

EDITORIAL

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Chronic rhinosinusitis, nasal polyposis and asthma: the united airways concept reconsidered?

This editorial discusses the findings of the paper in this issue by Williamson et al. [18].

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Although anecdotal descriptions of asthma and allergic rhinitis (AR) date from earlier times, it was not until the 19th century that a pathophysiological association between upper and lower airways was recognized. Since then, nose and lungs are considered as anatomically and functionally closely related organs. From this point of view, the relationship between AR and asthma seems rather obvious. Several epidemiological studies have indeed shown that AR often co-exists with, and even may precede allergic asthma. Therefore, AR is regarded as a risk factor for the development of asthma, especially in the presence of bronchial hyperresponsiveness (BHR).

AR and asthma can be discriminated on the basis of clinical history, variable airway obstruction and BHR. The distinction between allergic asthma and upper airway disease may be difficult to make as symptom perception is widely variable; lung function can be normal in mild asthmatics and, although BHR is a constant feature of asthma, it is also frequently present in AR, nasal polyposis and sinusitis.

In contrast to AR, the relationship between chronic rhinosinusitis, nasal polyposis and asthma is less studied. Similar to AR, chronic rhinosinusitis and nasal polyposis are also associated with asthma. Recent reports have demonstrated that approximately 30% of patients with nasal polyposis have asthma, while nasal polyposis is present in 7% of the asthma patients [1]. The prevalence is 13% in non-atopic asthma and 5% in atopic asthma. There is a definite relationship in patients with 'Samter triad': asthma, NSAID sensitivity and nasal polyps. In NSAID sensitivity, nasal polyps are found in 36–96% of patients [1].

The association between chronic sinusitis and asthma is even stronger: Over 50% of patients with sinus disease

have asthma [2, 3] and up to 90% of patients with mild-to-moderate asthma have abnormal computer tomography findings of the paranasal sinuses [4]. In patients with severe asthma, sinonasal involvement even approximates 100% [4].

Similar to AR, nasal polyposis [5] and chronic sinusitis [3] are also frequently accompanied by asymptomatic BHR. Although AR may exacerbate nasal polyposis and sinusitis, atopy, by itself, does not seem to play an important role in the pathogenesis of both conditions [6, 7]. In fact, the prevalence of nasal polyposis in allergic patients is rather low and usually under 5%. This stresses the importance of asymptomatic BHR as a risk factor for asthma, although other factors, such as atopy, may also contribute to this relationship [8].

Although eosinophilia in bronchial mucosa is regarded as one of the hallmarks of allergic asthma, this may not be a very specific finding. Also, in AR patients without asthma, signs of allergic inflammation have been found in induced sputum, broncho-alveolar lavage fluid and bronchial biopsies [9]. Likewise, eosinophilic infiltration was present in the upper airways of asthmatic patients without nasal complaints [10].

The nose acts as a filter and air-conditioner, therefore protecting the lower airways. Pathological conditions of the nasal mucosa hamper these functions, which leads to increased exposure of the lower airways to allergens. In susceptible persons, this may lead to inflammatory changes and an increase in BHR. Several authors have demonstrated that surgical treatment of chronic rhinosinusitis and nasal polyposis in asthmatic patients improved their asthmatic status [11, 12], suggesting that improvement of nasal function results in better asthma control.

BHR and chronic mucosal inflammation are considered important features of allergic asthma. Although several studies have pointed towards a relationship between bronchial inflammation and BHR, others have failed to detect a relationship. In fact, the presence of bronchial

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inflammation in non-asthmatic atopic patients, even in the absence of any airway symptoms at all, challenges the direct relationship between the presence of inflammatory cells, in particular eosinophils, and BHR [13]. Therefore, the threshold above which a bronchoconstrictive response is initiated in daily life is probably higher in patients with AR than in those with clinical asthma. Becky Kelly et al. [14] demonstrated in a bronchoprovocation model that the dose required to initiate comparable clinical responses was significantly lower in patients with asthma than in patients with AR without asthma. Moreover, the size of the inhaled allergen, as well as the duration and severity of the allergen exposure, could also affect the clinical manifestation [15]. On the other hand, some patients with AR and asthma have such a poor perception of nasal [16] and bronchial symptoms [17] that this may also partly explain the discrepancy between mucosal inflammation and clinical expression.

The article by Williamson et al. [18] in the current issue certainly contributes to the discussion about the applicability of the united airways concept to other airway pathology apart from allergic airways disease. The authors raise the question whether asymptomatic BHR and increased exhaled nitric oxide (FeNO) are predictors of asthma in non-atopic upper airway pathology. The aim of the study was to investigate the factors influencing lower airway dysfunction in patients suffering from chronic rhinosinusitis and nasal polyposis. This research question is interesting: not much work has been done in this field so far.

Although a high prevalence of asymptomatic lower airways dysfunction was detected in this population, surprisingly the authors could not find any relationship between nasal outcomes and abnormal spirometric findings. Multiple regression analysis suggested that lower airways dysfunction was more associated with the eosi-

nophilic phenotype than to features of nasal disease, such as polyp grade, rhinitis symptoms, nasal NO or duration of rhinitis. The study was well designed and the patients well characterized for upper and lower airway pathology. As the study was cross sectional we should, however, be cautious to conclude that there is no relationship at all in these type of patients. The 'inflammatory type' subgroup without current asthma symptoms could still represent a group at risk for developing asthma in the future. Moreover, only a small proportion (4 out of 17) of the patients in this subgroup really had increased BHR (< 8 mg/mL methacholine) and most of them were characterized 'inflammatory' based on increased FeNO (> 30 p.p.b.). So far, many factors have been identified that can increase FeNO and therefore the positive-predictive value for asthma may be low, particularly in this patient population. More direct sampling of nasal and bronchial inflammation using mucosal biopsy or lavage techniques would probably be the way to address this issue.

So in the end, this study raises more questions than it answers. The question remains to be solved concerning the causes of the discrepancy between airway symptoms, inflammatory markers and functional parameters. Moreover, atopy and BHR are evidently linked to asthma expression, but progression of the disease is unpredictable.

What eventually determines the clinical phenotype in allergic airway disease is still not completely understood. Generalized airway inflammation and BHR are present in patients with AR, sinusitis and nasal polyposis, even in the absence of clinical asthma. Whether these subjects represent a group at risk for the development of asthma requires further study including more extensive sampling of mucosal inflammation and a longer follow-up of the patients.

References

- 1 Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology* 2007; 20 (Suppl.):1–136.
- 2 Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106 (Suppl.): S201–5.
- 3 ten Brinke A, Grootendorst DC, Schmidt JT et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002; 109:621–6.
- 4 Bresciani M, Paradis L, Des Roches A et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001; 107:73–80.
- 5 Lamblin C, Gosset P, Salez F et al. Eosinophilic airway inflammation in nasal polyposis. *J Allergy Clin Immunol* 1999; 104:85–92.
- 6 Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax* 2000; 55 (Suppl. 2):S79–83.
- 7 Shapiro GG. Role of allergy in sinusitis. *Pediatr Infect Dis* 1985; 4 (Suppl.): S55–9.
- 8 Boulet LP. Asymptomatic airway hyper-responsiveness: a curiosity or an opportunity to prevent asthma? *Am J Respir Crit Care Med* 2003; 167:371–8.
- 9 Braunstahl GJ. The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease. *J Allergy Clin Immunol* 2005; 115:142–8.
- 10 Gaga M, Lambrou P, Papageorgiou N et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000; 30:663–9.
- 11 Dunlop G, Scadding GK, Lund VJ. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polyposis, and asthma. *Am J Rhinol* 1999; 13:261–5.
- 12 Ikeda K, Tanno N, Tamura G et al. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. *Ann Otol Rhinol Laryngol* 1999; 108:355–9.

- 13 Braunstahl GJ, Fokkens WJ, Overbeek SE, KleinJan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003; 33:579–87.
- 14 Becky Kelly EA, Busse WW, Jarjour NN. A comparison of the airway response to segmental antigen bronchoprovocation in atopic asthma and allergic rhinitis. *J Allergy Clin Immunol* 2003; 111: 79–86.
- 15 Witteman AM, Sjamsoedin DH, Jansen HM, van der Zee JS. Differences in nonspecific bronchial responsiveness between patients with asthma and patients with rhinitis are not explained by type and degree of inhalant allergy. *Int Arch Allergy Immunol* 1997; 112: 65–72.
- 16 Hellgren J, Toren K, Balder B, Palmqvist M, Lowhagen O, Karlsson G. Increased nasal mucosal swelling in subjects with asthma. *Clin Exp Allergy* 2002; 32: 64–9.
- 17 van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med* 2001; 164:2107–13.
- 18 Williamson P, Vaidyanathan S, Clearie K, Barnes M, Lipworth BJ. Airway dysfunction in nasal polyposis: a spectrum of asthmatic disease? *Clin Exp Allergy* 2011; 41 (this issue).