Asthma comes in from the cold

- Alan S. Beedle-

Infection with viruses, such as those responsible for the common cold, may be linked to exacerbation of asthma. As the link becomes clearer, it may provide pharmaceutical companies with a new target for developing anti-asthma drugs. At the joint 15th International Congress of Allergology and Clinical Immunology and the Annual Meeting of the European Academy of Allergology and Clinical Immunology (Stockholm, Sweden; June/July 1994), Professor Stephen Holgate from Southampton, UK, described how his group has used an elegant combination of epidemiology, clinical medicine and in vitro immunohistochemistry to investigate this relationship.

Previous research has shown a link between viral, but not bacterial, upper respiratory tract infection (URTI) and asthma. In line with this view, it would be expected that the human rhinovirus, which is known to be one of the main causes of the common cold, would be linked to asthma symptoms. However, until recently, the evidence for such a link was scarce.

Now Professor Holgate and colleagues have conducted studies which refocus attention on the role of viruses in asthma by showing that viral URTIs are the most frequent cause of asthma exacerbations in children and, most probably, in adults as well. Because of the importance of this link, and the considerable morbidity and mortality caused by asthma, he recommends that pharmaceutical companies should focus on the relationship between asthma and viral infection as a new target for developing antiasthma drugs.

Backed by epidemiology

In collaboration with the UK Medical Research Council's Common Cold Research Unit, Professor Holgate's team performed a 12-month study of a group of children aged 11-13 years who were known to be at risk of asthma attacks. The children's peak expiratory flow was measured daily, and if they had alterations in respiratory function, or an URTI, they provided samples of mucus and blood for virological analysis.

Previous studies of viral infection in the upper respiratory tract suffered from difficulties with detection methods. The human rhinovirus has over 100 serotypes and the coronavirus, another cause of the common cold, has multiple serotypes. These viruses are therefore very difficult to detect by serological methods. However, Professor Holgate's team used polymerase chain reaction methodology to develop oligonucleotide probes that could detect the presence of essentially all rhinoviruses and 90% of coronaviruses.

In the group of children studied, URTI was frequently associated with asthma. Overall, 228 episodes occurred in 12 months. The episodes were characterised by profound falls in peak expiratory flow that lasted some 4-6 weeks. Rhinoviruses and coronaviruses were the most commonly identified organisms associated with asthmatic episodes.

In addition, the infections and subsequent episodes of asthma coincided with return to school after vacations, suggesting that the children were being exposed to new strains of virus at this time. Furthermore, these episodes of viral URTI in the community coincided with peaks in local hospital admissions for diagnosed asthma, providing strong epidemiological evidence for viral infection being a major cause of episodes of childhood asthma.

Effects of rhinovirus infection...

Professor Holgate and his collaborators then went on to study the immunopathogenesis of airway dysfunction caused by human rhinovirus 16 infection under controlled conditions. They studied 3 groups of volunteers:

- normal individuals
- atopic individuals, i.e. healthy individuals with a predisposition to produce IgE on allergen challenge, and
- patients with asthma.

Upper and lower respiratory tract involvement were studied during and after volunteers were infected with human rhinovirus 16. In each case, airway tissue was obtained by lavage and biopsy and immunohistochemical methods were used to measure viral infection and leucocyte involvement. In addition, the clinical effects of infection were assessed by measurements of peak expiratory flow and bronchial hyper-responsiveness to inhaled histamine.

...in the upper airway

In the upper respiratory tract, colonisation of epithelial cells with rhinovirus could be demonstrated, but in none of the groups was there a significant accumulation of leucocytes in the tissues during the active phase of the cold. Thus, Professor Holgate believes that the upper respiratory symptoms seen during the active phase of an uncomplicated common cold are due to nonleucocyte pathways, possibly involving kinins.

Interestingly, however, atopic individuals developed more severe infections with human rhinovirus. This may be due to the upregulation of cellular adhesion molecules such as ICAM-1 on the epithelium as a result of cytokines released during the allergic process. The major class of human rhinovirus uses ICAM-1 on epithelial cells as a receptor to gain access to the airways.

...and in the lower airway

The effects of rhinovirus infection on the lower airways were studied by lavage and biopsy of lower airway tissue. In all individuals studied, infection with human rhinovirus 16 led to a decrease in peak expiratory flow lasting for 4-6 days, as well as major changes in the vascular network of the lower airway.

However, increases in bronchial hyper-responsiveness to histamine, lasting 4-6 weeks, could be demonstrated in atopic and asthmatic groups, but not in normal individuals. This suggests that the
airways undergo physiological change with rhinovirus infection.

In both healthy individuals and patients with asthma, CD4+ and CD8+ T cells increased in the epithelium and submucosa in response to rhinovirus infection. Similarly, there was an increased number of infiltrating eosinophils in response to infection. However, in those patients with asthma who remained hyper-responsive to histamine inhalation, the eosinophilia persisted for 4–6 weeks after infection, suggesting that inflammatory cascades activated by the virus had persisted for longer periods in people with asthma than in normal individuals.

**Speculation on the mechanisms**

Theories proposed for the mechanisms linking asthma and viral infection are speculative, said Professor Holgate. However, he suggested the following sequence of events:

- The proinflammatory cytokines interleukin 6 (IL-6), IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are expressed in higher than normal quantities in patients with asthma, recruit inflammatory cells such as eosinophils to the bronchial tissue, leading to chronic inflammatory changes in the airways.

- Infection with human rhinovirus 16 may lead to further upregulation of these cytokines in the epithelium via ICAM-1. This theory is supported by a recent study showing that infection of human bronchial epithelial cells in culture with human rhinovirus results in an increased capacity of the epithelium to secrete these 3 cytokines, and that this increased secretion is sensitive to inhibition by corticosteroids.

- The increased augmentation of cytokine production in bronchial epithelium is followed by increased recruitment of inflammatory cells and airway inflammation, in turn leading to an acute attack of asthma.