Eur Respir J 2006; 27: 884–888
DOI: 10.1183/09031936.06.00128105

PERSPECTIVE

Multiple inflammatory hits and the pathogenesis of severe airway disease

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ABSTRACT: Refractory or difficult-to-control asthma is associated with some clinical and pathological features normally associated with chronic obstructive pulmonary disease (COPD), raising the possibility that there are similarities in their pathogenesis. It is suggested that the coexistence of two or more inflammatory stimuli to the airway (multiple hits) is a key factor leading to the development of more severe airway disease. Airway inflammation in response to chronic inflammatory conditions elsewhere may be a particularly important additional inflammatory stimulus. The ''multiple hit'' hypothesis for the origins of severe airway disease has important implications for treatment and prevention, since identification and removal of additional inflammatory stimuli may delay progression of the underlying airway disease.

KEYWORDS: Asthma, asthma mechanisms, chronic obstructive pulmonary disease

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Received:
November 02 2005
Accepted after revision:
February 25 2006

One of the most important questions facing researchers with an interest in airway disease is: why do the clinical consequences of chronic airway inflammation vary so much between patients? Why do some patients with asthma have refractory or difficult-to-control disease? Why do only a minority of smokers develop clinically significant chronic obstructive pulmonary disease (COPD)? This article will first use these clinical examples to show that severe airway disease is associated with a number of shared clinical and pathological features. It will then be suggested that these common factors could develop in response to the coexistence of two or more inflammatory stimuli to the airway. Finally, the authors will speculate that the clinical consequences of multiple inflammatory ''hits'' may be ameliorated by removal of additional inflammatory stimuli.

COMMON CLINICAL AND PATHOLOGICAL FEATURES OF REFRACTORY ASTHMA AND COPD

Refractory asthma can be defined as asthma that cannot be controlled with inhaled corticosteroids [1, 2]. Many patients with asthma have refractory symptoms because of poor treatment concordance or because of persistent symptoms caused by the presence of comorbid conditions such as rhinitis and hyperventilation syndrome [3]. However, there remain an important number of patients who have genuinely severe, therapy-resistant disease. Refractory asthma has heterogeneous clinical features, though some of the most distinctive abnormalities are features normally associated with COPD including: persistent symptoms, recurrent exacerbations, the presence of fixed airflow obstruction, and a degree of resistance to the effects of inhaled, and sometimes systemic, corticosteroid therapy [1–5]. The pathology of refractory asthma also has features in common with COPD. It differs from the mild eosinophilic large airway inflammation seen in mild asthma in that there is a more complex lower airway inflammatory response, with increased neutrophilic as well as eosinophilic airway inflammation [2, 5] and involvement of the distal airways [4, 5]. As in COPD, the inflammatory response is associated with abnormal tissue remodelling and damage. Although in many other ways the pattern of airway inflammation and remodelling differs from that seen in COPD [6], there can be similarities in associated features, including the presence of radiological evidence of bronchiectasis and emphysema [7] and physiological evidence of fixed airflow obstruction [1, 8].

The common clinical and pathological features seen in refractory asthma and COPD raise the possibility that some of the factors involved in the development of severe clinical consequences of asthma might be similar to those that increase the susceptibility of a smoker to the development of

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

COPD. The authors suggest that one factor is the coexistence of two or more inflammatory stimuli to the airway. They highlight this because, if correct, it raises the possibility that identification and modulation of additional inflammatory stimuli might reduce progression of the underlying disease.

COEXISTENCE OF TWO OR MORE LOWER AIRWAY INFLAMMATORY RESPONSES

The hypothesis that multiple inflammatory stimuli are important in the pathogenesis of refractory asthma and COPD is supported by the frequent observation that when this occurs, many of the common clinical and pathological features previously highlighted tend to occur. Examples include the observations that patients with asthma who smoke have worse symptoms and lung function, a more neutrophil-dominated lower airway response, physiological evidence of involvement of the small airways, an impaired response to corticosteroids, and a more rapid decline in lung function over time [9, 10]. Smoking has also been shown to be an independent predictor of the development of COPD in patients with eosinophilic bronchitis [11], a common cause of chronic cough in middle age which is associated with eosinophilic airway inflammation but not the airway hyperresponsiveness or variable airflow obstruction characteristic of asthma. Occupational exposures may be an important additional chronic inflammatory stimulus in some: miners who smoke are more likely to develop COPD than non-exposed smokers [12] and there is evidence that other dusty occupations are associated with the development of COPD and more severe asthma [1, 13, 14]. Endotoxin, inhaled at work or at home, has been associated with the development of fixed airflow obstruction and more severe asthma [15]. Latent airway infection is another potential additional inflammatory stimuli: the presence of adenoviral E1A protein in airway epithelial cells has been associated with an abnormally amplified inflammatory response in the distal lung in patients with COPD [16], and both chronic *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infection have been implicated in the pathogenesis of refractory asthma [17]. Chronic viral infection is a potential explanation for increased CD8+ cell numbers in the airway, a feature which has been associated with more severe COPD [18] and with decline in forced expiratory volume in one second (FEV_1) in asthma [19]. Finally, colonisation and perhaps infection of the airway with *Aspergillus fumigatus* causes a mixed and intense eosinophilic and neutrophilic lower airway inflammatory response, which is associated with extensive airway damage and fixed airflow obstruction in patients with allergic bronchopulmonary aspergillosis [20].

The general principle that the coexistence of multiple inflammatory stimuli produces a more severe inflammatory response might also apply to acute inflammatory stimuli. This mechanism might be particularly important in the development of exacerbations of asthma and COPD. Experimental examples include the amplification of the acute lower airway response to inhaled allergen seen in subjects with atopic asthma after exposure to pollution [21] or inhaled endotoxin [22] and after viral infection [23].

AIRWAY INFLAMMATION IN RESPONSE TO CHRONIC INFLAMMATION ELSEWHERE AS A POTENTIAL ADDITIONAL INFLAMMATORY HIT

Observational studies of patients with cough or COPD who have neither significant smoking histories nor features suggesting underlying asthma or eosinophilic bronchitis have consistently found a high incidence of chronic inflammatory conditions elsewhere [24–26] suggesting that airway inflammation and dysfunction might complicate the primary inflammatory process. The most striking associations are seen with chronic inflammatory conditions involving organs that are embryologically related to the lungs, such as inflammatory bowel disease [27, 28], chronic hepatitis C infection [29], autoimmune thyroid disease [24, 28, 30] and *Helicobacter pylori*-induced gastritis [31], but airway disease is also commonly seen in more generalised inflammatory disorders such as rheumatoid arthritis [26, 32].

The physiological, radiological and pathological features of the airway disease seen in association with chronic inflammatory disorders have not been extensively investigated. There are some features in common with the obliterative bronchiolitis seen in chronic rejection in lung transplant recipients or chronic graft *versus* host disease in bone marrow transplant recipients [24–26], and it is possible that the airway disease is due to a similar, albeit low-grade inflammatory response involving aberrant homing of alloreactive lymphocytes to the lung.

Could the airway response to chronic inflammatory diseases elsewhere act as an important inflammatory hit? There is increasing evidence that it does. Studies in Japan show that chronic hepatitis C infection is associated with a more rapid decline in FEV_1 in smokers [29] and in patients with asthma [33]. The coexistence of chronic hepatitis C infection and asthma has also been associated with more severe asthma, which is less bronchodilator and corticosteroid responsive [33, 34]. *H. pylori*-induced chronic gastritis is another chronic inflammatory condition that might be particularly important in the pathogenesis of COPD and refractory asthma since it is common and treatable. There is some epidemiological support for the presence of a causal link between *H. pylori* infection and airway disease [31] and it has long been recognised that peptic ulceration is strongly and independently associated with the presence of COPD [35, 36]. In a recent study of Nottinghamshire (UK) miners, the present authors found that a past history of peptic ulceration (documented by barium studies, endoscopy or at surgery) was present in >50% of miners with severe COPD but only in 3% of miners with no respiratory symptoms and normal spirometric values [37]. After correction for potential confounding factors, such as smoking, a past history of peptic ulceration was associated with a 13.3% lower post-bronchodilator FEV_1 % predicted and 5.1% lower FEV_1/forced vital capacity %. Typically, peptic ulceration occurred 10–20 yrs before the onset of respiratory symptoms, suggesting that the natural history of the conditions is different and raising the possibility that it may be possible to delay or prevent the onset of symptoms and airway dysfunction in at-risk smokers.

HOW DO MULTIPLE INFLAMMATORY STIMULI RESULT IN MORE SEVERE AIRWAY DISEASE?

The effects of multiple inflammatory stimuli may be just additive. The net result of different inflammatory stimuli will then depend on: whether it is an acute or chronic inflammatory stimulus; variations in the host response to the stimuli; the extent to which the stimulus provoke an eosinophil- or neutrophil-dominated inflammatory response; and the site where the inflammatory response predominates (fig. 1). Thus, the ''multiple hit'' hypothesis for the origin of severe airway disease provides a basis for the heterogeneity of clinical and pathological features seen in refractory asthma and COPD [1–4, 8, 38].

There is also the possibility that the inflammatory response to different inflammatory stimuli interact in a synergistic fashion. This could occur at an early stage in the evolution of these responses. For example, smoking increases the risk of sensitisation to a variety of occupational high- and low-molecular weight sensitisers [39], and exposure to smoke or endotoxin has been associated with an increased risk of viral and bacterial infection [9, 15] and perhaps an increased potential for chronic infection. Many of the inflammatory stimuli previously highlighted are associated with activation of the innate immune response with upregulation of homing pathways and activation of effector inflammatory cells, such as neutrophils and monocyte/macrophages. This could have a knock-on effect on coexisting acute and chronic immune responses, leading to amplification and extension of these inflammatory responses. Mediators associated with innate immune responses have been implicated in the induction of corticosteroid resistance [40], which, as well as being associated with resistance to the effects of exogenous corticosteroids, might be associated with a diminished response to the natural anti-inflammatory brake provided by endogenous corticosteroids resulting in further amplification of the lower airway response. It is noteworthy that patients with asthma who smoke [41] and patients with refractory asthma [42] have a reduced cutaneous vasoconstrictor response to topical corticosteroids supporting the presence of a degree of endogenous corticosteroid resistance. Tumour necrosis factor (TNF)-α is expressed in increased amounts in the airway and on peripheral blood mononuclear cells in patients with refractory asthma when compared with patients with mild and moderate asthma [43, 44], and blood markers of TNF-α activity, including C-reactive protein and soluble TNF-α receptors, are increased in patients with COPD, particularly when the disease is severe or associated with wasting [45, 46]. Preliminary findings with anti-TNF-α therapy suggest that this mediator might be particularly important in the maintenance of the increased airway responsiveness and bronchoconstriction seen in some patients with severe airway disease [43, 44].

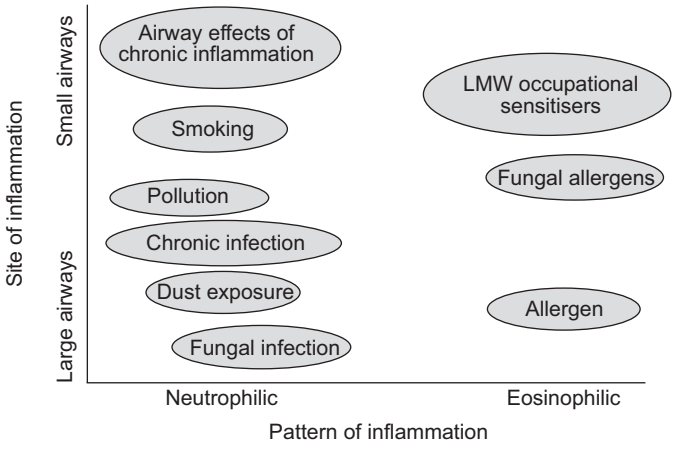

FIGURE 1. Likely pathological response and predominant site of the airway inflammatory response to different stimuli. The net result of multiple inflammatory stimuli will depend on variations in the host response to the stimuli, the extent to which the stimuli provoke an eosinophil- or neutrophil-dominated inflammatory response and the site where the inflammatory response predominates. For example, a smoking miner with chronic *Helicobacter pylori* infection would tend to develop a completely corticosteroid-resistant, neutrophil-predominant distal lung disease with extensive emphysema; in contrast, a smoking miner who develops eosinophilic airway inflammation in response to an occupational sensitiser, would have more mixed features. LMW: low molecular weight.

It is also possible that the number and importance of different inflammatory hits may change as the airway disease evolves. Severe COPD is associated with the development of lymphoid follicles in the small airways, implying the presence of an adaptive immune response [18]. This immune response could be due to chronic infection or the exposure of auto-antigens as a result of increasing tissue damage.

The extent to which the coexistence of more than one acute or chronic inflammatory stimulus produces additive or synergistic effects and the mechanisms of these interactions remains unclear; it is therefore an important area for further study. Any hypothesis needs to account for the contrary situation in which airway inflammatory stimuli appear to protect against lung immunological injury. For example, the granulomatous inflammatory diseases sarcoidosis and extrinsic allergic alveolitis are less common in smokers [47, 48]. Whether the interaction between particular inflammatory stimuli produces distinctive and readily recognisable pathological changes is another important area for further study.

COULD IDENTIFICATION AND REMOVAL OF ADDITIONAL INFLAMMATORY HITS REDUCE THE SEVERITY OF AIRWAY DISEASES?

A particular attraction of the multiple hit hypothesis is that it raises the possibility that identification and modification of inflammatory hits to the airway might lead to improved long-term outcome. Experience with smoking cessation [8–10, 49], removal of occupational dust exposure [12–14], avoidance of endotoxin exposure [15] and anti-fungal treatment in allergic bronchopulmonary aspergillosis [20] suggests that this might be the case. Intriguingly, there is also evidence that treatment of chronic inflammation outside the lung reduces the severity of associated airway diseases. The accelerated decline in FEV_1 seen in smokers and patients with asthma, and the impaired corticosteroid and bronchodilator responsiveness of asthma, improve following successful treatment of chronic hepatitis C infection with interferon [29, 34]. Other opportunities to investigate the effects of modulation of airway inflammation in response to chronic inflammation elsewhere are limited by the difficulty in treating some of these conditions; there is also contradictory information on the extent to which there is a

direct link between the intensity of inflammation in the primary site and the intensity of the associated airway inflammatory response [27–29, 34]. However, an obvious opportunity for an interventional study is to investigate the effects of *H. pylori* eradication on the natural history of asthma and COPD.

CONCLUSION

The authors' hypothesis raises the possibility that two of the more difficult clinical problems faced by chest physicians, the development of refractory disease in some patients with asthma and the abnormal rate of decline in lung function seen in some smokers, are due to multiple additive inflammatory stimuli to the airway. There are parallels between the authors' views on the pathogenesis of severe airway disease and current views on the pathogenesis of atheroma, where the importance of multiple causal factors is increasingly acknowledged. Perhaps a similar approach to management, with the emphasis on identification and modulation of the multiple hits to the airway, might be associated with the sort of clinical benefits currently being seen in vascular medicine.

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