Neutrophil airway inflammation in childhood asthma
C M McDougall, P J Helms

A novel and inviting therapeutic target?

Although asthma has its highest prevalence in childhood, it is generally less severe than in adolescents and adults.\(^1\) Whether the high population prevalence is because symptoms are more noticed by parents or whether the more physically active lifestyle and natural inquisitiveness of children, particularly young children, unmasks bronchial hyperresponsiveness and related symptoms remains elusive to investigation. Whatever the explanation, the population prevalence of asthma and associated symptoms including wheeze and cough remains high, although with recent evidence of stabilisation or even a decline in those countries (including the UK) at the top of national prevalence “league tables”.\(^1\)–\(^4\)

The investigation of underlying mechanisms is challenging in children because of ethical considerations and the limited applicability of invasive procedures such as bronchoscopy, bronchoalveolar lavage (BAL), and bronchial biopsy. In this context, the report by Li et al in the present issue of Thorax\(^5\) using the sputum induction technique raises a number of important issues and points to lines of investigation and management that merit further development.

COUGH

As pointed out by Li et al,\(^2\) cough is a well recognised and frequent accompaniment of asthma and wheezing illness, although when an isolated and prominent symptom it is a poor predictor of subsequent wheezing illness and asthma.\(^7\) Cough can have important habit and psychogenic contributions, appears to be viewed as an important and worrying symptom by parents,\(^6\) and is poorly responsive to a range of popular and widely available “over the counter” treatments including antihistamines and antitussives,\(^9\) as well as inhaled corticosteroids.\(^10\) However, in the context of a confirmed diagnosis of asthma, cough is a well established although imprecisely quantifiable feature, unless assessed objectively by recording devices such as that described by Li et al.\(^5\) As the majority of symptomatic asthmatic children are also atopic, it is widely assumed that all the accompanying symptoms (including cough) are associated with eosinophilic airway inflammation, a conclusion that appears to have been confirmed in a recent study from the same author, albeit in a more severely affected clinic based population.\(^11\) However, the major inflammatory cell type observed in induced sputum in Li’s present study\(^3\) in less severely affected children—likely to be more representative of the symptomatic population—was the neutrophil, cell counts of which were positively correlated with objectively recorded cough frequency. The observation that, during acute episodes in asthmatic children with cough as a major symptom, cough receptor sensitivity appears to be independent of the degree of airflow obstruction also suggests different mechanistic pathways.\(^12\)

SAMPLING THE AIRWAY

The advent of flexible bronchoscopy, bronchial biopsy, BAL, and induced sputum has enabled the assessment of airway inflammation to flourish. In adults the place of T cell driven eosinophil mediated airway inflammation in many cases of atopic asthma is established,\(^13\) although it is recognised that not all asthmatic inflammation is eosinophilic.\(^14\) Indeed, neutrophilic inflammation is found in severe persistent asthma,\(^15\) asthma exacerbations,\(^16\)–\(^17\) sudden onset fatal asthma,\(^18\) occupational asthma,\(^19\) and nocturnal asthma.\(^20\)

In children the study of airway inflammation is hampered by ethical and practical constraints and consequently many of the reported BAL/biopsy studies are opportunistic, using patients undergoing clinically indicated bronchoscopy.\(^21\)–\(^23\) The generalisability of the findings from such studies to the wheezing population as a whole is therefore questionable. However, studies using nonbronchosopic BAL in intubated children undergoing minor elective surgery for non-respiratory indications\(^24\)–\(^25\) and studies based on induced sputum are potentially more representative, although the latter technique is only possible in cooperative children generally above the age of 6–7 years.

AIRWAY INFLAMMATION

Although it is increasingly recognised that there are many different childhood wheezing phenotypes, studies of airway inflammation in symptomatic children have had differing inclusion criteria and have not always clearly defined the phenotypic characteristics of the participants. Furthermore, all the published studies are cross sectional with no longitudinal studies addressing the relationships between airway inflammation and disease progression. Notwithstanding these limitations, evidence of different patterns of airway inflammation during exacerbations and in the stable state in children—including some very young children—\(^21\)–\(^25\) is emerging. Increased total cell number in BAL fluid and/or induced sputum,\(^21\)–\(^26\) increased numbers of epithelial cells implying airway epithelial damage and desquamation,\(^22\)–\(^27\) activated alveolar macrophages\(^28\) and other markers of activated cells and mediator release\(^21\)–\(^25\) have all been reported. Several studies have confirmed the presence of eosinophils in atopic asthma,\(^21\)–\(^24\)–\(^27\) in keeping with findings in atopic asthmatic adults. However, children who wheeze only with viral infections do not have evidence of eosinophilic inflammation but rather inflammation more typically characterised by neutrophilia.\(^22\)–\(^24\) Some exacerbations of asthma in childhood have been shown to be associated with increased neutrophils in sputum,\(^29\)–\(^30\) and now we have evidence of an association between sputum neutrophils and objectively recorded cough frequency in children with mild atopic asthma.\(^3\)

High neutrophil counts may, in part, be due to bacterial and/or viral infection, particularly where samples were obtained in children with persistent treatment resistant symptoms including cough, or in those with persistent chest radiographic changes. In contrast to bronchial biopsies, BAL fluid specimens and sputum contain those cells that have “escaped” from the lung and caution must be exercised in assuming that the same cells will be abundantly present in the lung parenchyma. Furthermore, the numbers and percentages of cells detected by staining in BAL fluid or sputum may not accurately reflect their state of activation or the levels of mediators that they produce. BAL fluid or sputum cell counts may also be affected by patients’ medication. Corticosteroids can reduce eosinophil numbers while increasing neutrophil numbers through opposing effects on the rate of granulocyte apoptosis.\(^31\)–\(^32\) However, while acknowledging these...
caveats, the possible significance of neutrophilic inflammation in childhood airway diseases cannot be ignored and merits further investigation of the underlying mechanisms and long-term implications for disease progression.

MECHANISMS AND CONSEQUENCES

The presence of airway neutrophilia implies increased neutrophil recruitment, increased neutrophil survival, or both. The pathogenesis of airway neutrophilia is likely to be multifactorial, dependent on a complex interplay of chemokines and lipid mediators from both resident airway cells and infiltrating inflammatory cells, as well as enhanced adhesion molecule expression and neural activity. The airway epithelium plays a pivotal role in airway inflammatory responses and is an abundant source of chemokines with potent neutrophil chemotactic activity, the release of which is promoted by a range of stimuli. It has been argued that physical triggers such as viruses, lipopolysaccharides, and ozone may be more important inducers of airway neutrophilia than any primary immunological cause, and epithelial interleukin (IL)-8 has been implicated as one of the most likely neutrophil chemotactants in response to these insults. Epithelial secretion of LTs, primarily a product of macrophages and neutrophils but also released by keratinocytes, lymphocytes and mast cells, has also been shown to contribute significantly to neutrophil chemotactic activity in lung secrections.

Neutrophil apoptosis permits neutrophil recognition and ingestion by macrophages, leading to their clearance from sites of inflammation. Inflammatory mediators including IL-1β, tumour necrosis factor, granulocyte–macrophage colony stimulating factor, granulocyte colony stimulating factor, interferon γ, many of which have been implicated in asthma, have been shown to inhibit neutrophil apoptosis. Furthermore, this enhanced neutrophil survival is associated with functional longevity, with the cells retaining the capacity to generate and release toxic products. Neutrophil apoptosis is suppressed in acute respiratory distress syndrome in adults and in chronic lung disease of prematurity, both of which are associated with airway neutrophilia. It is therefore tempting to speculate that the neutrophilic inflammation observed in childhood wheezing and cough may also be associated with impaired neutrophil apoptosis.

It is also important to consider the consequences of neutrophilic inflammation and, with reference to the paper by Li et al., how such inflammation might contribute to persistent cough. In this context it is important to establish not only the presence of inflammatory cells in the lungs but also whether they are quiescent or activated. Although the presence of some quiescent neutrophils in the lungs may have no functional consequences, activated neutrophils could have a role in the pathophysiology of airway disease through their release of reactive oxygen species, cytokines, lipid mediators, and enzymes including elastase, cathespins and myeloperoxidases and non-enzymatic defensins. Neutrophil derived serine proteinases and defensins markedly affect the integrity of the epithelial layer, decrease ciliary beat frequency, and induce the synthesis of epithelium derived mediators that may influence the amplification and resolution of inflammation. Neutrophil proteases, especially neutrophil elastase, can also activate eosinophils and are important mucin secretagogues for goblet cells and submucosal gland cells and, by inference, likely to contribute to mucus hypersecretion. Neutrophil products may also be mediators of increased vascular permeability and may directly contribute to airway hyperresponsiveness.

Current anti-inflammatory treatments for asthma target inflammation in general or specific inflammatory pathways other than those involved in neutrophil recruitment. Not only do such treatments fail to tackle neutrophilic inflammation, but steroids may actually exacerbate it by enhancing neutrophil survival.

CONCLUSIONS

The present report by Li et al. adds to the emerging body of evidence that a significant proportion of asthma and wheezing illness in both adults and children is associated with neutrophilic airway inflammation and that this pattern is not limited to individuals with severe symptoms. This raises important and interesting questions regarding the mechanisms and consequences of neutrophilic inflammation, as well as presenting a novel and inviting therapeutic target.


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References


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OCCUPATIONAL ASTHMA

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Early cessation of exposure is important

Occupational asthma is the commonest form of occupational lung disease in many Western countries, having overtaken the pneumoconioses in these countries owing to improved control of exposure to silica, asbestos, and coal dust. The reported incidence ranges from 13 per million workers in South Africa to 174 per million workers in Finland. It has been estimated that occupational factors may be responsible for 15% of all cases of adult onset asthma. The financial costs of occupational asthma in the US alone were estimated at between $1.1 and $2.1 billion in 1996.

Although occupational causes are relatively uncommon, they are important because of the additional health risks associated with these occupations. Occupational asthma is eminently preventable. However, one of the challenges in prevention is the fact that there are several hundred known causes arising from many occupations in most major industries. This is one of the reasons why prevention strategies are often unsuccessful. To be successful, clinicians and occupational health practitioners need to be actively involved with the primary, secondary and tertiary prevention of occupational asthma.

Primary prevention is about the maintenance of safe working conditions and avoiding exposure to known sensitisers and irritants. A good example of which many readers would be familiar is the healthcare industry. A recent systematic review found evidence that substituting powdered latex gloves with latex free gloves or powder free gloves or low protein powder free gloves or latex free gloves greatly reduced latex aerosolisation, sensitisation, and asthma in healthcare workers. This evidence was rated as SIGN level 2+, indicating that it is from well conducted observational studies with a low risk of bias or confounding and a moderate degree of evidence that the relationship was causal.

Secondary prevention of occupational asthma involves screening of workforces at risk. Workers known to be exposed to asthmagenic agents should undergo regular health surveillance. Cases of occupational asthma need to be identified early because continuing exposure results in worse symptoms, a faster decline in lung function, and a poorer prognosis. Clinicians usually only become involved with diagnosis, management and rehabilitation—that is, tertiary prevention of occupational asthma. Respiratory symptoms from unrecognised or undertreated asthma cause work related respiratory disability among young adults in several industries. While a key principle of management, removal from exposure often entails loss of job with the consequent socioeconomic disadvantages.

In this issue of Thorax Anees and colleagues report a study of the decline in forced expiratory volume in 1 second (FEV1) in a series of patients with occupational asthma in Birmingham. The authors found that FEV1 was declining by 101 ml/year before removal from occupational exposure. Following removal from exposure, FEV1 actually improved by 12.3 ml and subsequently declined by only 27 ml/year, a rate similar to what would be expected in a working age population. The authors admitted the likelihood of selection bias and the fact that they could not always be certain precisely when removal from exposure had occurred. The lack of an effect of current smoking on decline in FEV1 was surprising and might be due to a “healthier smoker” effect.
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