

Impact of viral infection on bronchial hyperresponsiveness

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It is clinically very well known that upper and lower respiratory tract infections impair the asthma disease and induce obstructive exacerbations (1–4). Exaggerated bronchial responsiveness in normal subjects following upper respiratory infections was observed by Parker and co-workers already 30 years ago (5). Virus infections are responsible for the deterioration in asthma in connection to respiratory infections and also for the increased bronchial hyperreactivity observed during and following the infections (6, 7).

Pediatric research convincingly demonstrates the association between exacerbations of asthma and concomitant upper respiratory tract infection (8–10). Virus-induced airway infections are the most common triggers of acute asthma symptoms in children. The type of virus infections which are associated with asthma symptoms differ with age group. Respiratory syncytial virus (RSV) and parainfluenza virus have been isolated in connection with asthmatic symptoms, primarily in the youngest age group (8–10). Influenza A virus is primarily isolated in older children and human rhinovirus (HRV) is isolated in all age groups. Factors predisposing for development of bronchial hyperresponsiveness (BHR) and asthma in connection to respiratory tract infections are (modified from ref. 1):

1. Young child
2. Other atopic disease or earlier known BHR
3. Infection with RSV, HRV, influenza or parainfluenza virus. In the age group above 2 years also *Mycoplasma pneumoniae* is a common inducer of BHR.

Also in adults there is a correlation between asthma and concomitant upper respiratory tract infection (URTI). Furthermore, many adult asthmatics re-

late their start of asthma to an intense URTI. HRV, which produces 40–50% of all “common colds”, can just like infections with RSV, influenza, parainfluenza and adenovirus invade respiratory epithelium in the lower respiratory tract and produce asthma symptoms (11–12). During histamine provocation the Nadel group 20 years ago found a more than 200% increase in airway resistance in normal subjects with viral URTI compared with a 30% increase in healthy control subjects (13). The time course for responsiveness to return to normal was between 1 and 2 months. Similar observations were made also by investigators using carbachol challenge as well as exercise and cold air challenge in subjects with viral URTI (14–16).

Mechanisms for virus-induced bronchial hyperresponsiveness

The airway pathology after a virus infection shows many similarities to those observed in asthma. It is therefore easy to imagine that a virus infection can induce increased BHR and provoke asthma. A multifactorial influence from the virus infection is likely. There is support for epithelial cell damage as well as immunological influence (Table 1 modified from ref. 17).

Epithelial cell damage

Certain viruses are known to induce acute damage to the airway epithelium. Influenza A produces a diffuse inflammation of the bronchial tree with desquamation of epithelial cells, submucosal oedema and infiltration of neutrophil granulocytes. Due to impaired ciliary cell function, reduced mucocili-

Table 1. Possible mechanisms for virus-induced asthma and BHR (modified from ref. 17)

Direct effects on the lower respiratory tract

1. Epithelial cell damage
2. Increased release of inflammatory mediators
3. Expression of adhesion molecules
4. Virus specific IgE production
5. Downregulation of β -receptors
6. Chronic persisting virus infection

Indirect influence on the lower respiratory tract

Mouth breathing.

ary clearance can be noticed for up to a month after infection. Other viruses producing epithelial cell damage with impaired ciliary function are RSV, adenovirus and parainfluenza virus. Also the virus producing common cold, HRV, can produce mucosa damage. The epithelial cell damage can lead to asthma deterioration via several mechanisms:

1. Sensory nerve endings in the bronchi are exposed to irritating stimuli. This leads to increased efferent vagal activity and bronchoconstriction. Also in normal subjects increased cholinergic sensitivity has been demonstrated following URTI.
2. Airway epithelium produces endopeptidase which regulates levels of neuropeptides. Endopeptidase levels are reduced during virus infections. This may lead to increased neurogenic inflammation and increased BHR via disturbed intrabronchial regulation of substance P and other neuropeptides.
3. The epithelial production of stabilizing and regulating proteins like epithelial derived relaxant factor is impaired.
4. Increased penetration of allergens through a damaged epithelium combined with increased exposure to allergens due to impaired mucociliary transport may lead to increased allergic inflammation.

Increased release of inflammatory mediators

Viruses seem to have the ability to induce release of proinflammatory mediators from alveolar macrophages, neutrophil and eosinophil granulocytes as well as from mast cells in the airways. In patients with asthma the extent of histamine release from basophil granulocytes is correlated with the degree of BHR (18), and e.g. rhinovirus infections seem to enhance mediator release from mast cells and basophils (19). *In vitro* studies have shown that virus can stimulate increased mediator release either directly or via interferon. Busse and co-workers have demonstrated that the inflammatory response of the airways of asthmatics may be potentiated in response to virus infections especially if earlier exposed to

and sensitized to the virus (20). Furthermore, viral respiratory infections may interact with the T cells, which have an important role in directing the features of inflammation in asthma (21).

Virus specific IgE production

Viruses are antigenic and able to induce antibody production. Studies by Welliver and co-workers have demonstrated that RSV infections can induce production of virus-specific IgE, which have been found to be bound to exfoliated airway epithelial cells (22). The degree of this IgE production correlated to a concomitant increase of asthma symptoms. Children with genetic disposition for atopy were more likely to develop virus-specific IgE. It can be speculated that virus infections can induce asthma based on a preponderance to develop specific IgE to respiratory viruses. Welliver's group have demonstrated production of specific IgE antibodies also towards parainfluenza virus which correlated with presence of airway obstructive disease (23). An increased production of specific IgE antibodies induced by virus infections may have serious implications in the allergic individual. Mast cell-bound IgE causes degranulation and release of mediators when coupling to a virus antigen occurs. In that way a common cold in the predisposed individual may trigger a response leading to airway obstruction.

Another possible interaction between viral infections, and asthma and hyperresponsiveness is the association with development of allergy in children. Frick and co-workers in early studies demonstrated that, e.g., RSV and parainfluenza virus may contribute to the allergic sensitization process in children who are at high genetic risk of developing allergy (24).

Expression of adhesion molecules

In order for activated neutrophil and eosinophil granulocytes to accumulate at the site of epithelial damage, they must be recruited from the circulation and migrate through vascular endothelium and the subepithelial tissue. The first step in this process is mediated by receptor molecules on the granulocyte cell membrane and its counterpart in terms of adhesion molecules on the vascular endothelium surface. Expression of these adhesion molecules are induced by inflammatory cytokines (IL-1, TNF and interferon- γ). They then act as markers of a local inflammation. The granulocytes recognize and adhere to these molecules on the vascular endothelial cell surface and then migrate into the tissue and participate in the inflammatory reaction. Cultures of human airway epithelium can also produce increased levels of the adhesion molecule ICAM-1 when stimulated by

respiratory viruses such as RSV and parainfluenza virus. ICAM-1 mediates adhesion of eosinophils to vascular endothelium *in vitro*. It is likely that virus/ICAM-1 interactions influence the immune response in a respiratory virus infection.

Downregulation of β -receptors

Viral infections may also have other effects relevant to the development of exacerbation of asthma. In addition to relaxing smooth muscle in the bronchi, β -agonists inhibit release of mediators from mast cells and leukocytes. Virus infections can attenuate the responses to β -adrenergic stimuli. Granulocyte responses to isoprenaline are reduced in asthmatic patients during URTI (25). Similarly, in animal studies it has been shown that a virus infection can reduce the sensitivity to a β -agonist at an allergen provocation.

Chronic persistent virus infection

RSV may persist in the infected cells after the initial infection and may constitute a foreign protein leading to a chronic inflammation. Adenovirus is another well-known pediatric respiratory virus that may persist in a latent infection. Hogg and co-workers have demonstrated that the virus is able to "hide" from the immune defence and persist by means of parts of its DNA incorporated into the DNA of the host cell (27–30).

Mouth breathing

Nasal blockage is often part of the URTI symptoms and may cause long periods of mouth breathing. During these periods the air passes down to the lower respiratory tract without the usual filtration, warming and humidification. Cold and dry inspired air are factors which provoke symptoms in exercise- and cold-induced asthma. Also this mechanism may play a role in airway obstruction during virus induced URTI.

Conclusion

Viral airway infections are important triggers of acute asthma symptoms in children as well as in adults and induce bronchial hyperresponsiveness (BHR) during and following the infections. Infections with respiratory syncytial virus, parainfluenza virus, influenza virus, adenovirus and human rhinovirus are well-known inducers of not only asthma deterioration but also increase in BHR. The pathophysiological mechanisms for virus-induced BHR are multifactorial. Among these mechanisms are epithelial cell damage with inflammation of the bron-

chial mucosa and exposure of sensory nerve endings to irritating stimuli. Immunological mechanisms include virus-induced increased expression of adhesion molecules, virus-induced release of pro-inflammatory mediators from mast cells and basophils, neutrophil and eosinophil granulocytes and from alveolar macrophages, as well as virus-specific IgE production. Another mechanism which seems to play a role in virus-induced BHR is downregulation of β -receptors. Also a chronic persistent virus infection with e.g. respiratory syncytial virus or adenovirus seems to be a mechanism which can act to maintain BHR.

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