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The Impact of Allergic Rhinitis on Asthma: Current View

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1. Introduction

Although allergic rhinitis and asthma have been assessed and treated as separate diseases, they often occur together. The connection between asthma and rhinitis is not a new discovery. This association has been recognized since earlier times. In the second century, Galen hypothesized that sinonasal disease caused lung disease through a direct anatomic connection. But, the nature of the link between the nose and the lung has been poorly understood until recent years (McFadden, 1986). Because the prevalence rates of rhinitis and asthma, as with all allergic diseases, are increasing worldwide, there is a growing interest in the interaction between upper and lower airways (Bousquet et al.,ARIA Workshop Group. World Health Organization, 2001).

Allergic rhinitis (AR) is the most common atopic disease all over the world affecting almost 10% to 30% of population (Berger, 2003; Settipane, 2003). Although it generally is not considered a severe disorder, the socioeconomic costs of AR are substantial . It adversely affects quality of life of the patients, work productivity and school performance as well as increasing health care costs (Bachert et al., 2002; Meltzer et al., 2004). Patients who have asthma and rhinitis tend to have more severe disease with higher treatment costs. Treatment of rhinitis may improve asthma control, and early treatment of allergies may prevent the development of asthma (Marple, 2010).

The connection between upper and lower airways has become a topic of great interest over the past few decades. It is now well established that rhinitis and asthma frequently co-exist, with approximately 20-50% of AR patients have concomitant asthma and over the 80% of asthmatics have nasal symptoms (Bousquet et al., 2003; Braunstahl & Fokkens, 2003).

During this time of period, a body of evidence concerning the relationship between allergic rhinitis and asthma lead to the concept of unified airways or "one airway one disease". Recent advances in the understanding and knowledge of the underlying mechanisms has been integrated into the "Allergic rhinitis and its impact on asthma" international report (Bousquet et al., ARIA Workshop, 2001). This document have been provided an comprehensive overview of current knowledge on allergic rhinitis and asthma, and evidence-based guidelines for the treatment. Neverthless not all patients with rhinitis present with asthma, the reason why are unknown. The "united airway disease" hypothesis proposes that upper and lower airway disease are both manifestations of a single inflammatory process of entire respiratory tract (Togias, 2003).

2. Epidemiologic evidences

Several cross-sectional studies have demonstrated that allergic rhinitis, rhinosinusitis and asthma frequently coexist in the same patients, despite some methodologic limitations (Leynaert et al., 2000). In fact, allergic rhinitis is a ubiquitous disorder in patients with asthma. Because the prevalence of allergic rhinitis among patients with asthma is as high as 90% when the diagnosis of rhinitis was made by using strict diagnostic criteria. (Kapsali et al.,1997). The prevalence of allergic rhinitis among patients with asthma is as much as 80% which is significantly higher than the 20% prevalence rate in the general population. However, up to 40% of patients with allergic rhinitis suffer from asthma symptoms but only 5% to 10% of the general population (Danielsson & Jessen, 1997).

The Copenhagen Allergy Study investigated the frequency of asthma and rhinitis related to exposure to pollen, animal dander or mites. For people with pollen allergy, 41% of those with pollen-related rhinitis also had pollen-related asthma. Pollen-related asthma was almost not present (0.1%) in those without pollen-related rhinitis (Linneberg et al., 2001). Most patients with asthma have complaints of seasonal or perennial allergic rhinitis. It has been shown however, that perennial rhinitis is a risk factor for asthma, independent of allergy. By investigating cross-sectional data from the European Community Respiratory Health Survey. Leynaert et al found the adjusted odds ratios for the association between perennial rhinitis and asthma to be 8.1 among atopic and 11.6 among nonatopic subjects 20 to 44 years old. (Leynaert et al.,1999). Similarly, Guerra et al reported that the presence of rhinitis had a strong predictive value for the adult-onset asthma in both atopic and nonatopic patients regarding to skin test responses . In their study, there was a tendency of more stronger in the group of subjects with high total IgE levels (Guerra et al., 2002).

3. Etiopathogenesis

Allergic disorders such as allergic rhinitis and asthma, have a multifactorial origin. Both diseases are characterized by chronic airway inflammation based on common genetic and environmental factors. Rhinitis and asthma are often co-exist, and they share common causative risk factors including genetic such as atopy, and environmental exposure. Same triggers that provoke the diseases of the nose and the lungs contribute to the development of the allergic airway syndrome, and comprise inhalant allergens, viral infection, cold-dry air, tobacco smoke and air pollution (Bachert et al., 2004; Braunstahl, 2005; Slavin, 2008).

The inflammation is a central component of both conditions, in which eosinophils, mast cells and T-lymphocytes are predominant effector cells. As antigen-presenting cells, dendritic cells form a network that is localized within the epithelium and submucosa of the entire respiratory mucosa, capture allergens, break them into allergenic peptides, and migrate to lymph nodes, where they present them to naive CD4+ T lymphocytes. After sensitization process and production of allergen specific IgE antibodies by B cells, their binding to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils, rendering them "sensitized". Within minutes of contact of sensitized individuals with allergens, the IgE-allergen interaction takes place, leading to mast cell and basophil degranulation and the release of preformed mediators such as histamine and tryptase, and the *de novo* generation of other mediators, including cysteinyl leukotrienes (CysLTs) and prostaglandins, some of which induce the early-phase symptoms. The late-phase response is characterized by the recruitment and activation of inflammatory cells like eosinophils, basophils and T cells into the mucosa of end-organ. This infiltration of inflammatory cells can also be orchestrated by

T-helper type 2 (Th2) cells within the local microenvironment. It is likely that cell migration is due to the chemokines and cytokines released by the primary effector cells acutely and over several hours after allergen exposure leading to chronic on-going inflammation and the development of hyperresponsiveness (Rimmer & Ruhno, 2006; Sin & Togias, 2011).

The natural course of atopic disorders is called the "atopic march". It has been suggested that atopic dermatitis is a starting point for subsequent allergic disease according to this theory (Spergel, 2005). The German Multicenter Atopy study evaluated the atopic march in 1314 children during a 7-year study period. The authors found that 46% of children with severe atopic dermatitis had an increased risk of early wheezing compared to patients with mild atopic dermatitis (32%) (Lau et al.,2002). However, another study of Illi S et al was found to be not completely consistent with the hypothesis in which atopic dermatitis preceded wheezing in 56% whereas wheezing preceded atopic dermatitis in 33% (Illi et al.,2004). Furthermore, the presence of BHR and rhinitis or both for the development of clinical asthma has traditionally been interpreted as the progression of a common airway diseases because they are associated with atopic background.

Yet, the question remains as to why some individuals only manifest symptoms of rhinitis and not asthma. The hypothesis would be that those patients may still be part of the continuum, but have a milder form of the disease. If so, not only are their lower airways less affected (no asthma), but their upper airways should be less severe as well (Pawankar, 2006). In supporting this hypothesis, Hanes et al, have reported that patients with AR and concomitant asthma showed more severe nasal symptoms when they were exposed to cold-dry air than if they had AR alone (Hanes et al., 2006).

4. Clinical aspects

Asthma and rhinitis also represent the two ends of the clinical spectrum in the respiratory tract in which have wide range of changing severity. Allergic rhinitis alone without bronchial hyperresponsiveness is a mildest form of the spectrum (Togias, 2003). However, from previous studies also known that patients with rhinitis and no clinical evidence of asthma may have BHR to inhaled allergens and chemical or physical stimulants (Ramsdale, et al.,1985). Some individuals with allergic rhinitis exhibit only seasonal lung symptoms. This patients have been shown increased bronchial reactivity during the natural exposure or experimental setting to allergen and also nonspecific stimuli as well which may be thought as subclinical asthma (Boulet et al., 1989). Therefore, presence of BHR accompanying allergic or non-allergic rhinitis is considered as high risk factor for onset of asthma on follow-up. But, the factors that determine the progression of rhinitis to asthma are not yet clear.

The effect of rhinitis on the onset of asthma has been investigated in longitudinal studies. The one study of the Settipane et al, which had a 23-year follow-up, demonstrated that allergic rhinitis at inclusion resulted in a 3-fold risk of asthma development compared to the group without rhinitis (Settipane et al., 1994). Similarly, patients aged 18 to 45 years with hay fever have been shown to be at increased risk for asthma in a prospective cohort study in Finland (Huovinen et al., 1999).

Patients with rhinitis have been reported three times more likely to develop asthma than healthy control subjects. Therefore, it is suggested that rhinitis is an important risk factor for the development of asthma, especially when bronchial hyperresponsiveness (BHR) is present.

One of the main clinical features of asthma is an increase in non-specific airway hyperresponsiveness to methacholine or histamine. However, BHR can be present in some

patients with allergic rhinitis without clinical evidence of asthma when exposed to an allergen to which they were sensitized (Boulay & Boulet, 2003). However, which factors determine BHR in these subjects are clearly unknown. The development of BHR can depend on duration of an inflammatory process, such as the one that has been described in the lower airways of adult subjects with allergic rhinitis, or on other factors. BHR seems to reflect not only the airway inflammation but also the remodelling process. (Foresi et al., 1997; Polosa et al., 2000).

BHR among patients with hay fever has been shown to increase during the pollen season and to be predictive of the onset of lower airway symptoms (Braman et al., 1987; Madonini et al., 1987). In a study of Prieto et al, airway responsiveness to either methacholine or adenosine monophosphate was found significantly increased in patients with allergic rhinitis alone during the season compared with out of the pollen season. In addition, BHR in the asthmatic range was detected during the season in these subjects (Prieto et al., 2002). A recent paper by Sin et al. showed that in contrast to the population with both allergic rhinitis and asthma, patients with seasonal allergic rhinitis alone did not show a higher degree of airway hyperresponsiveness to exercise challenge test when compared to the methacholine challenge test during the pollen season (Sin et al., 2009).

Furthermore, Ciprandi et al, evaluated patients with perennial allergic rhinitis symptoms alone. The authors observed that 54 patients out of 100 showed positive methacholine challenge test and impairment of spirometric parameters especially reduced forced expiratory flow at 25 and 75% of pulmonary volume (FEF_{25-75}) values as a sensitive measure of lower airways (Ciprandi et al., 2004). A study of patients with allergic rhinitis showed impaired lung function. A lack of bronchodilator response to deep inhalation is a characteristic physiological abnormality of asthmatic patients. People with rhinitis had blunted response to a deep inhalation suggesting altered airway smooth muscle function (Skloot & Togias, 2003).

It has also been shown that BHR was associated with longer duration of AR and more severe nasal inflammation in the absence of asthma symptoms. Based on these data, the current concept is that AR precedes asthma in most patients, and worsening of one disease negatively affects the course of asthma. It has been postulated that patients with asthma and broad extent symptoms of rhinitis may have more severe asthma than those asthmatic patients who have minimal or no rhinitis (DREAMS study). From this point of view, it has been suggested that the severity of rhinitis and asthma follows a parallel track in correlation with the overall severity of the chronic allergic respiratory syndrome that allows for cross-talk between the upper and lower airways (Togias, 2003).

Allergic rhinitis may also be contributing factor in 25% to 30% of patients with acute maxillary sinusitis and in as many as 60% to 80% of patients with chronic sinusitis (Spector, 1997). At least, allergic rhinitis is associated with, and probably a predisposing factor in the development of rhinosinusitis (Meltzer et al., 2004). Despite the pathophysiologic link between allergic rhinitis and asthma have been well-studied, understanding of paranasal sinus diseases and its possible relationship with asthma still remain largely unclear. Chronic upper airway diseases include allergic rhinitis, non-allergic rhinitis (NAR), chronic rhinosinusitis (CRS) with and without nasal polyposis, and occupational rhinitis. They are commonly associated with asthma, and increase the complexity of management and costs Bousquet et al., 2009). The overall prevalence of CRS have been reported 10.9% in Europe and it was found to be more common in smokers.

In children, nasal sinus disease may lead to less asthma control. Peroni et al. studied the CT findings in children with severe asthma. They concluded that severe asthma patients appear

to have the most relevant abnormalities on CT scanning of the paranasal sinuses (Peroni et al., 2007).

Co-morbidity of other upper airway diseases including chronic rhinosinusitis with or without nasal polyps have also been linked to asthma severity. Many studies have reported that the severity of nasal and sinus disease parallel that of the lower airway disease (Pearlman et al., 2009; Ponte et al., 2008). On the other hand, the presence of nasal polyposis accompanying chronic rhinosinusitis and the duration of diseases were found to be correlated with extensive paranasal sinus computed tomography findings, and were related to the severity of asthma in adults (Dursun et al., 2006).

Sinus disease and lower airway comorbidity often present as severe clinical symptoms of the diseases such as nasal polyps, aspirin-exacerbated respiratory disease (AERD), and late-onset severe intrinsic asthma. However, many patients with aspirin hypersensitivity appear with SCUAD (extensive nasal polyposis and anosmia) and accompanying severe asthma (Bousquet et al., 2009).

AERD is a clinical syndrome combining from nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma and sensitivity to aspirin and other non-steroidal anti-inflammatory drugs that inhibits cyclooxygenase-1 (COX-1) enzymes. Its prevalence rises to 10-20% of asthmatics and up to 30-40% in those asthmatics with nasal polyposis despite occurring in 0.3-0.9% of the general population. Asthma may precede the sinonasal disease or develop later. Patients with AERD suffer from frequent attacks of upper and lower airway reactions such as nasal congestion with anosmi, rhinorrhea, progression to pansinusitis and nasal polyps, and also bronchospasm (Lee et al., 2011). Nasal polyps are consistently associated with severe asthma. It has been reported that patients with nasal polyposis and asthma have the highest rates of exacerbation and hospital admissions (Ceylan et al., 2007).

In fact, most severe forms of both upper and lower airway disease may occur in nonatopic patients. AERD develops according to a pattern, characterized by a sequence of symptoms. First, persistent rhinitis, appearing at a mean age of 29 years, then asthma, aspirin intolerance, and finally nasal polyposis. In half of the patients, asthma is severe, and steroid dependent (Szczeklik et al., 2000).

5. Proposed mechanisms for the interaction between upper and lower airways

The mechanisms by which allergic rhinitis may be a risk factor for asthma are not entirely understood, although a few studies have addressed this question. It seems that allergic rhinitis and asthma result from similar inflammatory processes induced by allergens in the upper as well as in the lower airways of sensitized subjects. The nose and lung should thus be seen as a continuum, with "information" travelling in both directions, rather than as two distinct compartments. In this regard, the concept of "united airways" has been proposed, and increasing numbers of studies have agreed with this model (Boulay & Boulet, 2003; Rimmer & Ruhno, 2006). The main difference between the upper and lower airways is that upper airway patency is largely influenced by vascular tone, whereas, in the lower airway, airflow is influenced predominantly by smooth muscle function. Despite some anatomical differences between asthma and rhinitis, they share common airway mucosa and epithelium with similar immunopathological features (Rowe-Jones, 1997). Both diseases are characterized by chronic inflammation of the entire respiratory mucosa and involve similar

inflammatory process. Many cells and cellular elements play a role in particular, mast cells, eosinophils, T lymphocytes (Th2, Tregulatory), macrophages and epithelial cells (Bourdin et al., 2009; KleinJan, et al, 2010; Sin & Togias, 2011). Several potential mechanisms have been proposed to explain the interaction between the nose and the lung. Among them, some strong evidences suggest that not only local or neural-vascular, but also systemic induction of inflammatory cells is involved in this relationship. Indeed, cells (Th2 effector cells), cytokines, chemokines and mediators from the upper airways are drained by the systemic circulation and can subequently affect tissues at a distance. In this regard, bidirectional relationship also exists between upper and lower airways. Although the precise mechanisms have not yet been elucidated in naso-bronchial cross-talk, there appear to be important links (Fasano, 2010; Togias, 2000, 2003).

One of them is that of a shift from nasal to mouth breathing due to the nasal congestion. In AR, loss of nasal warming, humidifying and filtering functions may result in an increased exposure of the lower airways to allergens and irritants. This condition may lead to inflammatory changes and an increase in BHR in susceptible subjects. As another possible explanations are the aspiration of nasal contents or secretions and the nasobronchial reflex (Alvarez et al., 2000; Togias, 1999). Today, most data suggest a systemic link between mucosal sites, involving bloodstream, bone marrow and the lymphoid tissues. Several studies using nasal allergen challenge models have demonstrated that patients with allergic rhinitis alone may have inflammatory changes within the lower airways such as increased sputum eosinophils which is suggestive as predictor of asthma (Braunstahl et al., 2001; Inal et al., 2008; Sin et al., 2002). In keeping with the united airways concept, it has been shown that provocation with relevant allergens of the nose induces lower airway inflammation. Indeed, Braunstahl et al., demonstrated that nasal allergen challenge results in an increase of eosinophils as well as increased expression of intercellular adhesion molecule-1 in both nasal and bronchial biopsies of allergic rhinitis patients without asthma. (Braunstahl et al., 2001a). In another study of these authors, a decrease in the mast cell numbers in the nose has been detected 24 h after segmental bronchoprovocation with allergen in nonasthmatic patients with allergic rhinitis, interpreted as a result of enhanced degranulation. At the same time, there was evidence for an influx of basophils from the blood into the nasal and bronchial mucosa. (Braunstahl et al.,2001b). Similarly, in patients with asthma, nasal biopsies showed eosinophilic inflammation, even in those who do not have symptoms of rhinitis. (Gaga et al., 2000).

As a similar phenomenon, segmental bronchial allergen challenge in nonasthmatic patients with allergic rhinitis induces increased numbers of nasal eosinophils, IL-5 expression in nasal epithelium and eotaxin-positive cells in nasal lamina propria (Braunstahl et al., 2000). Therofore, investigators concluded that the inflammatory response following allergen challenge is not restricted to a local effect. Systemic propogation of allergic inflammation from the nasal to the lower airway mucosa has been proposed to explain the rhinitis and asthma link (Togias, 1999, 2003). Local absorption of inflammatory mediators at the site of initial inflammation presumably leads to a more generalized systemic response involving mucosa-associated lymphoid-tissue and bone-marrow as well. (Braunstahl & Hellings, 2006).

Two parts of the systemic aspect are the systemic circulation and the nervous system. They probably include classical mediators of the acute allergic reaction, production of several cytokines and chemokines, the vascular endothelium and adhesion molecules, antigen-presenting dendritic cells and their interaction with T-lymphocytes, as well as a strong bone

marrow component. (Togias, 2004). Furthermore, local tissue factors, such as microbial stimuli and systemic inflammatory mechanisms appear to have a role in the clinical expression of the allergic airway diseases. Increasing evidence indicates a major involvement of airway epithelial cells in the pathogenesis of both rhinitis and asthma (Compalati et al., 2010).

Chronic airway inflammation has been considered an important hallmark in both asthma and rhinitis. However, collagen deposition to upper airways is not typically observed in the allergic rhinitis in contrast to the bronchi. Very few studies have investigated upper and lower airways simultaneously. Even increased basement membrane thickness together with eosinophilic inflammation was also shown in the bronchial mucosa of atopic nonasthmatics and allergic rhinitis alone (Chakir et al., 1996). In a publication by Ediger et al., authors reported that infiltration of inflammatory cells particularly eosinophils both in the nasal and the bronchial tissues obtained from same subjects do not remarkably differ between patients with nasal polyp alone without BHR and asthmatic patients with nasal polyp (Ediger et al., 2005).

Recent studies suggest that the *Staphylococcus aureus* enterotoxins (SAEs) may act as superantigens by amplifying eosinophilic inflammation and possibly inducing local IgE formation in severe persistent airway disease in AERD (Kowalski et al., 2011). Bachert et al also reported that within the group for chronic rhinosinusitis with nasal polyp, patients with Th_2-biased eosinophilic inflammation have increased risk of severe asthma development (Bachert et al., 2010). However, nasal tissue and bronchial biopsies reveal extensive eosinophilic infiltration and degranulated mast cells in patients with AERD. Furthermore, once the disease established, production of proinflammatory cytokines and Th_2 type cytokines (IL-2, IL-3, IL-4, IL-5, IL-13, GM-CSF) have been found to be increased. Most patients with AERD synthesize excessive amounts of leukotrienes even before the exposure the disease. Recent evidences showed high expression of transforming growth factor beta (TGF-β) and the deposition of collagen in CRS with or without nasal polyp (Stevenson et al., 2006). Furthermore, increased epithelial desquamation has also been detected in the lower airways of atopic subjects, even before the onset of clinical symptoms whereas no structural changes was found in the nasal mucosa of allergic patients despite the presence of inflammatory cells (Braunstahl et al., 2003). The reasons why remodeling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still unclear (Bousquet et al., 2004).

6. Therapeutic implications

AR, even though not a serious disease, is a clinically relevant while it may responsible for some complications and affects quality of life. In a number of retrospective database analyses, the severity of allergic rhinitis was demonstrated to be directly correlated with asthma severity. Those patients whose allergic rhinitis was mild or well controlled, had better asthma control. Therefore, this data suggest that effective treatment of one disease may improve the other (Henriksen & Wenzel, 1984; Ponte et al, 2008).

The study by Crystal-Peters et al. was a retrospective cohort design to evaluate the treatment effects of AR on asthma-related health care resource utilization. In their analysis, the risk of emergency room visit or hospitalization due to the acute asthma attacks was almost 50% lower for patients treated with nasal steroids or oral antihistamines compared to those who did not receive these drugs (Crystal-Peters et al., 2002). Moreover, another

studies have demonstrated that among patients with asthma and concomitant AR, those receiving therapy for AR have a significantly lower risk of subsequent asthma-related events than those not treated. (Bousquet et al., 2005; Corren et al., 2004).

In a study conducted by Shaaban et al, it has been shown that subjects with rhinitis sensitized to indoor allergens such as mites or cat, were probably at increased onset of BHR. The authors also reported that BHR remission was more frequent in patients with rhinitis treated by nasal steroids than in those not treated. (Shaaban et al., 2007).

Although rhinosinusitis plays an important role in initiating or exacerbating asthma, there is no concensus whether its treatment is effective on asthma control. Some authors considered rhinosinusitis as a trigger factor, whereas others support the idea of comorbidity. (Smart, 2006). In either case, rhinosinusitis has been shown to worsen the symptoms of asthma. Therefore, controlling upper airway infection, inflammation, and symptoms may also improve the asthma outcomes (Pawankar & Zernotti, 2009). Both medical therapy and sinus surgery has been found to have a positive impact on improvement of asthma. (Ragab et al., 2006).

In some cases, the presence of upper airway inflammation like sinus disease or nasal polyposis renders the clinical course of asthma more severe and treatment more cumbersome. Several studies demonstrated that appropriate treatment of sinonasal disease reduces lower airway symptomatology, and improves asthma control (Dixon, 2009). Management options for AERD are the standard medical and surgical interventions with complete avoidance of COX-1 inhibiting drugs or aspirin desensitization and continuously receiving aspirin drug (Lee et al., 2011). Patients mostly require long-term therapy with oral corticosteroids. Furthermore, leukotriene modifiers improve the control of asthma in patients using high dose inhaled corticosteroids (Bousquet et al., 2009).

Nasal therapy has a beneficial effect on bronchial hyperresponsiveness and airway inflammation. (Corren et al., 1992). In a recent study, the combination of intranasal and intrabronchial administration of corticosteroid preparation has been resulted in the highest reduction of blood eosinophil count and serum ECP, and better quality of life as well. (Nair et al.,2010). Scichilone et al., reported that in patients with allergic rhinitis and mild asthma, intranasal corticosteroids caused important fall in nasal eosinophils and effective asthma control associated with improvement in health- related quality of life. (Scichilone et al., 2011). However, although optimal medical treatment of allergic rhinitis is known to be a prerequisite for a good therapeutic result in asthma, it remains to be clarify whether early and timely introduction of drugs may prevent the progression to asthma. (Koh & Kim, 2003). Allergen specific immunotherapy has demonstrated benefit in allergic rhinitis and allergic asthma in appropriately selected patients. It may also prevent the subsequent development of asthma and new sensitizations in children. (Fiocchi & Fox, 2010; Pipet et al., 2009). Furthermore, patients with moderate to severe persistant allergic asthma has been observed to achieve significant additional clinical benefit for their symptoms of concomitant allergic rhinitis and improvement in quality of life after receiving Omalizumab, a recombinant, humanized, monoclonal anti-IgE antibody. (Humbert et al., 2009; Vignola et al., 2004).

Better understanding of mechanisms related to inflammation in the nose and the lung has lead to combined therapeutic approaches targeting both diseases. (Greenberger, 2008; Nathan, 2009). Current ARIA guidelines strongly encourage dual evaluation of these patients and given therapies. Therefore, the effectively treatment of upper airway disease can significantly improve established asthma outcomes as well as may prevent the future

development of asthma (Brozek et al., 2010). Consequently, a therapy that addresses the systemic aspects of AR is more beneficial than a therapy with only local effects because it improves both AR and concomitant inflammatory disorders that might be present. (Borish, 2003).

It should be emphasized that because upper and lower airway diseases commonly comorbid conditions, it is important to consider the respiratory system as an integrated unit. By increasing the awareness of sinonasal and lung involvement in any patient, appropriate diagnostic and therapeutic options will significantly improve the level of care among those different specialties or primary care physicians. (Krouse et al., 2007; Rimmer & Ruhno, 2006).

In conclusion, elegant studies confirm that sinonasal disorders are very crucial co-morbidities in people with asthma, and they should be treated with an integrated approach. Further investigations are needed to determine if early intervention of rhinitis and/or sinusitis could prevent or delay the onset of asthma.

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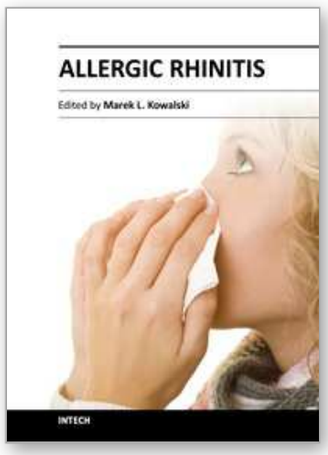
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Allergic rhinitis, while troublesome for a patient, may be also a challenge for the physician. That is why physicians must still learn more on the pathophysiology, clinical spectrum and novel diagnostic and therapeutic approaches to the disease. The 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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