REVIEW

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The nose: gatekeeper and trigger of bronchial disease*

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SUMMARY

The nose is strategically placed at the entrance of the airway. Nose breathing takes place under physiologic circumstances and protects the lower airways from exposure to unconditioned air and exogenous particles. Alternatively, nasal disease may have a negative impact on lower airway biology, being involved in aggravation of bronchial disease. The interaction between upper and lower airway disease has been recognized for centuries. Due to the increase in prevalence of allergic diseases during the last decades, new interest has been gained in understanding the mechanisms underlying the interaction between rhinitis and asthma. Nowadays, allergic rhinitis and asthma are considered part of a global airway disease, with both diagnostic and therapeutic consequences for every day clinical practice. Besides allergy, other inflammatory conditions of the upper airways are associated with lower airway disease via unknown mechanisms. Viral rhinitis often coincides with exacerbations of bronchial disease, chronic sinus disease with or without nasal polyps frequently relates to bronchial dysfunction and occupational rhinitis and asthma are often present in the same individuals. In spite of the clinical relevance of considering the airway as one organ with major involvement of disease in upper, lower or both parts, many clues to understand the pathology still remain to be explored. This manuscript aims at providing a comprehensive overview of the current knowledge on the interaction between nasal disease and lower airway biology and stresses the importance of further research on this important matter.

Key words: asthma, COPD, rhinitis, sinusitis, united airways

INTRODUCTION

Due to its strategic position at the entry of the airway, the nose plays a crucial role in airway homeostasis. By warming up, humidifying and filtering incoming air, the nose is essential in the protection and homeostasis of lower airways. Nose and bronchi are linked anatomically, are lined with a pseudo-stratified respiratory epithelium and equipped with an arsenal of innate and acquired immune defense mechanisms. It is not hard to imagine that nasal conditions causing nasal obstruction may become a trigger for lower airway pathology in susceptible individuals. In chronic sinus disease with nasal polyps, total blockage of nasal breathing may occur, hence bypassing nasal functions that may be relevant in preventing lower airway disease. It is however evident that the nasobronchial interaction is not restricted to bronchial reactions to reduced nasal air conditioning. Nose and bronchi seem to communicate via more indirect mechanisms such as neural and systemic pathways. The occurrence of bronchoconstriction following cold air challenge suggests that neural reflexes connect nose and lung.[1] The precise origin of the nasobronchial reflex has not been studied in detail so far. Recently, the systemic nature of the interaction between nose and bronchi has been proposed. Indeed, many inflammatory diseases of the upper airways show a systemic immunologic component involving the blood stream and bone marrow [2,3]. Several inflammatory processes like allergic rhinitis and chronic rhinosinusitis (CRS) with/without NP are not limited to the upper airways and show systemic signs of upper airway inflammation, like elevated levels of interleukin (IL)-5 in the blood and increased bone marrow eosinopoiesis [2,4,5]. Viral rhinitis is associated with a systemic increase of granulocyte colony-stimulating factor (G-CSF) and probably bone marrow neutropoiesis [6]. In addition, genetic factors may also play a role in the manifestation of nasal and/or bronchial disease [7,8]. This article aims at providing a comprehensive overview of the current knowledge of nasobronchial interactions in different rhinologic diseases (Figure 1), including consequences for treatment and future research directions.

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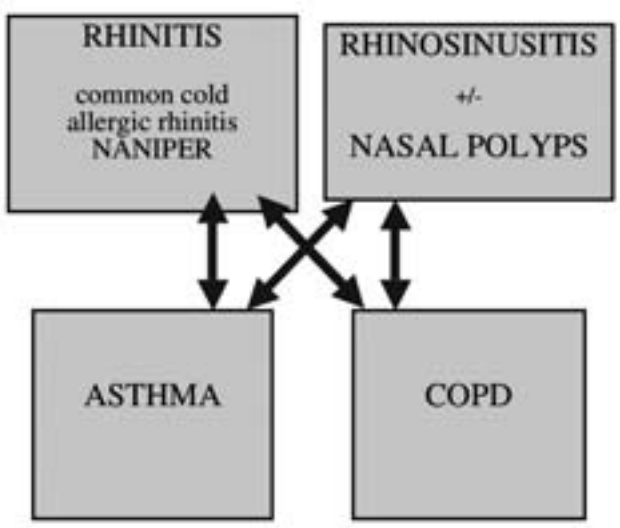

Figure 1. Interactions between different rhinologic diseases.

ALLERGIC RHINITIS AND LOWER AW DISEASE

Prevalence

The link between nasal and bronchial disease has been studied most extensively for allergic rhinitis and asthma. During the last decade, the concept of "united airways allergy" has become widely accepted and has even been included in the World Health Organisation state-of-the-art document Allergic Rhinitis and its Impact on Asthma (ARIA) [9]. The epidemiological association between these two disease entities is obvious. The incidence of both allergic rhinitis and asthma is increasing rapidly in the industrialized world and both disorders often coexist. Up to 90% of individuals with asthma have allergic rhinitis and one third of allergic rhinitis patients suffers from asthma [10,11]. Moreover, having allergic rhinitis increases the risk of developing asthma later in life threefold, even independent of the atopic status [12].

Pathophysiology

Besides epidemiological arguments, pathophysiological mechanisms also support the united airway disease concept. In both allergic rhinitis and asthma, similar immunological processes such as IgE dependent mast cell degranulation and T helper (Th)-2 lymphocyte activation lead to an inflammatory infiltrate of predominantly eosinophils [13]. In a mouse model, there is simultaneous development of upper and lower airway inflammation after inhalation of the allergen [14]. The most convincing proof of the linkage of upper and lower airways comes from experimental studies in which allergen deposition in either nose or bronchi leads to inflammatory changes at a distant site of the airways. Braunstahl et al showed an up-regulation of eosinophils, ICAM-1, VCAM-1 and E-selectin in both nasal and bronchial tissue following a nasal allergen provocation in allergic rhinitis patients [15]. Alternatively, an increase in eosinophils, mast cells, basophils, IL-5 and eotaxin-positive cells was found in nasal tissue following segmental bronchial allergen provocation [16]. Mechanisms of this bi-directional nasobronchial crosstalk remain unexplained. Most evidence points towards a systemic linkage of upper and lower airways. Increased blood eosinophilia and bone marrow eosinopoiesis have been shown after airway allergen challenge in both mice and humans [4,5,15,17]. Induction of systemic IL-5 has repeatedly been found following allergen provocation [4,14,16], and may represent the stimulus for bone marrow eosinopoiesis [5,18]. Besides systemic pathways, other mechanisms may play a role in the induction of inflammatory changes at a distance, such as neural reflexes, post-nasal drip with aspiration of allergens, inflammatory cells or mediators, or nasal obstruction resulting in decreased air conditioning and other physiologic functions of the nose [19].

Treatment

Evidence-based guidelines for treatment of allergic rhinitis are summarized in the ARIA document [9]. In view of the interaction between nose and bronchi, treating allergic rhinitis in patients with concomitant asthma may lead to a better asthma control, taking into consideration that allergic rhinitis tends to be undertreated in asthma patients [20]. The efficacy of rhinitis treatment in reducing lower airway symptoms is best documented for nasal corticosteroids. Nasal steroids have been shown to reduce bronchial hyperresponsiveness in allergic rhinitis patients with or without clinical asthma [21-23], in one study even more efficiently than inhaled steroids [24]. Nasal steroids reduce asthma symptoms in patients with concomitant rhinitis [25] and decrease asthma-related emergency department visits [26]. In contrast, a recent large randomized placebo-controlled study, performed by the SPIRA study group [27], showed no beneficial effect of the use of nasal fluticasone on asthmatic symptoms, bronchial responsiveness or inflammation in patients with allergic rhinitis and asthma. H1 antihistamines are very effective in the treatment of allergic rhinitis, but their role in the treatment of asthma is still controversial. Although not suitable as monotherapy for asthma, second-generation non-sedative antihistamines give some protection in histamine-induced bronchoconstriction and are beneficial in patients suffering from the combination of allergic rhinitis and asthma [28,29]. Cysteinyl leukotrienes are mediators in the pathogenesis of both allergic rhinitis and asthma. In addition, they play an important role in the systemic inflammatory response following allergen contact by promoting bone marrow eosinopoiesis and eosinophil recruitment towards the airway [30], making them an ideal target for treatment of global airway allergy. Indeed, leukotriene receptor antagonists are effective in reducing symptoms of both allergic rhinitis and asthma, and diminish the need for rhinitis and asthma medication [31,32]. Immunotherapy (IT) is another example of a systemic therapy for allergic patients. Besides causing a long-term reduction of symptoms of allergic rhinitis and medication-use [33], IT is effective in mild asthma and can even prevent the development of asthma in allergic rhinitis patients [34]. Recently, much interest has been gained in sublingual IT, which is probably equally effective as subcutaneous IT without report-

ed systemic side effects. Novel approaches like anti-IgE (omalizumab) could also be very useful for treating patients with global airway allergy [35]. The study of omalizumab in comorbid asthma and rhinitis, called the SOLAR study [36], showed significant improvement in asthma and rhinitis clinical symptoms, asthma and rhinitis-related quality of life and lung function parameters. In addition, patients treated with omalizumab experienced significantly fewer asthma exacerbations.

INFECTIOUS RHINITIS AND LOWER AW DISEASE

Prevalence

Common colds account for approximately 50% of all illnesses and are even more frequent in young infants [37]. Besides inducing rhinitis symptoms such as nasal obstruction, rhinorrhoea and sneezing, upper respiratory tract infections are also known to cause exacerbations of pre-existing lower airways diseases such as asthma or chronic obstructive pulmonary disease (COPD). The majority of acute asthma exacerbations are precipitated by respiratory virus infections in all age groups. When sensitive methods such as RT-PCR are used, viruses are found in 80 % of wheezing episodes in school-aged children and in almost 50 % of asthma exacerbations in adults. Rhinovirus (RV) is the most frequently detected pathogen [38,39]. The causal relationship between RV infection and asthma exacerbations has been proved by experimental infection models. When asthmatic patients inhale a nebulized RV-16 suspension, this gives rise to the induction of rhinitis symptoms together with worsening of their asthma state [40]. Moreover, a decrease in FEV1, increased airway hyperresponsiveness and augmented eosinophilic bronchial inflammation are found following experimental RV infection [40,41]. Even in non-asthmatic patients with atopic rhinitis, RV inoculation increases airway hyperreactivity and induces a drop in FEV1 [42]. Beside causing the majority of wheezing episodes in asthmatic patients, common colds are also associated with more than 40% of COPD-exacerbations, with RV being the most common viral pathogen [43]. In general, symptom scores at the onset of viral exacerbations are higher as compared to non-viral exacerbations, and viral exacerbations have a more protracted course [43].

Pathophysiology

The mechanisms of virus-induced exacerbations of asthma and COPD remain to a large degree elusive. A first and crucial question is whether RV can reach and replicate in the lower airways and cause lower airways symptoms by direct infection, or if indirect mechanisms are responsible for exacerbations of lower airways diseases [44]. Recent evidence supports the first hypothesis. The presence of RV in bronchial biopsy specimens after experimental upper respiratory RV infection in human volunteers was confirmed by in situ hybridization and immunohistochemistry [45,46]. By using the latter methods, the authors avoid contamination from the upper airways, which could not be excluded in previous studies where RV was detected in broncho-alveolar lavage or sputum [47,48]. However, the importance of bronchial penetration and replication of RV during natural infection is still uncertain. Ninety percent of RVs infect airway epithelial cells via binding to the receptor ICAM-1, followed by intracellular penetration and replication. RVs are able to up-regulate the expression of ICAM-1 via NF-kappa B-dependent mechanisms, thus enhancing their own infectivity and promoting inflammatory cell infiltration [49]. Moreover, in bronchial cell cultures, RV infection induces a variety of pro-inflammatory cytokines and chemokines such as IL-6, IL-8, IL-16 and RANTES, which may lead to the chemotaxis and activation of neutrophils, lymphocytes, monocytes and eosinophils, thereby enhancing lower airway inflammation [45,50]. Beside a direct effect of RV on bronchial epithelial cells, indirect mechanisms could play a role in increasing lower airway inflammation during a common cold. Following experimental RV-16 infection in allergic individuals, G-CSF levels increase not only in nasal secretions but also in the circulation. G-CSF levels in serum correlate with the blood neutrophilia, suggesting that G-CSF acts on the bone marrow to increase the neutrophilia in blood [6]. Beside the pro-inflammatory effect of RV on airway epithelium, host factors also play an important role in the development of acute exacerbations. Several risk factors for experiencing more severe viral exacerbations of lower airway disease are described, including age (being an infant or an elderly), smoking and having low neutralizing antibody titers to RV [6]. Moreover, atopic asthmatic individuals are more prone to virus-induced wheezing, possibly via less IFN-γ production in response to RV, which reflects a defective Th1 immune response [51]. However, Avila et al. showed a delayed onset of cold symptoms and a shortening of their duration, when inoculation with RV was preceded by allergen challenge in subjects with allergic rhinitis. In this experimental setting, allergic inflammation may be protective for RV-infection, probably depending on the timing and intensity of antigen exposure [52].

Treatment

Although acute viral exacerbations account for a large part of the burden associated with asthma and COPD, currently available treatments are unsatisfactory. To treat viral-induced asthma and COPD exacerbations, one can target either the virus itself or the host immune response [6]. No RV vaccination exists because of the wide variety of serotypes of human RV. A range of antiviral agents has been tested in preclinical or clinical trials. The first agent tested was intranasal interferon (IFN)-α at high dose [53], which was effective in preventing the onset of cold symptoms. However, high doses of nasal IFN-α caused local irritation and had no therapeutic effects in established colds. Moreover IFN-α was not effective in the prophylaxis of RV-associated exacerbations of bronchial diseases [54]. Other antiviral agents, such as sICAM-1, capsid-binding agents and rhinovirus 3C protease inhibitors are in different stages of development [55]. Some show antiviral activity in clinical trials, but their efficacy in preventing exacerbations of asthma or COPD has not been demonstrated so far. Another

therapeutic strategy is to prevent the inflammatory reaction caused by RV infection. Glucocorticosteroids are the cornerstone of current asthma and COPD maintenance therapy. However, they disappoint in the treatment of acute exacerbations. In persistent asthma, daily administration of inhaled corticosteroids has only limited effect in reducing the number of wheezing episodes, both in adults and children [56,57]. Also doubling the dose of inhaled steroids during asthma attacks is ineffective [58-60]. In exacerbations of COPD, corticosteroids have no major therapeutic efficacy as they reduce the absolute treatment failure rate by only 10%, increase the forced expiratory volume in 1 second (FEV1) by only 100 ml, and shorten the hospital stay by 1 to 2 days [61]. Inhibiting Nf-kappa B signaling may also represent an interesting therapeutic option, since Nf-kappa B is involved in both the virus-induced up-regulation of ICAM-1 as well as in the transcriptional activation of a large number of the pro-inflammatory mediators involved in RV infection. Nf-kappa B inhibitors are however in an experimental stage of development and it remains to be determined if the anti-inflammatory properties of these agents will not be counterbalanced by the simultaneous inhibition of protective, anti-viral mediators such as interferon [62].

NON-ALLERGIC, NON-INFECTIOUS RHINITIS AND LOWER AW DISEASE

Non-allergic, non-infectious persistent rhinitis (NANIPER) is a heterogeneous group of nasal disorders comprising occupational rhinitis, drug-induced rhinitis, hormonal rhinitis, rhinitis of the elderly and idiopathic rhinitis [63]. So far, the patient population with NANIPER is not studied extensively nor well characterized, leaving us with a heterogeneous and ill-defined group of patients. Apart from occupational rhinitis and asthma, no association between upper and lower airway disease has been established in the other NANIPER patients. Occupational asthma is better characterized than occupational rhinitis. Many of the causative agents of occupational asthma are able to induce rhinitis. These agents are divided in low-molecular-weight (LMW; various chemicals) and high-molecular-weight compounds (HMW; proteins from plants or animals). About 90% of occupational asthma patients report rhinitis symptoms at some time [64].

While the prevalence of rhinitis symptoms are equal in asthma caused by HMW or LMW agents, rhinitis symptoms are more severe in the HMW group. Moreover, in the HMW group, rhinitis often precedes the onset of asthma [64]. Patients with occupational rhinitis are at high risk to develop asthma, especially during the year following rhinitis notification [65]. In a recent prospective trial, 6 and 3 % of workers exposed to organic acid anhydrides developed upper and lower airway symptoms respectively in a dose-related manner [66]. Interestingly, smoking and atopy increased the risk of developing airway symptoms. However, the mechanisms of induction of respiratory symptoms in upper, lower or global airway in occupational disease remain unclear. Among chronic airway diseases, occupational airway disease takes a unique place, as resolution of airway symptoms occurs when exposure to causative agents is discontinued.

RHINOSINUSITIS WITHOUT NP AND ASTHMA

Prevalence

Bronchial asthma is considered a comorbid condition of CRS. In some centers, around 50% of patients with CRS have clinical asthma [67,68]. Interestingly, most patients with CRS who do not report to have asthma show bronchial hyperreactivity when given a metacholine challenge test [68]. In this way, Ponikau et al. concluded that 91% of patients with CRS had either asthma or increased bronchial hyperreactivity. Others report that 60 % of patients with CRS have lower airway involvement, assessed by history, pulmonary function and histamine provocation tests [69]. Alternatively, sinonasal symptoms are frequently reported in asthmatic patients, ranging up to 80 % in some studies [70]. Radiologic imaging of the sinuses has demonstrated mucosal thickening of the sinus mucosa in up to 84 % of patients with severe asthma [71]. However, these epidemiologic and radiologic data should be interpreted with caution as they may reflect a large reference bias.

Pathophysiology

CRS is currently thought to have a multifactorial etiology, in which host factors like anatomical, local defense and immunologic factors, act in synergy with microbial and environmental factors in the development and chronicity of the disorder [72]. Histopathologic features of CRS and asthma largely overlap. Heterogeneous eosinophilic inflammation and features of airway remodeling like epithelial shedding and basement membrane thickening, are found in the mucosa of CRS and asthma [68]. Cytokine patterns in sinus tissue of CRS highly resemble those of bronchial tissue in asthma [73], explaining the presence of eosinophils in both conditions. Therefore, eosinophil degranulation proteins [74] may cause damage to the surrounding structures and induce symptoms at their location in the airway. Finally, lavages from CRS patients show that eosinophils were the dominant cell type in both nasal and broncho-alveolar lavages in the subgroup of patients with CRS with asthma [75]. Beside the similarities in pathophysiology, sinusitis has been etiologically linked to bronchial asthma, and vice versa. As is the case in allergic airway inflammation, sinusitis and asthma can affect and amplify each other via the systemic route, involving interleukin (IL)-5 and the bone marrow [2]. In both CRS and allergic asthma, similar pro-inflammatory markers are found in the blood. Recently, nasal application of Staphylococcus aureus enterotoxin B has been shown to aggravate the allergen-induced bronchial eosinophilia in a mouse model [76]. Here, mucosal contact with enterotoxin B induced the systemic release of IL-4, IL-5 and IL-13, leading to aggravation of experimental asthma. However, the interaction between both rhinosinusitis and asthma in not always clinically present, as Ragab et al. found no correlation between rhinosinusitis and asthma severity [69]. However, CT scan abnormali-

ties in severe asthmatic patients correlated with sputum eosinophilia and pulmonary function [71].

Effects of treatment of CRS on bronchial disease

Endoscopic sinus surgery (ESS) for CRS aims at alleviating sinonasal symptoms but also improves bronchial symptoms and reduces medication use for bronchial asthma [77-81]. After a mean follow-up period of 6.5 years, 90% of asthmatic patients reported their asthma was better than it had been before the ESS, with a reduction of the number of asthma attacks and medication use for asthma [67]. Also in children with sinusitis and asthma, sinus surgery improves the clinical course of asthma, reflected by a reduced number of asthma hospitalizations and schooldays missed [82]. Lung function in asthma patients with CRS was reported to benefit from ESS by some authors [77,81] but denied by others [78,80,82]. Of note, not all studies show beneficial effects of ESS on asthma [83]. The reason for the inconsistency in study results between studies relates to the heterogeneity and small number of patients included in these studies, and difference in outcome parameters studied. Interestingly, the presence of lower airway disease may have a negative impact on the outcome after ESS. Outcomes after ESS were significantly worse in the asthma compared to the non-asthma group [77,79]. Poor outcomes after ESS have also been reported in patients with aspirin-intolerant asthma.[84-86] On the other hand, other authors report that asthma does not represent a predictor of poor symptomatic outcome after primary [87,88] or revision ESS [89]. In a series of 120 patients undergoing ESS [90], Kennedy reports that asthma did not affect the outcome after ESS when comparing patients with equally severe sinus disease, except for the worst patients, in which asthma did adversely affect the outcome.

Until recently, no well-conducted clinical trials have been performed showing beneficial effects of medical therapy for CRS on bronchial asthma. Ragab et al.[91] published the first randomized prospective study of surgical compared to medical therapy of 43 patients with CRS with/without NP and asthma. Medical therapy consisted of a 12 weeks course of erythromycin, alkaline nasal douches and intranasal corticosteroid preparation, followed by intranasal corticosteroid preparation tailored to the patients' clinical course. The surgical treatment group underwent ESS followed by a 2-week course of erythromycin, alkaline nasal douches and intranasal corticosteroid preparation, 3 months of alkaline nasal douches and intranasal corticosteroid, followed by intranasal corticosteroid preparation tailored to the patients' clinical course. Both medical as well as surgical treatment regimens for CRS were associated with subjective and objective improvements in asthma state. Interestingly, improvement in upper airway symptoms correlated with improvement in asthma symptoms and control.

RHINOSINUSITIS WITH NP AND ASTHMA

Prevalence

Seven percent of asthma patients have nasal polyps [92]. In non-atopic asthma and late onset asthma, polyps are diagnosed more frequently (10-15%) [15,70,92]. Aspirin-induced asthma is a distinct clinical syndrome characterized by the triad aspirin sensitivity, asthma and nasal polyposis and has an estimated prevalence of one percent in the general population and ten percent among asthmatics [93].

Pathophysiology

At present, the etiology of NP remains obscure. As nasal polyps represent a chronic inflammatory disease affecting the mucosa of ethmoidal sinus cavities in susceptible individuals [70], one may speculate on airborne micro-organisms being able to induce or aggravate the inflammation seen in NP. Recently, new light was shed on the pathology of NP by Van Zele et al. showing increased colonization of NP by *Staphylococcus aureus* and presence of specific IgE directed against *Staphylococcus aureus enterotoxins* in NP tissue [94]. Interestingly, rates of colonization and IgE presence in NP tissue was increased in subjects with NP and co-morbid asthma or aspirin sensitivity. By their superantigenic activity, enterotoxins may activate inflammatory cells in an antigen-unspecific way. Recently, Hellings et al. demonstrated that nasal application of *Staphylococcus aureus* enterotoxin B is capable of aggravating experimental allergic rhinitis and asthma, parallelled with an increase in bronchial and systemic Th2 cytokine levels [76]. Besides bacterial enterotoxins, Ponikau et al. report on the potentially important role of fungi, especially Alternaria, in the generation of chronic sinus disease with NP [95]. By their capacity to induce eosinophil degranulation [96], Alternaria may contribute to the inflammatory spectrum of CRS with/without NP. So far, we have no idea whether microbial stimuli may represent the etiology of NP formation or whether colonization with micro-organisms is favored in the presence of NP.

Treatment

At present, no trials have been performed studying the effects of medical therapy for NP patients on asthma. Therefore, well-designed trials on antibiotic use, vaccination therapy or anti-leukotriene treatment in patients with NP and asthma are warranted. After ESS for NP in patients with concomitant asthma, a significant improvement in lung function and a reduction of systemic steroid use was noted, whereas this was not the case in aspirin intolerant asthma patients [86] In a small series of patients with nasal polyps, endoscopic sinus surgery did not affect the asthma state [97]. However, nasal breathing and quality of life improved in most patients [97].

RHINOSINUSITIS AND COPD

Up to 88 % of patients with COPD presenting at an academic unit of respiratory disease may experience nasal symptoms, most commonly rhinorrhoea [98]. Nasal symptoms in COPD patients correspond well with an overall impairment of the quality of life [98]. So far, no other studies on nasobronchial interaction have been performed in COPD patients.

CLINICAL IMPLICATIONS AND FUTURE NEEDS FOR RESEARCH

Several medical specialties are involved in the medical care of patients with chronic airway disease. In asthmatic and COPD patients, physicians need to enquire routinely about the existence of sinonasal symptoms. To this purpose, the use of a simple and validated questionnaire for the presence of sinonasal symptoms may be helpful and has good negative predictive value for excluding rhinosinusitis [99]. In case of positive history for upper airway symptoms, anterior rhinoscopy, nasal endoscopy or CT scan of the sinonasal cavity can help in making a correct estimation of upper airway involvement in asthma and COPD. Alternatively, bronchial symptoms need to be asked for in patients presenting with rhinitis / rhinosinusitis. When lung function tests are performed in this patient population, most of them will show bronchial hyperresponsiveness making us aware of global airway impact of the upper airway disease. However, several clues to fully understand the nasobronchial interaction are still missing, complicating our clinical approach of individuals with upper and/or lower airway disease. For example we cannot predict in individual patients with allergic rhinitis if and when allergic rhinitis will progress into the development of clinical asthma. It may therefore be important to evaluate bronchial function in all patients with allergic rhinitis, aiming at a strict anti-allergic treatment regimen in those with preclinical asthma. In patients with NP and concomitant asthma/COPD, we do not know whether sinus surgery or any other medical treatment for rhinosinusitis will have beneficial effects on lower airway pathology. Therefore, prospective clinical trials on outcomes of upper airway therapy should not only concentrate on parameters of upper airway disease but also take into account the effects of treatment on lower airways. Alternatively, the impact of asthma or COPD on rhinosinusitis remains obscure. As upper airway inflammation may be induced by bronchial inflammation [16], rhinologists need to closely collaborate with pneumologists to design a therapeutic strategy which aims at obtaining the optimal condition for both parts of the airway.

A minority of CRS and asthma patients are refractory to standard medical therapy and sinus surgery procedures. In these patients, the disease development still remains incompletely understood. Therefore, one of the future tasks remains to delineate factors that contribute to severe CRS and asthma like exposure to environmental or occupational agents, underlying gastro-esophageal reflux, and/or infection or colonization with micro-organisms. Recently, fungal extracts [100] and bacterial enterotoxins [101] have been linked to the etiology of NP. Research in the field of microbial triggers and their interplay with airway biology should be extended to viruses and atypical bacteria like *Mycoplasma* and *Chlamydia*. In addition, the cellular source as well as the mechanisms of systemic release of pro-inflammatory mediators like IL-5 [4] and eotaxin [102] by allergen inhalation are still unknown. Whether the systemic release of these mediators represents diffusion of locally produced molecules, or rather systemic release by circulating cells, remains to be explored. After full comprehension of the mechanisms of systemic mediator release, novel treatment strategies can be designed aiming at reducing the systemic immune response with its impact on global airway disease.

Epithelial cell dysfunction may be a common factor in the development of upper and lower airway disease. Defective IFN-γ production by bronchial epithelial cells is thought to contribute to the development of asthma [51]. So far, we do not know to what extent intrinsic epithelial dysfunction may be related to the phenotype of chronic upper airway disorders like allergy or nasal polyp formation.

For clinical practice, there is a need for non-invasive markers of inflammation in upper and lower airways. Among non-invasive biologic markers of inflammation, nasal and bronchial nitric oxide (NO) measurement may represent a novel tool for diagnostic purposes as well as for the prediction of the success of therapy [103]. In spite of the validity of NO measurements in exhaled air in asthma patients [104], its role in upper airway inflammation needs to be studied further. Induced sputum, another non-invasive tool for research, may provide us with relevant information on the involvement of bronchial inflammation in patients with upper airway disease [105]. Further studies are needed for delineating its validity in rhinologic practice.

CONCLUSION

Upper and lower airway inflammation share common pathophysiologic mechanisms, frequently co-exist and communicate via the systemic circulation. The treshold for developing symptoms in upper and lower airways relates to intrinsic and extrinsic factors. Genetic predisposition, organ susceptibility and breathing patterns are believed to be involved in the manifestation of bronchial symptoms in patients with rhinitis / rhinosinusitis. Extrinsic factors like the dose of exposed allergens, the microbial micro-environment and occupational factors, may all contribute to the complex picture of global airway disease. Many questions related to the generation of symptoms in patients with airway inflammation remain unanswered so far. However, the awareness of bronchial symptoms in patients with upper airway inflammation and vice versa, may at this stage represent a major step forward in the diagnostic and therapeutic approach of affected patients. The full appreciation of involvement of upper and lower airway disease in one patient can only be executed in a multidisciplinary clinical setting, involving doctors being able to examine and interpret clinical abnormalities of upper and lower airways. Anterior rhinoscopy and nasal endoscopy should be combined with lung function tests in patients with any chronic airway disorder. The validation of non-invasive parameters of airway inflammation like NO measurement, and the optimization of combined treatment strategies for patients with upper and/or lower airway disease will be one of our major tasks for the upcoming decade.

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