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Allergic Rhinitis and Its Impact on Bronchial Asthma

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1. Introduction

Allergic rhinitis and bronchial asthma are two entities often coexisting. In fact, during recent years the concept "one airway, one disease" has been proposed. Many asthmatic patients, particularly those with allergic asthma, also have allergic rhinitis (AR). The mucosa of the upper and lower airways is continuous, and the type of inflammation in AR and asthma is very similar, involving T-helper type 2 lymphocytes, mast cells, and eosinophils. It is now well understood that the epidemiological association between bronchial asthma and AR is very strong. In addition, the two entities seem to share common genetic and environmental risk factors, while the immunopathology of rhinitis and asthma are virtually the same. Current evidence indicates that co-morbid AR may have clinically relevant effects on asthma. Consequently, new knowledge about the pathophysiologic mechanisms of allergic inflammation of the human airways has resulted in better therapeutic strategies. In this chapter, a detailed presentation of the similarities between AR and bronchial asthma is performed giving emphasis on the interactions between the upper and lower airways and any associated clinical implications. Moreover, a few important differences between the two entities are discussed based on original research previously published by the authors.

2. Epidemiologic relationship between asthma and rhinitis

Epidemiologic studies have consistently shown that asthma and rhinitis often coexist [Dixon, 2006; Leynaert, 2000; Greisner, 1998]. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines first developed in 1999 by the World Health Organization and an international panel of experts and updated in 2008, recognizes the importance of this relationship [Bousquet J, 2008]. Prevalence rates of allergic rhinitis range from 15% to 40%. Similarly, asthma is a prevalent disorder that affects approximately 7% of the United States population [Meltzer, 2005]. Asthma and AR, however, occur together at rates that greatly exceed what would be expected from the baseline prevalence of each disorder alone (Fig. 1). AR is associated with asthma in 40% of patients, whereas 80% to 95% of patients with allergic asthma also have rhinitis. In a classical, 23-year follow-up study in more than 1800 college students initially evaluated for the presence of asthma, AR, and positive allergen skin tests, those presenting with AR and positive skin tests were three times more likely to

eventually develop asthma [Settipane, 1994]. This study was confirmed by two other studies in Sweden [Plaschke, 2000] and the United States [Guerra, 2002]. In the Copenhagen Allergy Study, which relied on direct questioning and examination of study subjects, 100% of subjects who had allergic asthma induced by pollen had AR from pollen. Eighty-nine percent of subjects who had allergic asthma caused by animals had AR from animals, and 95% of subjects who had allergic asthma caused by mites had AR from mites. When re-evaluated eight years after initial screening, all patients who developed allergic asthma also had AR to the same allergens, leading the investigators to the conclusion that AR and allergic asthma are manifestations of the same disease entity [Linneberg, 2002]. However, epidemiologic differences may exist when comparing the developing world to western countries. One study showed that AR is far less common among asthmatic subjects in rural China (6%) than in asthmatic subjects in industrialized countries with a western lifestyle [Celedon, 2001].

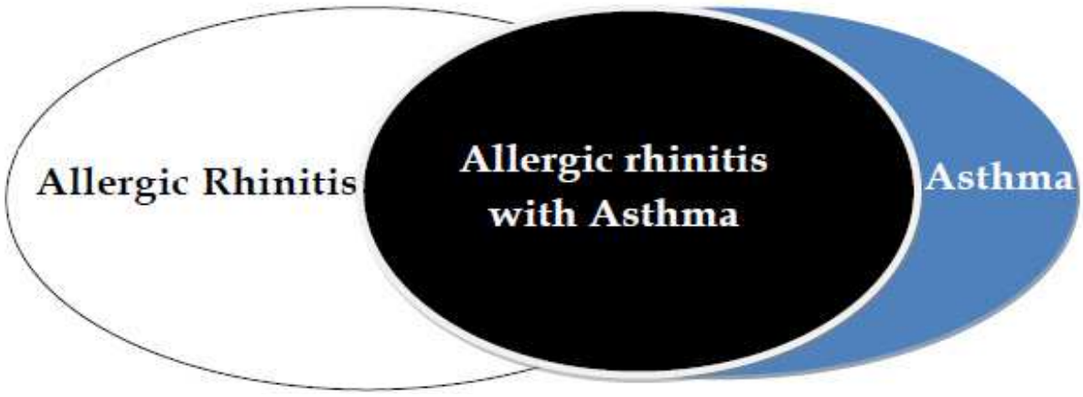

Fig. 1. Relative populations with asthma, allergic rhinitis, or a combination of both.

When assessing AR cases for asthma, a unique subset of rhinitis patients may be identified with a physiologic behaviour that separates them from patients with asthma and normal subjects. They exhibit increased bronchial sensitivity to methacholine or histamine, especially during and slightly after the pollen season. Bronchial hyper-responsiveness is common in people with AR, even if they have no asthma symptoms, and asymptomatic airway hyper-responsiveness is associated with increased risk for developing asthma [Boulet, 2003; Porsbjerg, 2006]. In one study, up to 40% of patients with AR showed hyper-responsiveness to methacholine challenge; those showing hyper-responsiveness were more likely to develop asthma over the following 4–5 years [Braman, 1987]. There are large differences in the magnitude of airway reactivity between asthmatics and people with rhinitis that are not explained by the allergen type or degree of reactivity. The finding that patients who have rhinitis without asthma diagnosis or asthma symptoms have bronchial hyperreactivity lends further support to the notion that asthma and rhinitis are different manifestations of a single respiratory system disease.

3. Rhinitis as a risk factor for asthma

AR is considered a risk factor for the development of asthma; an association which has been supported by multiple studies [Greisner, 1998; Settipane, 1994; Wright, 1994; Guerra, 2002].

The Children's Respiratory Study in 1994 showed that the presence of AR in infancy was independently associated with doubling of the risk for asthma by age 11 years [Wright, 1994]. The age of onset of atopy seems to be an important factor for the development of asthma and rhinitis or rhinitis alone. In an Australian study, atopy diagnosed at an early age (<6 years) was a significant predictive factor for the persistence of asthma into late childhood, whereas atopy presenting later in life was associated only with seasonal allergic rhinitis [Peat, 1990]. Burgess et al also reported that childhood AR was significantly associated with overall presence of asthma: 42% of participants with AR had asthma, compared to only 12.9 % of asthmatics without AR [Burgess, 2007]. In accord with these findings the term "allergic march" was introduced to describe the progression of allergic disease from the nose and sinuses down to the airways of the lung [Almqvist, 2007]. Patients with persistent and severe rhinitis have the highest risk for asthma. It is not clear whether AR represents an earlier clinical manifestation of allergic disease in atopic subjects who eventually develop asthma or if the nasal disease itself is causative for asthma. However, the presence of rhinitis appears to be associated with more severe asthma. In a study of hospital admissions in 2961 children from Norway, even when correcting for severity of asthma, children with AR had a higher risk of hospital readmission and more hospital days per year when compared to asthmatic patients without rhinitis [Kocevar, 2004]. Similar findings have been noted in the United Kingdom. Using a general practice database, the investigators estimated that asthmatic children who had a recorded diagnosis of AR had more general practitioner visits and were more likely to be hospitalized during the 12-month follow- up period of the study compared with children who had asthma alone [Thomas, 2005]. Moreover, when asthma and rhinitis coexist, in addition to increased severity of disease, healthcare costs are also increased. In a study of 1245 asthmatics in the USA, yearly medical care charges were 46% higher in those patients who had concomitant asthma and rhinitis [Yawn, 1999]. Halpern and colleagues [Halpern, 2004] performed an analysis of a medical claims database, and found that the presence of AR was associated with more asthma medication prescriptions and higher asthma prescription costs. These studies suggest that the diagnosis of AR may be more common in individuals who have severe asthma and that those individuals who exhibit both rhinitis and asthma symptoms suffer a more severe disease complex than those who have only upper or lower airway symptoms. Environmental factors may also affect the progression of disease to the lower airways in patients with AR. One environmental factor that should be addressed in allergic patients is tobacco smoke. In a study of patients with allergic rhinitis smoking increased the risk of developing asthma by approximately threefold [Polosa, 2008]. Another common factor that is now recognized as a risk factor for asthma, obesity, does not appear to affect the presence or progression of the allergic march. A population based study showed that obesity was associated with an increased prevalence of asthma, but not AR, suggesting that the pathogenesis of asthma in the obese may be through a different pathway than that linking AR and asthma [Loerbroks, 2008]. Family history has also been shown to play an important predictive role in the development of asthma and AR. A Swedish study concluded that adults with a family history of asthma or rhinitis had a 3- to 4-fold higher risk for developing asthma and a 2- to 6-fold higher risk for developing AR compared with adults without family history [Lundback, 1998]. Another report by the Multi-centre Allergy Study (MAS) group found that history of maternal asthma and/or maternal smoking were strong

predictive factors of childhood asthma, even more than early atopic sensitization and AR. The MAS authors suggest that this predisposition to asthma precedes the pattern of allergic sensitization, contrary to the view that asthma results from a sequential progression of atopic sensitization beginning in childhood with early food allergy and AR [Illi, 2001]. Most patients with asthma present seasonal or perennial AR symptoms. Rhinitis, however, may be a risk factor even in non-atopic subjects, as shown in the Tucson Epidemiologic Study of Obstructive Lung Diseases. After adjustment for atopic status, age, sex, smoking status, and presence of chronic obstructive pulmonary disease, rhinitis still significantly increased the risk for asthma, in both atopic and non-atopic patients [Guerra, 2002]. In the European Community Respiratory Health Survey, an association between asthma and rhinitis was also observed in non-atopic individuals [Leynaert, 2004]. These results cannot be fully explained by shared risk factors and support the hypothesis that upper airway disorders may directly affect the lower airways.

4. Inflammation in allergic rhinitis and asthma

AR and asthma exhibit important similarities in their pathophysiology and involve common inflammatory mechanisms. The nasal and bronchial mucosas are histologically similar; both have ciliated pseudostratified columnar epithelium and an underlying basement membrane. The inflammation in rhinitis is similar to that seen in the bronchial mucosa of asthmatics, consisting mainly of mononuclear cells, lymphocytes, and eosinophils. Additionally, the cytokines, adhesion molecules, and other inflammatory mediators are the same in both diseases [Bachert, 2004]. The same inhaled allergens and irritants stimulate both upper and lower respiratory tracts resulting in a Th2 pattern of proinflammatory cytokine activity [Casale, 2004]. Both AR and asthma symptoms are triggered by atopic sensitization and the allergic cascade, resulting in the generation of allergen-specific IgEs. Circulating levels of allergen-specific IgEs, and the presence of increased total serum IgE is a risk factor for asthma even in non-allergic individuals [Sherrill, 1999; Beeh, 2000]. After sensitization occurs, antigenic fragments of the allergens are presented to T-helper cells, which release cytokines that induce allergen-specific IgE antibody production by B lymphocytes and plasma cells. These antibodies then bind to the surface receptors of mast cells and basophils present in the mucosa of both the upper and lower airways. Re-exposure to the airborne allergen, triggers antigenic binding to the cell-surface specific IgE and activates the mast cells and basophils, resulting in degranulation and release of inflammatory mediators, including histamine, leukotrienes (LTC4, LTD4, LTE4), various proteases and cytokines. These mediators, in turn, trigger vasomotor and glandular responses in the upper airway, and smooth muscle contraction and mucosal edema in the lower airway, leading to airway obstruction [Casale, 2004; Marshall, 2000]. A late-phase reaction occurs approximately 4 to 8 hours after the initial IgE-mediated reaction to allergen exposure. In both the upper and lower airways, this late reaction is characterized by obstruction (nasal congestion, bronchoconstriction), and chronic inflammatory changes involving T cells, mast cells and eosinophils. There is also evidence to suggest that basophils may also play an important role in the late phase of AR [Arshad, 2001]. Recent studies have suggested that additional pathways may contribute to the pathophysiology of AR including local synthesis of IgE in the nasal mucosa, the epithelial expression of cytokines that regulate Th2 cytokine responses

(i.e., thymic stromal lymphopoietin, IL-25, and IL-33), and the activation of histamine receptors other than H1 and H2, such as H4-histamine receptors [Broide, 2010].

Systemic inflammation affecting first the upper and then the lower airways plays a major role in the relationship between AR and asthma. AR and asthma exhibit many elements of a systemic disease in that effector cells are recruited from the circulation, white cell progenitors are stimulated in the bone marrow, and systemic effector cells are primed. Exposing the lower airways of animals to allergens causes the white cell progenitors in the bone marrow to proliferate and differentiate, and leads to high number of eosinophils in the lung, suggesting there is communication between the lung and bone marrow after allergen exposure. Eosinophilic inflammation is a common finding of AR and allergic asthma. The pathways involved include interleukin (IL)-5, supporting the hypothesis of a common pathway in allergic disease [Inman, 2000]. IL-5 is one of several cytokines with a central role in Th2-driven allergic responses in the airways and novel anti-IL-5 strategies have emerged for the treatment of severe persistent eosinophilic asthma [Castro, 2011; Walsh, 2009]. Evidence of inflammation in the lower airway has been documented after local nasal allergen provocation. In a study by Braunstahl et al, nasal allergen provocation was performed in subjects with seasonal allergic rhinitis with bronchial and nasal biopsy specimens obtained before and 24 hours after the provocation. Eosinophils and expression of intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E–selectin were increased in bronchial epithelium 24 hours after nasal provocation, suggesting that the airway inflammation occurs through upregulation of adhesion molecules [Braunstahl, 2001]. In another study, exhaled nitric oxide (eNO) was measured in children with allergic rhinitis and asthma after allergen-specific nasal challenge and found to be significantly higher than in control groups [Marcucci, 2007].

Differences between the upper and lower airways do exist however. The nose filters irritants and allergens from the inhaled air, thus, reducing the exposure of the airways to environmental allergens and pollutants and constituting a critical barrier. The nose has a complex microcirculation that serves multiple functions, including the heating and humidifying of inspired air and the regulation of airflow, via vasodilation and vasoconstriction. The exudation of plasma into the submucosa provides the necessary fluid for copious secretions. Inflammation and excessive mucosal secretions lead to nasal congestion and rhinorrhea and are the hallmarks of AR. The lower airway has a much larger surface area than that of the upper airway. Its patency is mainly controlled by smooth muscle. In allergic asthma, the characteristic response is bronchial smooth muscle contraction or bronchoconstiction. The latter is mediated by various inflammatory and neurogenic factors, including muscarinic pathways specific to the lower airway, resulting in reduced airflow. Other hallmarks of chronic asthma are structural changes or remodelling of the lower airway, which takes the form of epithelial shedding, sub-basement membrane thickening, and smooth muscle hypertrophy and hyperplasia. The pathologic extent of nasal remodelling in patients with rhinitis seems to be far less extensive than that in the bronchi of asthmatic patients. In AR, the epithelium of the nasal mucosa tends to remain intact and the reticular basement membrane does not appear to be largely thickened; moreover, epithelial apoptosis is far greater in the bronchial mucosa of asthmatic patients than in the nasal mucosa of patients with AR [Bousquet, 2004]. The degree and clinical importance of upper airway remodelling are less pronounced than in allergic asthma [Chanez, 1999]. The reasons

why remodelling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still under investigation, but two hypotheses have been proposed: on one hand, the cytokine production of smooth muscle cells might partly explain differences in remodeling of the two sites of the airways. On the other hand, the genes of the embryologic differentiation might persist in the nose and bronchi or might be re-expressed in asthma and rhinitis. Because the nose is of ectodermal origin and the bronchi of endodermal origin, these genes might also govern remodelling patterns. A better understanding of nasal and bronchial remodelling might help to identify new pathways and new therapeutic strategies to reduce bronchial remodelling in asthma [Bousquet, 2004].

5. Therapeutic links between rhinitis and asthma

Treatment of rhinitis has been shown by many studies to reduce asthma severity. In one study, subjects with allergic rhinitis and asthma were treated with intranasal corticosteroid (beclomethasone) or placebo for the entire allergy season. Intranasal beclomethasone therapy prevented the increase in bronchial hyper-responsiveness that was seen in the placebo group [Corren, 1992]. This beneficial effect of intranasal corticosteroids on bronchial hyperresponsiveness was confirmed by another study in asthmatic patients with allergic rhinitis. The subjects who used intranasal fluticasone propionate during the allergy season exhibited less nasal symptoms and the expected increase in bronchial hyper-responsiveness was attenuated [Foresi, 1996]. Treatment of AR in asthmatic patients has also been shown to decrease asthma-related emergency room visits and hospitalizations. A large, retrospective cohort study involving approximately 5000 subjects with allergic asthma showed that asthma related events requiring emergency room visits or hospitalizations occurred more often in those not receiving treatment for AR compared with those receiving regular treatment (6.6% vs. 1.3%) [Crystal-Peters, 2002]. Another retrospective cohort study performed in 13,844 asthmatics over the age of 5 concluded that patients who received intranasal corticosteroids had a reduced risk for emergency department visit compared to those who did not receive this treatment [Adams, 2002]. An important therapeutic issue under debate is allergen immunotherapy, as several studies have shown that apart from treating AR symptoms, immunotherapy may also decrease the development of asthma in children and adults. Immunotherapy can alter the atopic phenotype by restoring the normal equilibrium between Th1 and Th2 lymphocytes [Moller, 2002]. In one study, patients with seasonal AR but no asthma were randomized to receive either immunotherapy or placebo and followed for 3 years. Although sputum eosinophils and bronchial hyperresponsiveness to methacholine did not change, immunotherapy appeared to prevent progression to asthma (14% in immunotherapy group vs. 47% in placebo group) [Polosa, 2004]. The Preventive Allergy Treatment (PAT) study in children who received specific immunotherapy for grass and/or birch pollen or no immunotherapy for 3 years, showed significantly less asthma in the immunotherapy group two years after the end of treatment [Niggemann, 2006]. Patients with AR should be evaluated for asthma periodically by good history taking, physical examination, and pulmonary function testing so that early intervention can be started when asthma is detected. However, all patients with asthma should always be examined and aggressively treated for concomitant AR. A systemic approach using medications that treat both rhinitis and asthma, including corticosteroids

(intranasal and inhaled), leukotriene receptor antagonists, immunotherapy, and immunomodulation, is advocated by many physicians. In detail, the intranasal treatment of rhinitis using corticosteroids was found to improve asthma and there is strong evidence to support this as first-line treatment. Drugs administered by the oral route may have an effect on nasal and bronchial symptoms. Oral H1 antihistamines are routine treatment for AR. Although studies have found some effect on asthma symptoms at the recommended dose in the treatment of seasonal asthma, these drugs are not recommended for the treatment of asthma [Baena-Cagnani, 2003; Van-Ganse, 1997]. Oral administration of leukotriene receptor antagonists (montelukast) has been shown to be effective in the maintenance treatment of asthma and to relieve symptoms of seasonal allergies [Meltzer, 2000]. While other allergy treatments (such as antihistamines or corticosteroids) treat only the symptoms of allergic disease, immunotherapy is the only available treatment that can modify the natural course of allergic disease, by reducing sensitivity to allergens. A three-to-five-year individually tailored regimen of injections may result in long-term benefits [Durham, 1999]. Allergen-specific immunotherapy based on the allergen sensitization rather than on the disease itself, is particularly likely to be successful if it begins early in life or soon after the allergy develops for the first time. Recently a sublingual immunotherapy tablet (Grazax) was approved, containing a grass pollen extract, which is similarly effective with injection immunotherapy, with few side effects. This form of immunotherapy can also be used by asthmatic patients who are at high risk for injection-based desensitization [Nasser, 2008; Durham, 2011]. Finally, the anti-IgE antibody, omalizumab, has been shown to be effective in patients with seasonal and perennial allergic rhinitis and moderate-to-severe allergic asthma [Casale, 2001; Corren, 2003].

6. Rhinitis and asthma: A continuum of disease?

The pathology of rhinitis and asthma are similar and the inflammation present in the lungs can also be identified in the nose, even in patients without clinical rhinitis. A similar phenomenon, of bronchial inflammation in rhinitis patients without asthma has also been observed. Inflammatory infiltration, characterized by the presence of eosinophils and CD4+ T cells, was similar in the nasal mucosa of rhinitis patients regardless of the presence of asthma or the allergic status of the patient [Lambrou, 2007]. In another study, asthmatic patients without nasal symptoms exhibited eosinophilic inflammation in the nose [Gaga, 2000]. Djukanovic and colleagues compared biopsies from atopic asthmatics and atopic non-asthmatics and found that atopic non-asthmatics had basement membrane thickening and eosinophilic inflammation resembling asthma. They reported a continuum of severity, with atopic non-asthmatics having milder inflammation and basement membrane thickening compared to atopic asthmatics [Djukanovic, 1992]. Another study in non-asthmatic patients with seasonal AR analyzed bronchial biopsies in and out of pollen season. The results showed that pollen exposure leaded to increased expression of IL-5, increased lymphocytes and eosinophils in the bronchial mucosa [Chakir, 2000]. These results suggest that atopy in general is associated with airway inflammation and that the clinical picture is determined by the severity of inflammation at different airway sites. Several theories have been proposed to explain the links between the upper and lower airways. Proposed mechanisms for the close association between the nasal and bronchial airways include (1) the

nasobronchial neural reflex, inducing bronchial obstruction during allergen-specific challenge of the nose [Corren, 1992], (2) pulmonary aspiration of inflammatory material from the nose [Huxley, 1978], (3) loss of protective function of the nose, and (4) allergy as a systemic disease. Mouth breathing caused by nasal obstruction might also be a contributing factor. Regarding the nasobronchial reflex, studies showing bronchoconstriction after nasal exposure to dry, cold air and increased bronchial responsiveness following nasal allergen provocation have long supported this theory [Fontanari, 1997; Braunstahl, 2001; Corren, 1992]. However, there have been studies showing inconsistent results and contradicting this hypothesis [Schumacher, 1986]. Direct drainage of inflammatory or infected material from the nose to the lungs had been considered in the past a straightforward mechanism for inflammatory interaction between the nose and lungs. Aspiration of nasal secretions can occur, especially during sleep and in impaired individuals. However, studies using radiolabeled substances have not shown nasal material draining into the bronchial airways in patients with increased bronchial responsiveness [Bardin, 1990].

7. Microsatellite DNA instability in allergic rhinitis and asthma

Genomic microsatellites (MS) are repetitions of simple 1-6 base pairs nucleotide sequences, present in both coding and non-coding regions of the chromosome. MS are characterized by high levels of polymorphism and although they are mostly considered as evolutionary neutral DNA markers, a small part seems to play significant role in biological phenomena such as gene transcription, translation and other [Samara, 2006]. Genomic MS are associated with high mutational rates, as compared with the rates of mutation at coding chromosome regions [Metzgar, 2000]. The most important genetic alterations in microsatellite markers include microsatellite instability (MSI), which occurs due to frequent errors that appear during the replication of short nucleotide repeats, and loss of heterozygosity (LOH), meaning the loss of genetic material in one allele [De la Chapelle, 2003]. With the use of polymerase chain reaction technology, MS DNA has been converted into a highly versatile genetic marker. Both MSI and LOH have been initially reported in a number of human malignancies and then detected in various benign airway diseases, including chronic obstructive pulmonary disease (COPD), asthma and pulmonary fibrosis [Siafakas, 1999; Paraskakis, 2003; Vassilakis, 2000]. Therefore, MSI and LOH have been proposed as important genetic screening tools. These genetic alterations were successfully detected in sputum cells of patients with asthma, so given the very close relationship between AR and asthma the authors investigated the presence of LOH and/or MI in nasal cytology samples of patients with AR. Nasal brush samples and peripheral blood from 20 patients with allergic rhinitis were analyzed. DNA was extracted and analyzed for MSI and LOH using microsatellite markers D16S289, D4S2394, D4S1651, DXS8039, D3S3606, and D2S2113, harboring potential susceptibility genes for allergic rhinitis and atopy. Microsatellite analysis was also performed in non-atopic control subjects. No MSI and/or LOH were noted in either the allergic rhinitis or the control group. Although MSI and LOH are detectable phenomena in sputum samples of patients with asthma, this seems not to be the case for nasal cytology samples of patients with allergic rhinitis. As already mentioned, remodeling patterns in nasal mucosa of subjects with AR are rather limited and epithelial disruption and desquamation is a feature of bronchial epithelium in asthma and is less marked in the

nasal epithelium of patients with rhinitis. Such differences in remodeling between the bronchial and nasal mucosa could be related to the smooth muscle cells interacting with the epithelium and mesenchymal cells. Therefore it makes sense that genetic alterations such as LOH and/or MSI that possibly contribute to the remodeling of the airways would be absent in AR where this phenomenon is far less extensive. Further studies using additional microsatellite markers are needed in order to exclude the presence of LOH and/or MSI in AR [Karatzanis, Am J Rhinol, 2007]. In support of the theory that MSI is a specific finding for the target organ of asthma, i.e. the lungs, despite the fact that inflammation coexists in the nasal mucosa of asthmatic patients, we studied COPD patients and assessed the presence of MSI in nasal cytological samples comparing the results with sputum samples of the same individuals [Karatzanis, Oncol Rep, 2007]. Although MSI was detected in the sputum samples of 7 COPD patients (35%), no instability was found in the nasal cytological samples of the same patients. On the other hand, MSI was successfully detected in nasal samples of patients with nasal polyposis [Karatzanis, 2009]. These studies support the hypothesis that MSI in certain chromosomal loci is not only disease specific as has been previously reported, but is also specific for the target organ of COPD or asthma, i.e. the lung. Microsatellite DNA could have a functional protective role in "shielding" DNA from environmental hazards, as previously hypothesized [Martin, 2005], which is lost through genetic alterations that take place specifically in the lower airways.

8. Conclusion

The relationship between AR and asthma is strongly supported by genetic, epidemiologic, pathophysiologic, and clinical evidence. The one-airway theory underlines the close interaction between upper and lower airways. The majority of asthmatic patients have AR. Both diseases exhibit an array of atopic manifestations all involving IgE-mediated responses leading to release of inflammatory mediators into the nasal and bronchial systems. Genetic predisposition, organ susceptibility, and breathing patterns are likely to be involved in the development of bronchial symptoms in patients with rhinosinusitis. Furthermore, systemic inflammation induced from either the upper or lower airways is postulated to elicit the involvement of both areas. In patients with rhinitis, it is essential to evaluate for asthma, sinusitis, atopic dermatitis, and food allergy as early as possible so that allergen avoidance, diagnostic, and therapeutic approaches can be coordinated. Treatment of allergic rhinitis seems to delay or prevent development of asthma in children. The full appreciation of involvement of upper and lower airway disease in one patient can only be achieved in a multidisciplinary clinical setting, involving doctors being able to examine and interpret clinical abnormalities of upper and lower airways.

9. References

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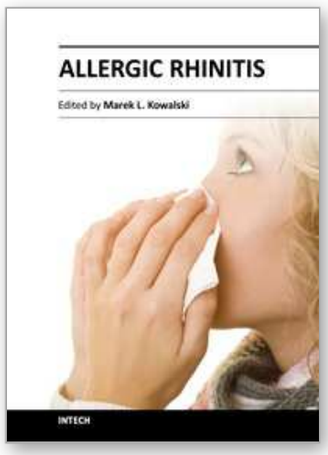

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Allergic rhinitis, while troublesome for a patient, may be also a challenge for the physician. That is why physicians must still learn more on the pathophysiology, clinical spectrum and novel diagnostic and therapeutic approaches to the disease. The chapters of this volume address a variety of important topics related to allergic rhinitis. They begin with a description of innovative translational approaches allowing for unification of animal and human models. Contributing authors provide up-to-date reviews of clinical aspects of allergic rhinitis in children, its association with bronchial asthma and other co-morbid conditions. They also discuss the impact of allergic rhinitis on sleep and sports. Together with articles on diagnostic approaches as well as novel treatments, the book offers a comprehensive and stimulating review of the topic. May this book find a wide readership among allergists and other physicians interested in allergic disease, and also among pediatricians, general practitioners and other specialists who increasingly have to deal with this seemingly benign, but sometimes extremely troublesome, disease.

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