South Wales, Australia, the prevalence of reported wheeze in the preceding 12 months increased from 10.4% in 1982 to 27.6% in 1992. Over the same period, the prevalence of airway hyperresponsiveness (AHR), an objective measure closely related to asthma, increased from 9.8% to 19.8%.[5] This rapid rise in prevalence implied that changing environmental factors must be responsible.

At the same time, evidence emerged of substantial geographic variation in the prevalence of asthma and other allergic disorders, some of which seemed unrelated to racial, ethnic or genetic factors. For example, among primary school children, those living in the former West Germany had a higher prevalence of current asthma (5.9%) and AHR (8.3%) than those living in former East Germany, where the prevalence was 3.9% and 5.5%, respectively.[6] Other studies showed substantial variation in the prevalence of asthma symptoms among children living in various northern, central and eastern European countries.[7] Similarly, the prevalence of ever having wheeze or asthma among ethnic Chinese children in Hong Kong and in a nearby city in southern China was 11.6% and 1.9%, respectively.[8] These regional variations strongly support the view that factors related to lifestyle or the local environment influence the risk of developing asthma.

If changing environmental factors contribute to the aetiology of asthma then, potentially, further changes can be implemented to prevent asthma. The search for specific environmental factors that cause asthma, particularly those that are potentially modifiable, was stimulated by the need to make public health recommendations for the prevention of the disease. Targeting these interventions to high-risk groups most likely to benefit requires knowledge of the interaction among environmental factors and between environmental exposures and hereditary attributes.

The heterogeneity of asthma and the complex natural history of the disease both contribute to the contextual framework within which potential contributors to the aetiology and course of asthma must be assessed. While many cases of asthma arise in childhood and persist,[9] in others the disease remits and may later relapse. There is also evidence that asthma may first arise in adult life.[10,11] Furthermore, even among children with asthma, differences between transient early wheeze, which remits before age six, and late-onset wheeze, which starts after age three years, and persistent wheeze have been described.[12] There is also variability in the pathological basis of the disease. Eosinophilic inflammation has long been recognised as a characteristic feature of asthma which underpins approaches to treatment of the disorder.[13] However, in recent years there is increasing recognition of the existence of a non-eosinophilic inflammation, in which neutrophils play a key role, which is associated with an illness otherwise indistinguishable from asthma.[14] Finally, there is clearly substantial variability among people with asthma in the triggers that elicit airway narrowing and symptoms, the underlying severity of the disease and in the effectiveness of various modes of therapy.[2,15,16]

In this paper I will summarise the basis of various hypotheses for the role of environmental factors in the

aetiology of asthma, some of which have been, or are being, tested in randomised controlled trials. I will examine evidence that hereditable factors influence the likelihood of an asthmatic response to environmental factors and finally conclude by describing a proposed model for further investigation of the impact of the environment on asthma.

Allergen hypothesis

One of the earliest clinical observations about asthma was that it is closely linked, either within individuals or within families, to hay fever and eczema and that all three of these illnesses are strongly associated with the presence of specific IgE antibodies directed against common environmental proteins.[17] The strong association between allergy to proteins arising from house dust mites, cockroaches, domestic animals, fungi, and pollens and the presence of asthma or AHR has now been replicated in many clinical studies.[18-21] Furthermore, it is well established that individuals who are sensitised to specific allergens and have non-specific AHR, develop acute bronchoconstriction and a prolonged exacerbation of asthma, after inhalation of that allergen in a laboratory-based challenge.[22] This has been also demonstrated after natural exposure to specific allergen.[23,24] Finally, although clinical trials testing allergen avoidance interventions within the house have largely been unsuccessful in improving outcomes in people with asthma,[25,26] there is evidence that effective removal from allergen exposure, for example by moving to an allergen-free environment at altitude, leads to improvements in the clinical manifestations of asthma.[27,28] The importance of allergy and allergens in the expression of asthma is well established.

The role of allergen exposure in causing asthma is less clear. In the special case of occupational asthma, there is little doubt that exposure to the occupational allergen is a prerequisite for the development of occupational asthma and early removal from exposure reduces the risk of acquiring persisting asthma.[29] Early studies in Europe suggested that a similar phenomenon may exist for natural exposure to domestic allergens. In Denmark, higher levels of house dust mites (HDMs) were found in the homes of children with asthma than in the homes of those without asthma.[30] In southern England, among children born to atopic parents, those who were exposed to > 10µg/g HDM allergen in their beds at age one year had a 4.8 times higher risk of having asthma at age 11 years compared with children with lower levels of HDM allergen in the bed.[31] An early randomised controlled trial, conducted in the Isle of Wight, lent further support to the hypothesis that early life allergen exposure was important in the aetiology of asthma.[32,33] Among 120 infants at increased risk of allergy due to a positive family history, an intervention directed at avoidance of inhaled and ingested allergens during the first nine months of life, led to a reduction in the prevalence of allergen sensitisation (10.9% *vs* 30.7%) and reduction in the prevalence of wheeze (14% *vs* 27%, $p = 0.08$) and nocturnal cough (14% *vs* 32%, $p = 0.02$) at age eight years.

Subsequent clinical trials of house dust mite allergen avoidance are less convincing. A randomised controlled trial on house dust mite allergen avoidance implemented from birth in children with a family history of asthma in Sydney showed no change in the prevalence of asthma-like symptoms at age three years.[34] Similar findings were observed in the Manchester Asthma and Allergy Study, which was also conducted in high risk children and which used stringent allergen avoidance measures.

There is emerging evidence that allergen exposure in early life actually may confer some protection against the development of allergic illness.[35] The observation that people who own pets, an important source of domestic allergen exposure, may be relatively protected against the development of allergic illness, including asthma, is discussed below under the heading of the hygiene hypothesis.

With the present state of knowledge, it seems unlikely that variation in environmental exposure to allergen is a major contributor to geographical and temporal variation in the prevalence of asthma. The ultimate role of allergen avoidance as a clinical tool to prevent asthma in high risk children will be clearer when the randomised controlled trials referred to above report the findings of longer-term follow-up.

Diet hypotheses

Diet varies considerably with life-style and culture and has changed over recent decades. Hence, diet is a plausible candidate to explain variation in the prevalence of asthma. There are observational studies to suggest that dietary intake of salt,[36] anti-oxidant vitamins and trace elements[37-39], and fish oil[40] may all influence the risk of having asthma. More convincing evidence, in the form of randomised controlled trials conducted in an at-risk population, is generally lacking. Early results from a trial of fish oil supplementation from infancy show a reduction in cough but no difference in the prevalence of wheeze or diagnosed asthma at age three years.[34] Although anti-oxidant vitamin supplementation has not been effective in improving clinical outcomes in people with established asthma,[41] no clinical trials have been conducted to test the effect of this intervention in preventing the onset of asthma in high risk individuals.

Aspects of diet remain as potentially important factors in the aetiology of asthma. The final conclusion on their role awaits the results of further investigations.

Hygiene hypothesis

The term “hygiene hypothesis” is attributed to David Strachan, who coined it in 1989 to explain his observation that hay fever was less common in children who grew up in large families.[42] Since then a considerable body of epidemiological evidence has accumulated around the protective effect of environmental and life-style factors that seem to have a link with hygiene.

Among the most consistent associations is Strachan’s original observation that exposure to other children reduces the risk of being allergic, and consequently, of having

allergic illnesses such as asthma and hay fever.[43-45] In the absence of a large family, exposure to children in early child care[46,47] has a similar protective effect. Childhood exposure to animals also reduces the risk of acquiring allergic disease. This exposure may occur on farms e.g.[48,49] or in the domestic environment.[50-52] The findings concerning exposure to domestic pets are complex and, in some cases conflicting, in relation to the specific pets and the specific outcomes averted. However, there is some consistency among all these hygiene-related exposures that it is early life exposure that confers protection.[52]

Other exposures such as enteric infections,[53] use of antibiotics,[54] and mycobacterial exposure in the form of Bacille Calmette Guerin (BCG) vaccination[55] have also been proposed as relevant to the hygiene hypothesis. However, the data for these exposures is less consistent and its interpretation as evidence for a hygiene-related protective factor is less straight forward.

The nature of the actual exposure that is responsible for the protective effects remains unknown. Much attention has focused on the role of microbial pathogens and, in particular, bacterial endotoxin, a lipopolysaccharide (LPS) that is known to activate innate immunological pathways *via* Toll-like receptor (TLR) 4.[56] Among children living in farming and non-farming environments in central Europe, higher levels of endotoxin in mattress dust were protective against the development of atopic wheeze.[57] However, the evidence is complicated by the adverse respiratory effects of endotoxin exposure both in early life[58] and in the workplace[59] so that both positive and negative associations between endotoxin exposure and allergic and respiratory symptoms have been reported (reviewed in Liu, 2002.[60]) Indeed, the same central European study[57] showed that the prevalence of wheeze among non-atopic children was higher at high levels of endotoxin exposure. It is not known whether these epidemiological associations with endotoxin exposure indicate a specific action of LPS or, alternatively, that endotoxin is simply a marker for exposure to general or specific microbes or microbial components. The mechanism by which activation of the innate immune system *via* this pathway protects against allergic illness remains unknown.[61] However, there is experimental evidence to suggest that this pathway is critical to the development of Th2 responses to inhaled allergen.[62]

Evidence that heredity modifies the response to environment

While it has long been known that predisposition to asthma runs in families and considerable effort has been expended in identifying genetic risk factors for the disease, recent evidence has highlighted the potential importance of gene-environment interactions in aetiology of asthma. Among adults and children with a family history of allergic illness, exposure to cats protects against the presence of allergy to cat.[63,64] However, among people without a family history of allergy, there is no protective effect. Similarly, in a cohort of Australian-born children of ethnic Chinese, Vietnamese or Filippino origin, neonatal BCG vaccination protected against subsequent development of wheeze and AHR during childhood in those with a family history of allergic disease.[55] However, in those without a positive family history there was no protection. In fact, among this sub-group there was a trend towards increased wheeze and AHR in BCG vaccinated subjects. The observation that a family history of allergic disease modifies the response to hygiene-related environmental factors implies that there are genetic determinants of this protective effect.

Genes that modify responses to the environment

One candidate for this protective effect is the CD14 cell surface protein, which is part of the receptor for bacterial LPS. Expression of CD14 on the surface is correlated with airway inflammation following inhalation of bacterial endotoxins.[65] Polymorphisms in the promoter region for CD14 gene have been linked to the presence of atopy in some[66,67] but not all[68] populations. In a population-based cohort followed from primary school age, it was found that CD14 -159CC genotype was associated with an increased risk of early onset (i.e. before age 12) atopy and AHR (Figure 1).[69] Subjects with CD14 -159CC had an odds ratio of 2.2 (95% CI = 1.2-4.2; p = 0.018) for early-onset atopy compared with subjects with genotype -159CT and -159TT. Polymorphisms in the TLR4 gene have also been associated with an increased risk of asthma in Swedish schoolchildren.[70] As CD14 and TLR4 form part of the TLR-LPS signalling pathway, it has been proposed that polymorphisms in these genes underlie variation in effects of hygiene-related exposures, including specifically endotoxin, on the risk of developing allergic sensitisation and allergic disease.[71]

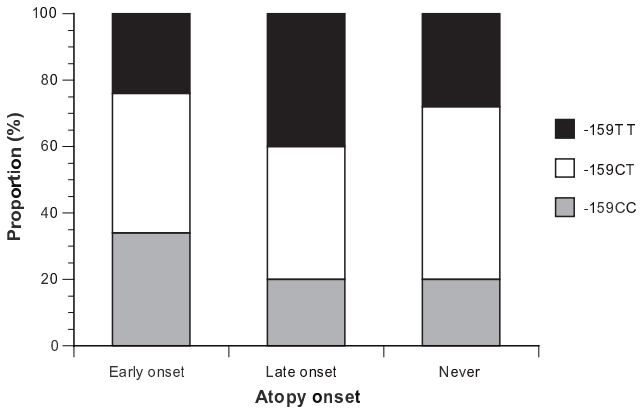

Figure 1. Relation between polymorphisms in the gene for CD14 and the presence and timing of onset of atopy in primary school age children, Belmont, New South Wales, Australia. *"Early onset" refers to atopy onset before age 12. "Late-onset" refers to atopy onset between age 12 and 25 years. Source: O'Donnell* et al.[69] *Am. J. Respir. Crit. Care Med. 2003;* ***169:****615-22, Official Journal of the American Thoracic Society. ©American Thoracic Society.*

Conclusions

This brief overview summarises some aspects of a possible model for investigating the impact of environmental and genetic factors on the asthma. A relevant and useful model should encompass a broad range of exposures and outcomes relevant to asthma. It should also allow for interacting effects of environmental and genetic factors and should encompass intermediate phenotypes, which are important both in understanding basic mechanisms and in providing measurable attributes that can be used in population studies. The elements of the model canvassed in this review are necessarily limited. A more comprehensive model for asthma must accommodate a wider range of exposures, genes, intermediate phenotypes and outcomes (Figure 2). Testing this model requires cooperative research in populations, clinical settings, animal models and molecular studies. Studies investigating gene-environment interactions will need data from large, well-characterised populations in a variety of settings.

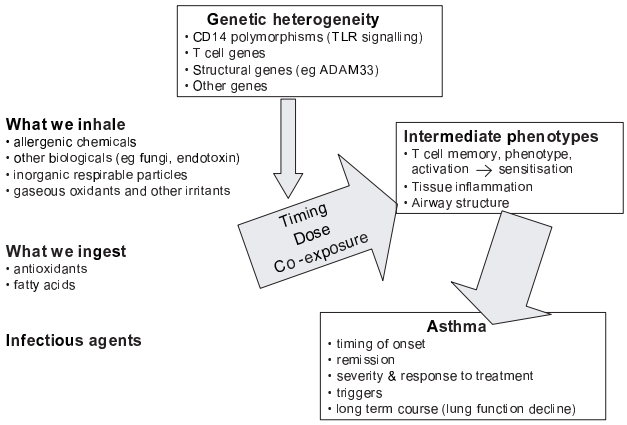

Figure 2. A model for studying the impact of the environment and genetic factors on asthma.

A more complete understanding of the pathways underlying the development and persistence of asthma will lead to advances in preventing the disease and ameliorating its consequences.

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