Postgraduate Course ERS Copenhagen 2005

Biological and therapeutic implications of the united airways concept

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Educational aims

- ▶ To introduce the factors involved in the expression of allergic phenotypes.
- ▶ To define the mechanisms that may play a role in nasobronchial cross-talk.
- ▶ To identify current and future therapies for combined asthma and rhinitis.

Summary

The condition of the nose affects the bronchi and *vice versa*. Local allergen exposure leads to a generalised airway response in atopic individuals, involving the systemic circulation. Therefore, upper and lower airways need to be regarded as one functional entity. This also has implications for rhinitis and asthma therapy, providing a rationale for combined treatment of both upper and lower airways. The systemic link between the upper and lower airways may provide new opportunities for systemic treatment.

▶ The key to a diagnosis lies in taking a good medical history. This rule especially applies to allergic rhinitis and asthma, which are both often underdiagnosed and lack proper treatment.

Allergic rhinitis and asthma frequently occur together. Almost 40% of allergic rhinitis patients have lower airways involvement, whereas >80% of allergic asthma patients have concomitant rhinitis symptoms. The latter percentage approaches 95% when a careful nasal history is taken and a physical examination is performed. Patients with allergic rhinitis have a three times higher risk of developing

asthma than healthy people, suggesting that rhinitis is an important risk factor for the development of asthma.

Several specialists are involved in the treatment of allergic diseases, *i.e.* ophthalmologists, dermatologists, otorhinolaryngologists, pulmonologists, paediatricians, allergologists and general practitioners. The differentiation between allergic specialists often results in attention being focused on the primary affected organ alone. Disregarding the interaction between the organs involved in allergic disease leads to treatment strategies lacking a combined approach.

Key points

- ▶ Rhinitis is an important risk factor for the development of asthma.
- ▶ The nose interacts with the bronchi through the systemic circulation.
- ▶ Treatment of allergic rhinitis in patients with concomitant asthma provides better asthma control.
- ▶ Novel therapies are aimed at the systemic elements of allergic airway disease.

This article was modified from an ERS Postgraduate Course held at the 2005 ERS Congress in Copenhagen. Original slides, web casts and original material can be found at www.ersnet.org/elearning

Figure 1
Concept of chronic airway disease.
Factors involved in the expression
of the allergic phenotype.

Allergic phenotypes

Genetic and environmental factors largely contribute to the clinical expression in allergic disease. Atopic diathesis requires appropriate allergen exposure in order to result in the production of specific immunoglobulin (Ig)E in a genetically susceptible host. The initial sensitisation typically occurs in childhood and depends on lifestyle influences, such as indoor allergen exposure, viral infections and maternal smoking. The clinical manifestations of the atopic syndrome may vary during a lifetime and depend on complex interaction mechanisms between the nose, lung, skin and gastro-intestinal tract. The specific structure and function of the mucosal tissue involved could also be contributing factors to the development of allergic airway disease (figure 1).

Figure 2
Nasobronchial cross-talk. The systemic circulation as an important pathway in the interaction between upper and lower airways. IL: interleukin.

Nasobronchial interaction

Pathophysiologically, the relationship between nasal malfunction and subsequent bronchial airway involvement is obvious. The nose protects the lower airways through filtering and air conditioning of the inhaled air. In allergic rhinitis, the nose can be blocked and mouth breathing is favoured. The reduced filter and air-conditioning function of the nose leads to increased exposure of the lower airways to allergens. In susceptible persons, this may lead to inflammatory changes and an increase in bronchial hyperresponsiveness (BHR).

Several mechanisms have been held responsible for the interaction between the nose and lungs. Aspiration may play a role in patients with depressed consciousness and impaired cough reflex, such as mechanically ventilated patients. The neural reflex mechanism certainly contributes to immediate bronchoconstriction and BHR in asthmatic patients after nasal exposure to cold air. Studies in patients with allergic rhinitis, asthma and other atopic diseases have also shown a consequent rise in circulating inflammatory cells and progenitors after allergen inhalation, followed by recruitment to sites of allergic inflammation (figure 2). The systemic allergic response is further characterised by increased expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and E-selectin, on nasal and bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue.

Therapeutic implications

Accumulating evidence underlines the influence of allergic rhinitis on the control of asthma. A clear relationship has been found between the severity of allergic rhinitis and lower airway symptoms (figure 3). Treatment of allergic rhinitis in patients with concomitant asthma significantly reduces the risk of severe asthma exacerbations and hospitalisation (figure 4). An overview of current asthma and rhinitis therapy is given in table 1.

Topical treatment

Few studies have investigated the effect of nasal treatment on asthma. Topical treatment with intranasal corticosteroids reduces lower airway symptoms and decreases BHR in allergic rhinitis patients with seasonal asthma. In one study, delivery of beclomethasone to the nose had an even greater effect on BHR than delivery of the same dose *via* the oral route. Another report demonstrated a reversed response, *i.e.* bronchial treatment with inhaled corticosteroids had a beneficial effect on nasal symptoms and inflammation.

Systemic treatment

Despite the benefit of antihistamines and cromoglycates in seasonal allergic rhinitis, their effects on lower airways are still doubtful. However, second-generation antihistamines seem to exert some beneficial effect on lower airway inflammation, possibly through their anti-inflammatory properties. Leukotriene receptor antagonists (LTRAs) have proved to have an additional therapeutic effect on asthma. Recent data have also shown that leukotrienes may also be of importance in inflammatory upper airways disease, which emphasises a role for LTRAs in the treatment of allergic rhinitis.

Immunomodulating therapy

Immunotherapy may be effective for both asthma and rhinitis on a long-term basis. A 3-year course of specific immunotherapy (SIT) in children with seasonal allergic rhinitis significantly reduced the risk of developing asthma (figure 5). In a comparative study between nasal steroids (NS) and short pre-season SIT in patients with allergic rhinitis and asthma, NS appeared to be more effective in local disease control than SIT. However, SIT had a positive influence on systemic and bronchial parameters in these patients, whereas NS had no apparent effect on the lower airways.

Figure 3

The severity of allergic rhinitis and asthma symptoms. Modified from Togias 1999.

Figure 4

Treatment of allergic rhinitis in patients with concomitant asthma reduces the risk of severe asthma exacerbations and hospitalisation. Modified from Crystal-Peters et al. 2002.

Novel therapies

Increases in eosinophils and circulatory mediators, such as interleukin (IL)-5, are associated with impaired lung function parameters and enhanced mucosal inflammation in asthmatics, as well as in non-asthmatic rhinitis patients. Efforts to translate this concept into

Table 1 An overview of current asthma and rhinitis therapy

	Asthma	Rhinitis
β_2 -agonists	+	-
α -agonists	-	+
Anticholinergic agonists	+	+
Antihistamines	±	+
Antileukotrienes	+	+
Corticosteroids	+	+
Anti-IgE	+	?
Immunotherapy	Selected patients	+
		(seasonal)

+: positive effect; -: negative effect. Modified from Mygind 1997.

Educational questions

1. Which factors are involved in the clinical expression of allergic rhinitis and asthma?
2. Which mechanisms or pathways may play a role in nasobronchial interaction?
3. Which mechanism is considered to be most important in nasobronchial interaction?
4. Do nasal steroids have an effect on asthma and, if so, which parameters are influenced?
5. Do antihistamines work in asthma?
6. Which therapy can really influence the course of allergy?
7. What is the rationale for most new allergy treatments?

clinical practice have been disappointing, since depletion of eosinophils by anti-IL-5 therapy has not shown a significant effect on lung function in mild asthmatic patients.

Recently, phosphodiesterase (PDE)4 inhibitors, which exert an anti-inflammatory effect by blocking IL-13 production, have shown some potential for therapy. However, these drugs are still in development and need to be proved as safe and effective in both asthma and rhinitis.

Anti-IgE antibodies are promising tools in asthma and rhinitis therapy. They prevent IgE

from binding to receptors on mast cells and basophils, thereby eliminating allergic inflammation at the initial step of the inflammatory cascade. Anti-IgE treatment has proved to be effective in asthma, since it reduces symptoms, asthma exacerbations and the need for steroids. Its usefulness in allergic rhinitis, particularly as a steroid-sparing agent, has yet to be determined.

Conclusion

The relationship between allergic rhinitis and asthma has been well established in epidemiological studies and clinical trials. However, little is known about the immunopathological mechanisms that underlie the interaction between upper and lower airways. The condition of the upper airways can influence the lower airways and *vice versa*. Local allergen exposure at one end of the respiratory system induces mucosal inflammation at the other end. Therefore, upper and lower airways need to be regarded as one functional entity. Although physiological mechanisms may also contribute to nasobronchial cross-talk, the most recently published data are in favour of a systemic pathway, involving bloodstream and bone marrow. This also has implications for rhinitis and asthma therapy, providing a rationale for systemic treatment.

Figure 5

The percentage of children after 3 years of immunotherapy with and without asthma among those without asthma before treatment (n=151). Modified from Moller et al. 2002.

Suggested further reading

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- An excellent review on the pathophysiological role of leukotrienes in allergic rhinitis and asthma and the therapeutical implications.*
- Schmidt BM, Kusma M, Feuring M, et al. The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis. *J Allergy Clin Immunol* 2001; 108: 530–536.
- Holgate S, Bousquet J, Wenzel S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin* 2001; 17: 233–240.
- Meta-analysis based on three randomised trials investigating the efficacy and public health impact of omalizumab as an add-on therapy in severe allergic asthma.*

Suggested answers

1. Genetics, lifestyle influences, local mucosa factors and tissue remodelling.
2. Mouth breathing, aspiration of nasal contents, nasobronchial reflex and systemic circulation.
3. Systemic circulation.
4. Yes, they have an effect on bronchial symptoms and BHR.
5. New generation antihistamines have some effect on asthma symptoms through anti-inflammatory properties.
6. Immunotherapy.
7. Novel therapies are targeting systemic elements of allergic disease providing a more global approach for the allergy problem.