

Editorial

Nose and lung, two of a kind?

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Over the last decade, the united airways concept has influenced ideas about the pathophysiology and treatment of disease in the respiratory system. The ARIA document (1, 2), but also publications on the relation between rhinosinusitis and lower airway disease (3–6), have emphasized the need to take the entire respiratory tract into account when treating asthma. The definition of allergic rhinitis in intermittent and persistent is now widely accepted (7–12).

The relationships between asthma and rhinitis are well studied and have been examined in many recent papers published in *Allergy* (13–19). We acknowledge that most patients with asthma also suffer from rhinitis (1) and that the rhinitis symptoms of asthma patients have to be treated to improve quality of life in asthma patients. Moreover, Corren et al. (20) have recently shown that, in patients with asthma, the treatment of concomitant allergic rhinitis was associated with significant reductions in the risk of emergency room treatment and hospitalization for asthma. Ronald Dahl et al. (21) have reported on a large multi-centre study showing that both upper and lower airways need to be treated in patients with asthma and rhinitis to ensure optimal quality of life. Despite the attention for the united airways concept, under-diagnosis of lower airway disease is still a feature in many patients with rhinitis. In the present issue, Pascal Demoly et al. (22) show that 30% of rhinitis patients without diagnosed asthma might be considered, on the basis of a questionnaire, to be asthmatics.

Although the relation between allergic rhinitis and asthma has received increasing attention lately, the impact of rhinitis on other upper airway disease is largely underexposed. Peter Hellings et al. (23) point out the important role of IgE-mediated inflammation in the large

number of patients with upper airway diseases like chronic rhinosinusitis, adenoid hypertrophy, otitis media, and laryngitis. This knowledge is of utmost importance for general practitioners, allergologists and otorhinolaryngologists because a denial of the role of allergy in these conditions will regularly result in the unsatisfactory treatment of the disease.

Despite the similarities between IgE-mediated inflammation in upper and lower airway disease and the extensive research in the rhinitis and asthma field, it is still largely unknown why some subjects are sensitized but never develop allergic airway disease, why others develop rhinitis, and why some develop asthma. In this issue of the *Journal*, members of the GA2LEN work-package on 'IgE and allergic diseases', review potential factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens (24). They describe a complex interplay of multiple factors, like a family history of atopy, the levels of total serum IgE and of allergen-specific IgE or IgG4, epitope-specificity of IgE and their degree of polyclonality (mono- vs poly-sensitized), the balance of T regulatory cells (Treg) and Th1/Th2 cells, the polymorphisms of the FcεRI and other factors regulating the activation of FcεRI-bearing cells (25, 26). Many of these factors will be further studied in the multinational study of asymptomatic subjects and subjects with sensitization to Parietaria or birch pollen (SANAS study) that is being performed within GALEN at the moment. One might expect that an increased knowledge of differences between the manifestation of allergic disease and mere sensitization to aeroallergens will also lead to ideas for unravelling the differences between patients with rhinitis who develop asthma and those who do not.

The united airway concept has indicated significant similarities between rhinitis and asthma (1, 27). The differences between the two diseases might help us to understand the pathophysiology and lead us to new treatment options. For example, the fact that antihistamines are much more effective in rhinitis than in asthma has led to the suggestion that mast cell degranulation and histamine effects play a more important role in rhinitis. Combination therapy with inhaled corticosteroids and salmeterol has been reported to improve asthma control (28). Additive or synergistic effects have been reported *in vitro*, and the positive effects in asthma control are thus believed to be due to the potentiation of the anti-inflammatory effect. However, authors from the Firestone Institute in Hamilton show in this issue that in a nasal allergen provocation study, efficacy is not increased with the combination of a long-acting beta-agonist and an intranasal steroid (29). Can we conclude from this study that the improved asthma control is merely due to bronchodilatation and not an additive or synergistic anti-inflammatory effect? Or do nose and bronchi, and even inflammation in the nasal and bronchial mucosa, differ more than we believe at present?

Local tissue remodelling has always been seen as a typical lower airway event (30). Apart from inflammatory

cells such as eosinophils, activated T cells, mast cells and macrophages, also structural tissue cells such as epithelial and mesenchymal cells release cytokines, chemokines and growth factors. Together these mediators cause persistence of the inflammatory infiltrate and induce structural changes in the airway wall, such as increased thickness of the basement membrane, increased collagen deposition, and smooth muscle hypertrophy and hyperplasia (31, 32). The different embryonic origin of the epithelium and the presence of smooth muscle cells in the lower airway have traditionally been put forward as the chief differences between the lower and the upper airways (30). However, recent findings point to the same signs of remodelling in the upper airways, examples being epithelial shedding, thickening of the basal membrane and myofibroblast formation (33). This is not a feature of rhinitis, but it is found in more advanced airway disease like chronic rhinosinusitis with or without nasal polyps. Our understanding of remodelling in the upper airways and the consequences for local interaction between cell types, environmental factors or disease manifestations is far from complete. Comparing similarities and differences between various aspects of rhinitis, chronic rhinosinusitis, asthma and COPD will help us to unravel further the pathophysiology of, and treatment options for, these diseases.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(5 Suppl.):S147–334.
2. ARIA in the pharmacy: management of allergic rhinitis symptoms in the pharmacy. Allergic rhinitis and its impact on asthma. *Allergy* 2004;**59**:373–387.
3. Fokkens W. Evidence based diagnosis and treatment of rhinosinusitis and nasal polyps. *Rhinology* 2005;**43**:1.
4. Fokkens W, Lund V, Bachert C, Clement P, Hellings P, Holmstrom M et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. *Allergy* 2005;**60**:583–601.
5. Bachert C, Patou J, Van Cauwenberge P. The role of sinus disease in asthma. *Curr Opin Allergy Clin Immunol* 2006;**6**:29–36.
6. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J* 2006.
7. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, Akerlund A et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. *Allergy* 2004;**59**:406–414.
8. Bachert C. Persistent rhinitis – allergic or nonallergic? *Allergy* 2004;**59**(Suppl. 76):11–15, discussion 15.
9. Wang DY, Chan A, Smith JD. Management of allergic rhinitis: a common part of practice in primary care clinics. *Allergy* 2004;**59**:315–319.
10. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;**60**:350–353.
11. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Palleschini E et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005;**60**:882–887.
12. Bousquet J, Demarteau N, Mullol J, van der Akker-van Marle ME, Van Ganse E, Bachert C. Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 2005;**60**:788–794.
13. Mavale-Manuel S, Alexandre F, Duarte N, Albuquerque O, Scheinmann P, Poisson-Salomon AS et al. Risk factors for asthma among children in Maputo (Mozambique). *Allergy* 2004;**59**:388–393.
14. Cunha SS, Cruz AA, Dourado I, Barreto ML, Ferreira LD, Rodrigues LC. Lower prevalence of reported asthma in adolescents with symptoms of rhinitis that received neonatal BCG. *Allergy* 2004;**59**:857–862.
15. Raheison C, Montaudo M, Stoll D, Wallaert B, Darras J, Chanez P et al. How should nasal symptoms be investigated in asthma? A comparison of radiologic and endoscopic findings. *Allergy* 2004;**59**:821–826.
16. Bousquet J, Boushey HA, Busse WW, Canonica GW, Durham SR, Irvin CG et al. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy* 2004;**34**:897–903.
17. Guerra S, Sherrill DL, Baldacci S, Carrozzi L, Pistelli F, Di Pede F et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy* 2005;**60**:343–349.
18. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;**60**:165–170.

19. Valero A, Serrano C, Valera JL, Barbera A, Torrego A, Mullol J et al. Nasal and bronchial response to exercise in patients with asthma and rhinitis: the role of nitric oxide. *Allergy* 2005;**60**:1126–1131.
20. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004;**113**:415–419.
21. Dahl R, Nielsen LP, Kips J, Foresi A, Howarth P, Richards DH et al. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy* 2006;**60**:875–881.
22. Demoly P. The diagnosis of asthma using a self-questionnaire in those suffering from allergic rhinitis. *Allergy* 2006;**61**:699–704.
23. Hellings PF, Fokkens WJ. Allergic rhinitis and its impact on otorhinolaryngology. *Allergy* 2006;**61**:656–664.
24. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Cramer R et al. Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA²LEN project. *Allergy* 2006;**61**:671–680.
25. Kosnik M, Silar M, Bajrovic N, Music E, Korosec P. High sensitivity of basophils predicts side-effects in venom immunotherapy. *Allergy* 2005;**60**:1401–1406.
26. Kuster H, von Manstein S, Ruocchio-Wiglinghaus S, von Brunn A, Reinhardt D. Mutations in the high-affinity IgE receptor beta-chain are not associated with nonresponder status. *Allergy* 2005;**60**:1040–1045.
27. Cruz AA. The 'united airways' require an holistic approach to management. *Allergy* 2005;**60**:871–874.
28. Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an inhaled corticosteroid reduces allergen-induced serum IL-5 and peripheral blood eosinophils. *J Allergy Clin Immunol* 2005;**116**:1007–1013.
29. Parameswaran K, Fanat A, O'Byrne PM. Effects of intranasal fluticasone and salmeterol on allergen-induced nasal responses. *Allergy* 2006;**61**:731–736.
30. Bousquet J, Jacot W, Vignola AM, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodeling the upper airways? *J Allergy Clin Immunol* 2004;**113**:43–49.
31. Lazaar AL, Panettieri RA Jr. Airway smooth muscle: a modulator of airway remodeling in asthma. *J Allergy Clin Immunol* 2005;**116**:488–495, quiz 96.
32. Pascual RM, Peters SP. Airway remodeling contributes to the progressive loss of lung function in asthma: an overview. *J Allergy Clin Immunol* 2005;**116**:477–486, quiz 87.
33. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003;**112**:877–882.