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Childhood Asthma

Causes, Epidemiological Factors and Complications

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Abstract

Asthma is common in children and its prevalence in this age group is increasing. While the reasons for this reported increase, and indeed the true magnitude of the increase, remain unclear, there can be no doubt that asthma is now a major health problem in children worldwide. Fortunately, our knowledge of the pathophysiology of asthma is also increasing. It is now known that asthma is a chronic inflammatory disease regulated by a variety of mediators, of which perhaps the leukotrienes are among the most important. This new understanding of the pathophysiology of the disease has spurred the development of the antileukotriene agents, which can be expected to play an increasingly important role in the management of childhood asthma.

Asthma is the most common chronic illness in childhood[1] and is becoming more prevalent in this age group.[2,3] The good news is that more is known about the pathophysiology of asthma than ever before, and, as a consequence of this increased knowledge, a much wider range of treatment options is now available to manage the condition. The bad news is that asthma in children continues to be underdiagnosed and undertreated.[1] It is arguable that a clearer understanding of the pathophysiology of asthma in children would aid both the recognition and the treatment of the condition in this age group.

1. Definition and Classification of Childhood Asthma

1.1 Definition

The definition of asthma has evolved over the last few decades. During the 1950s, the key component was reversibility of airflow obstruction. In the 1960s, the criterion of bronchial hyperresponsiveness (BHR) was added to the definition. Subsequently, repeatedbronchoscopicevaluations conducted in the 1980s showed that the underlying pathology – even in patients with newly diagnosed and mild asthma – is generalised and persistent airway inflammation. As a result, asthma is now defined as a chronic or recurring inflammatory disease of the airways in which BHR is associated with reversible airway obstruction.[3-5]

Unfortunately, difficulties arise when this definition of asthma is applied to preschool children. Chanarin et al.[4] have made the following points:

- There is no evidence of a persistent inflammatory process in the airways of wheezy young children.
- BHR has not been shown to be more common in wheezy young children than in non-wheezy young children.
- There is little or no information regarding the variability of airway obstruction in young children.

However, the above findings may reflect a lack of data regarding airway inflammation and BHR in wheezy young children.

The situation is compounded by the relatively nonspecific nature of signs and symptoms of airway obstruction in children. Thus, some infants and young children with asthma may be diagnosed as having wheezy bronchitis or chest infection; conversely, wheeze in children and young infants may be attributed to asthma when it is in fact due to non-asthmatic causes such as anatomical abnormalities or infection.[1,6]

More uncertainty stems from the complex interrelationships between BHR, the diagnosis of asthma, and asthma symptoms. When Pattemore et al.[7] investigated a random sample of 2053 children aged 7 to 10 years, they found no asthma diagnosis in 53% of those with BHR, and no current asthma symptoms in 41%. Conversely, 48% of children with diagnosed asthma, and 42% of those with diagnosed asthma and current symptoms, did not have BHR. Thus, clinical asthma and BHR do not always coexist (fig. 1), and BHR may not be the gold standard of diagnosis in childhood asthma.[5] This lack of a universally accepted and clearly delineated definition of asthma together with the absence of a single objective diagnostic test for the condition continue to be key problems in paediatric asthma.

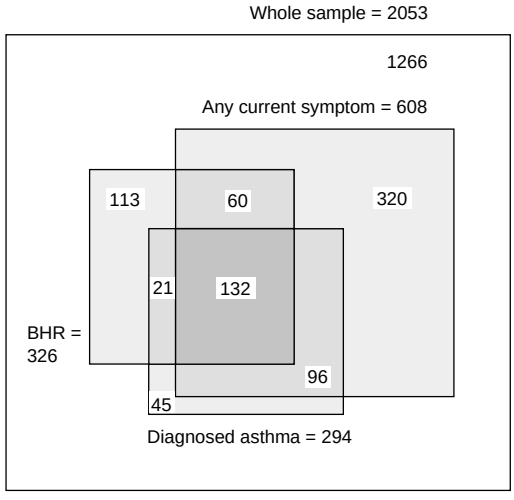

Fig. 1. Overlap of children with any current symptom, those with diagnosed asthma, and those with bronchial hyperresponsiveness (BHR) in a sample of 2053 children aged 7 to 10 years.[7]

1.2 Classification

The available evidence suggests that wheezing illness in infants and young children is not a single disease entity.[4,8] For example, Martinez et al.[8] described 2 distinct phenotypes of wheezing illness – 'transient early' and 'persistent' – in children up to the age of 6 years. The characteristics of these 2 types of wheezing illness are as follows:

- *Transient early wheezing:* This resolves by 3 years of age; reduced pulmonary functional residual capacity is documented shortly after birth; affected children are more likely to have mothers who smoked during pregnancy; wheezing is probably due to congenitally smaller airways.
- *Persistent wheezing:* Wheezing is present in children aged from 0 to 6 years; pulmonary function is within normal limits during the first year of life but decreases by the age of 6 years (suggesting more severe disease or the long term consequences of recurrent airway obstruction); affected children are more likely than non-wheezing or transient early wheezers to be atopic and to have mothers with asthma.[8]

2. Prevalence of Asthma in Children

The true prevalence of asthma in children is difficult to determine. Reasons for this include the lack of a single, objective diagnostic test for asthma, differing methods of classification of the condition, and the uncertain influence of increasing public and professional awareness of asthma on prevalence.[2,3] Another reason for confusion about the actual prevalence of asthma is the uncertain relationship between viral infections, episodes of childhood wheezing and true asthma. Epidemiological studies have demonstrated a correlation between the seasonality of viral upper respiratory tract infections (RTIs) [e.g. respiratory syncytial virus, rhinovirus] and asthma exacerbations (including hospitalisations).[9-14] Indeed, children with mild, intermittent asthma and those less than

3 years of age may wheeze only during viral infections.[8] Lemanske et al.[15] have also shown that rhinovirus RTI enhances airway reactivity and predisposes the allergic patient to the development of late asthmatic reactions. Thus, it can be difficult to distinguish between viral infection with asthma-like symptoms and viral infection-induced exacerbations of asthma.

These flaws in the available data, together with local differences in climate, environment etc., might help explain the variations in asthma prevalence reported in different countries. In one recent review,[16] for example, the reported prevalence of childhood asthma ranged from 2.8% in Finland in 1991 to 10.5% in Australia in 1992. Similarly, a study of 463 801 children aged 13 to 14 years in 155 collaborating centres in 56 countries found that the highest 12-month prevalence of asthma was about 20 times higher than in the centre with the lowest prevalence (range 1.6 to 36.8%).[17] The highest prevalences were from centres in the UK, Australia, New Zealand and the Republic of Ireland; the lowest prevalences were from centres in a number of Eastern European countries, Indonesia, Greece, China, Taiwan, Uzbekistan, India and Ethiopia.[17] Regardless of global variations in asthma prevalence, however, the worldwide trend over the last 2 to 3 decades has been an increase in the prevalence of this condition,[2] particularly among children, teenagers and young adults (table I).[3,16]

Table I. Changes in prevalences of current asthma in children of different countries[16]

Country	Year	Current asthma (%)
Australia	1982	5.6
	1992	10.5
Finland	1977-79	1.0
	1991	2.8
England	1985	6.0
	1988	8.9
Wales	1973	4.2
	1988	9.1
New Zealand	1975	5.0
	1989	8.0
USA	1981	3.2
	1988	4.3
Taiwan	1974	1.3
	1985	5.1

3. Risk Factors for the Development of Asthma in Childhood

3.1 Gender

Male gender is a risk factor for asthma in children aged less than 14 years,[3] probably because of the higher prevalence of atopy in boys than in girls.[18] However, young females may experience a greater deficit in pulmonary function.[19]

3.2 Atopic Status

Atopy is strongly associated with the development of asthma and BHR in children,[3,6] as well as with its persistence into later life.[18] Atopy may also be associated with a less favourable prognosis of asthma.[3]

3.3 Genetic/Familial Factors

A genetic component in the development of asthma is suggested by the clustering of asthma in families and the results of genetic linkage analysis.[3] Indeed, most studies find the occurrence of asthma within families to be the strongest risk factor for the development of asthma in children.[6] Maternal history of asthma appears to be most important; Martinez et al.[8] found that children with persistent wheezing from early childhood to the age of 6 years were more likely to have mothers with a history of asthma than children who never wheezed ($p < 0.001$).

3.4 Respiratory Infections

While it is clear that viral RTIs often trigger asthma exacerbations, it is less clear whether such infections play a causal role in the development of asthma. However, the results of a study[20] showing that a history of bronchiolitis or croup in early

childhood is predictive of later BHR suggest that early RTIs may play an aetiological role in childhood asthma.

3.5 Outdoor Air Pollution

There is conflicting evidence about the role of outdoor air pollution in asthma. Some studies have linked oxidant pollutants such as nitrogen dioxide and ozone, and airborne allergens such as soybean dust, to exacerbations of asthma.[3] However, the results of studies showing that the prevalences of asthma, BHR and atopic sensitivity are higher in less polluted areas of West Germany and Sweden than in more polluted areas of East Germany and Poland[21-23] cast doubt on the suggestion that high levels of sulphur dioxide and particulate matter cause asthma and allergy.

Similarly, while some studies have suggested that road traffic-related air pollution is a risk factor for asthma,[2] others have found no such relationship.[6]

3.6 Indoor Risk Factors

Early life allergic sensitisation after exposure to house dust mites, cats, rats, mice, cockroaches, moulds or chemical emissions in the indoor environment may be responsible for the presence and severity of childhood asthma.[2,6]

3.7 Cigarette Smoking

Exposure to tobacco smoke in infancy is a major risk factor for the development of asthma and atopy,[2] particularly if the mother is a smoker,[2,8,18,24] whereas not all studies show that smoking among other household members alone increases the risk of developing wheezy bronchitis and asthma.[24]

In utero exposure to tobacco may affect airway responsiveness and reduce the infant's airway function after birth.[25]

3.8 Prematurity

While premature and full term children do not differ in terms of atopic sensitivity, there have been reports of the increased prevalence of cough and wheeze, and reductions in lung function, in children and adolescents born prematurely or of low birthweight.[26-28] Such reports may be attributable to persisting anatomical respiratory abnormalities in premature or low birthweight babies, and hence represent a wheezing phenotype different to that responsible for childhood asthma.[6]

3.9 Diet

Diet may play an important – albeit unclear – role in some children with asthma. It is known, for instance, that asthma is the most common pulmonary clinical manifestation of adverse food reaction, and studies using double-blind food challenges have reported prevalences of food-induced lower airway reactions ranging from 2 to 29% in selected populations.[29] Such findings suggest that avoiding proven food antigens may be important in some children with asthma.[29,30]

There is also evidence to suggest that another dietary manipulation, i.e. increasing the daily intake of dietary fish oil lipids, may protect against bronchial inflammation. An association between high fish consumption and improved baseline levels of forced expiratory volume in 1 second (FEV_1) was noted in the first US National Health and Nutrition Survey.[31] Peat et al.[32] have also shown that Australian children with a high intake of fresh oily fish have a lower prevalence of current asthma (odds ratio 0.22; 95% CI 0.08 to 0.63; $p < 0.001$). Double-blind studies of fish oil supplementation of the diet of individuals with asthma or allergy have yielded conflicting results. It has been suggested that the reason some studies have failed to show an effect is because polyunsaturated fatty acids must be substituted for saturated fats in the diet, not simply added to them. If dietary fish oil lipids are protective against asthma, a possible explanation is that omega-3 fatty acids in fish oils inhibit the generation of pro-inflammatory mediators (including leukotrienes [LTs])[33] derived from arachidonic acid, thereby modulating humoral and inflammatory components of the allergic response.

The role of breastfeeding in childhood asthma is uncertain. While prospective studies have found evidence of a beneficial effect of breastfeeding on wheezing illnesses, atopic sensitisation, eczema and food allergy in the first few years of life,[34,35] it is not clear that any persistent protective effect against childhood asthma is obtained from breast feeding.[36,37]

3.10 Climatic Factors

Climatic factors may help determine the incidence of asthma. The greater prevalence of asthma reported for the colder parts of some countries, for instance, may be due to differences in the levels of house ventilation or indoor humidity, or to the tendency for children to spend more time inside.[2] In addition, many studies have suggested that rapid changes in temperature or humidity can provoke the asthmatic airway.

4. Interplay of Genetic and Environmental Factors in the Aetiology and Pathology of Childhood Asthma

After reviewing the available data concerning the relationships between BHR, atopy, airway inflammation and asthma, Warner[5] drew the following conclusions:

- BHR may occur in non-asthmatic individuals and is not always demonstrable in people with asthma. Thus, BHR and asthma can exist separately.
- Atopic eczema and allergic rhinitis can occur in individuals who do not have asthma, and asthma (particularly in adults) can occur in the absence of allergy. Thus, allergy and asthma can also exist separately. This means that some component other than atopy must determine whether allergy will influence the course of asthma, and it may be that a predisposition to both allergy and BHR must be present before asthma develops in most children.
- Airway inflammation occurs very early in the natural history of asthma, perhaps even before the onset of the first symptoms.

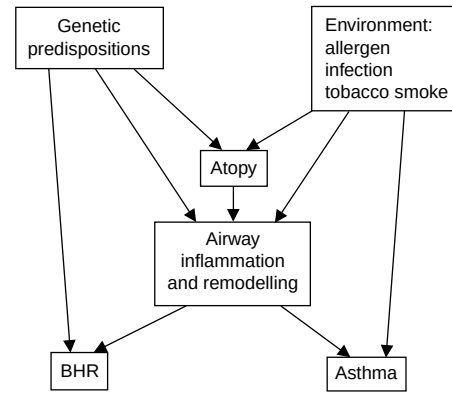

Fig. 2. A unifying hypothesis linking atopy, bronchial hyperresponsiveness (BHR) and airway inflammation, in which perhaps closely linked genetic predispositions together with environmental influences produce asthma.[5] © 1998 Munksgaard International Publishers Ltd, Copenhagen, Denmark.

- Airway remodelling may also occur early in the course of asthma, perhaps even simultaneously with inflammation. However, few data are available about airway remodelling in children.
- The airway epithelium may play a pivotal role in the remodelling process.
- A fundamental defect at the airway inflammation and remodelling level 'might explain how atopy sometimes produces airway inflammation and thereby BHR and asthma' (fig. 2).[5]

If the prevalence of asthma is increasing, the prevalence of this fundamental defect must also be increasing. However, it is much more likely to be an acquired defect than to be a true increase in genetic predisposition.

5. Inflammatory Cells and Mediators Involved in Asthma Pathophysiology

Asthma is a chronic inflammatory condition regulated by a variety of mediators released by blood leucocytes infiltrating the lung. The particular hallmarks of the asthmatic lung are mast cell activation and eosinophil infiltration.[38]

Allergen-induced episodes of acute asthma begin with an immediate early asthmatic response, which is thought to result from allergen interacting with

IgE bound to mast cell receptors. This leads to the release of a number of bronchoconstrictor and pro-inflammatory mediators (histamine, prostaglandins, cysteinyl-LTs and platelet-activating factor), resulting in smooth muscle contraction and mucosal oedema. Eosinophils and mast cells also release pro-inflammatory cytokines and agents that damage bronchial epithelium (basic proteins, proteolytic enzymes and oxygen radicals).[38]

The early asthmatic response is followed by a late-phase response, which has many of the characteristics of chronic asthma, including chronic eosinophilic inflammation and BHR. When present for long periods, inflammation is believed to cause structural changes in the airways, which result in irreversible airflow obstruction.[4,38]

6. Role of Leukotrienes in Asthma Pathophysiology

LTs play an important contributory role in the pathogenesis of asthma and the mediation of bronchoconstriction and inflammation.[38] They can be divided into 2 classes: the nonpeptide LTs (LTA_4, LTB_4) and the cysteinyl-LTs (LTC_4, LTD_4 and LTE_4). The cysteinyl-LTs were formerly collectively known as the slow-reacting substance(s) of anaphylaxis.

LTs are lipoxygenase products formed during the oxidative metabolism of arachidonic acid (fig. 3). Activation of phospholipase A_2 in response to various stimuli results in the release of arachidonic acid from membrane phospholipids. The resulting free arachidonic acid can then be converted by cyclo-oxygenase to form prostaglandins and thromboxane. Alternatively, it is converted by 5-lipoxygenase and the 5-lipoxygenase-activating protein (FLAP) to produce LTA_4, a common precursor of LTB_4 and LTC_4. The latter undergoes further metabolism by ubiquitous peptidase enzymes to form LTD_4 and LTE_4.[38]

Cysteinyl-LTs induce several pathophysiological effects relevant to asthma, including the following:

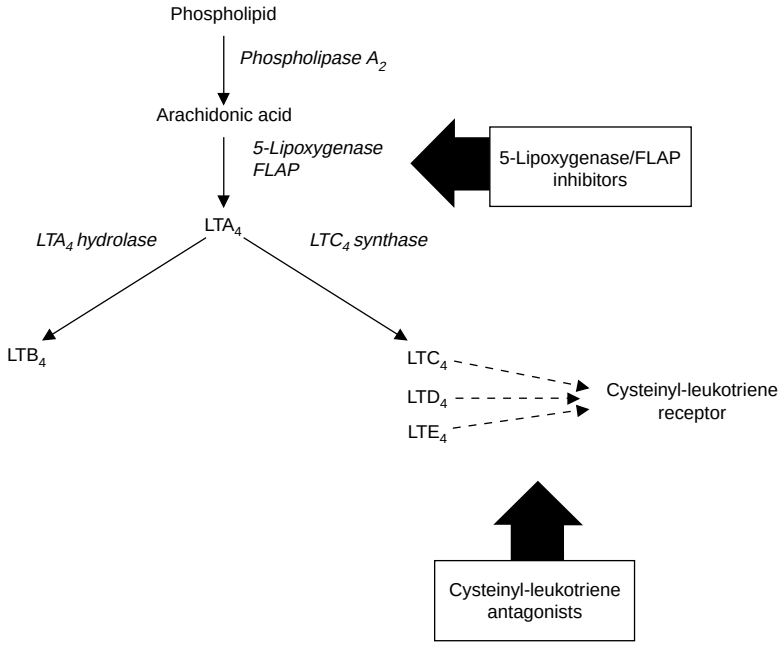

Fig. 3. The 5-lipoxygenase pathway of leukotriene synthesis.[38] **FLAP** = 5-lipoxygenase-activating protein; **LT** = leukotriene.

- Smooth muscle contraction leading to bronchoconstriction.[39] In this respect, cysteinyl-LTs are 1000-fold more potent than histamine *in vivo*[40] and produce a much longer-lived contraction than that obtained with histamine (30 to 40 minutes versus 5 to 10 minutes, respectively).[41]
- An increase in vascular permeability *in vivo*.[42]
- An increase in mucus production *in vitro*.[43]
- Inflammatory cell infiltration into the lung *in vivo*.[44,45]

LTs may also contribute to BHR.[46] Furthermore, several studies have reported increased levels of LTs in the bronchoalveolar lavage fluid and urine of patients with spontaneous episodes of asthma or after antigen or exercise challenge.[39]

Recognition of the role of LTs in asthma, and that corticosteroids do not inhibit the synthesis of these substances,[47,48] led to the development of anti-LT agents. These can be broadly classified as synthesis inhibitors of the 5-lipoxygenase enzyme system (e.g. zileuton) or FLAP to prevent LT formation in inflammatory cells, or LT receptor antagonists (e.g. montelukast and zafirlukast), which block the actions of cysteinyl-LTs on target tissues.[38,39]

7. Conclusions

Asthma is common in children and its prevalence appears to be increasing. However, while a number of risk (trigger) factors for childhood asthma have been identified, none have been conclusively shown to account for the reported increase of the condition in this age group. Indeed, the increased prevalence of asthma in children may, at least to some extent, be factitious: greater awareness of the disease probably accounts for some of the reported increase, and the difficulties of defining and diagnosing asthma in children mean that current prevalence data for paediatric asthma are probably flawed. Nevertheless, it remains a fact that more children throughout the world are considered to suffer from asthma now than ever before. It is also clear that the underlying pathology in these children is inflammation of the airways, and that LTs play an important role as mediators of this inflammation. The role of anti-LT drugs for the long term treatment of asthma in children can be expected to expand as more clinical data accumulate.

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