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Review Article

An Association Between Upper and Lower Respiratory Tract Diseases

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Abstract

Both allergic rhinitis and bronchial asthma are inflammatory diseases in the respiratory tract. The upper and lower airways share many anatomical, physiological, and histological properties. A close relationship between allergic rhinitis and asthma has been established, and the "united airway disease hypothesis" proposes that upper and lower airway diseases are both manifestations of a single inflammatory process. Systemic therapies can resolve both diseases simultaneously. Although the association between asthma and allergic rhinitis has been examined extensively, the effect of other upper airway diseases on the onset and development of lower airway diseases is not fully understood. Rhinosinusitis is a common sinus infection, and recent studies have reported the possible role it plays on the pathogenesis of lower respiratory diseases. This article reviews the most up-to-date findings regarding the linkage and relationship between upper (rhinitis and rhinosinusitis) and lower (asthma and chronic obstructive pulmonary disease) airway diseases.

ABBREVIATIONS

CRSsNP: Chronic Rhinosinusitis without Nasal Polyposis; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; AFRS: Allergic Fungal Rhinosinusitis; Ig: Immunoglobulin; CT: Computed Tomography; IL: Interleukin; COPD: Chronic Obstructive Pulmonary Disease

INTRODUCTION

Rhinitis and rhinosinusitis are the most common diseases in the upper respiratory tract, and are frequently concomitant. Rhinitis has many causes; the types of chronic rhinitis are summarized in (Table 1) [1,2]. The most common type of chronic rhinitis is allergic rhinitis.An estimated 10% to 25% of the population has allergic rhinitis andits prevalence continues to increase worldwide [1]. Allergic rhinitis is the result of an immunoglobulin (Ig) E-mediated, type I hypersensitivity allergic reaction in response to the specific allergen [2-4]. Chronic rhinosinusitis is a persistent sinonasal inflammatory condition. General population-based surveys have shown that the incidence of chronic rhinosinusitis is 5 to 16% [5-7]. Chronic rhinosinusitis is defined by the presence for 12 weeks or longer of two or more of the following symptoms: (1) nasal blockage/obstruction/congestion, (2)nasal discharge (anterior/posterior nasal drip), (3) facial pain/pressure, and/or (4) reduction or loss of smell. These symptoms indicate inflammation in the nose and sinuses in addition to the presence of endoscopic findings (such as (1) nasal polyps, (2) mucopurulent discharge primarily from the middle meatus, and/or (3) oedema/mucosal obstruction primarily in the middle meatus) and/or mucosal changes within the ostiomeatal complex and/or sinuses by computed tomography [6]. Chronic rhinosinusitis is a heterogeneous disease and is subclassified into chronic rhinosinusitis without nasal polyposis (CRSsNP), chronic rhinosinusitis with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis (AFRS) [6, 8]. Rhinosinusitis is usually accompanied by rhinitis. Because there is an important interrelationship between ostiomeatal unit dysfunction and the swelling of the nasal mucosa, recent studies have adopted the term rhinosinusitis rather than sinusitis. In this review, rhinosinusitis and sinusitis are used synonymously.

The association between allergic rhinitis and asthma is well documented. Several studies have shown the possible relationship between chronic rhinosinusitis and lower respiratory conditions [2, 4, 9,10]. However, many specialists treat the upper respiratory tract (nose and paranasal sinus) and lung as separate entities [11]. Patients with chronic rhinosinusitis have obstructive lung function changes regardless of the presence of asthma or allergic sensitization (Figure 1). The purpose of this review is to summarize recent developments regarding the link existing between the upper and lower airways, and to emphasize the importance of identifying the condition of the lung during the treatment of upper respiratory tract diseases.

Asthma

Asthma is an inflammatory and sometimes life-threatening disease of the small airways of the lung. Because of the similarity of epidemiological, clinical, and immunological findings, allergic rhinitis and asthma are considered two clinical manifestations of a single disorder of the airways [2,12]. The impact of allergic rhinitis on asthma is of special concern, and the presence of allergic diseases, allergic rhinitis in particular, increases the probability of a diagnosis of asthma in patients with respiratory symptoms [13].

In epidemiological studies, between 19% and 38% of patients with allergic rhinitis also have asthma, and allergic rhinitis is present in 50% to 85% of asthmatic subjects [14-17]. Only particles smaller than 5 μm will enter the alveoli, and most particles of pollen are larger than that, with a size of approximately 22 to 100 μm. However, there are also smaller particles, such as ragweed pollen, with a size of 0.2 to 5.25 μm, and cat allergens, of which 40% are smaller than 5 μm [18]. These small allergens directly reach and affect all of the airway components, inducing allergic rhinitis and asthma.

Allergic rhinitis and asthma are usually treated by drugs such as glucocorticoids. Although these conventional therapies may be effective at reducing symptoms, they are limited to moderating disease progression because of their insufficient effect on the underlying, dysregulated immune response [19]. Allergen-specific immunotherapy is the only etiology-based treatment capable of disease modification [20]. Sublingual immunotherapy, which has been shown to be an effective treatment for airway allergies, is now being introduced on a large scale. Recent studies suggest that sublingual immunotherapy has the possibility of being the first choice for treatment of allergy including allergic rhinitis and asthma compared with medication and subcutaneous immunotherapy [21]. In addition, genetic engineering has been applied, and a recombinant DNA-derived humanized IgG monoclonal antibody that specifically binds to free human IgE (Omalizumab) has been reported to be highly effective in treating severe persistent asthma. Omalizumab is also statistically significantly associated with symptom relief, decreased rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis [22]. The effect of rhinitis other than allergic rhinitis on asthma has not been well examined.

Table 1: Classification of rhinitis [1,2].

Infectious rhinitis
Viral
Bacterial
Other infectious agents
Allergic rhinitis
Intermittent
Persistent
Occupationalrhinitis (allergic and non-allergic)
Intermittent
Persistent
Drug-induced rhinitis
Rhinitis medicamentosa
Oral contraceptives
Antihypertensive and cardiovascular agents
Aspirin / Non-steroidal anti-inflammatory Drugs (NSAIDs)
Other drugs
Hormonally induced rhinitis
Pregnancy
Menstrual cycle related
Atrophic rhinitis
Idiopathic rhinitis (Vasomotor rhinitis)
Irritant triggered
Cold air
Exercise
Undetermined or poorly defined triggers
Other causes
Food
Emotional
Gastroesophageal reflux
Non-allergic rhinitis with eosinophilia syndrome (NARES)

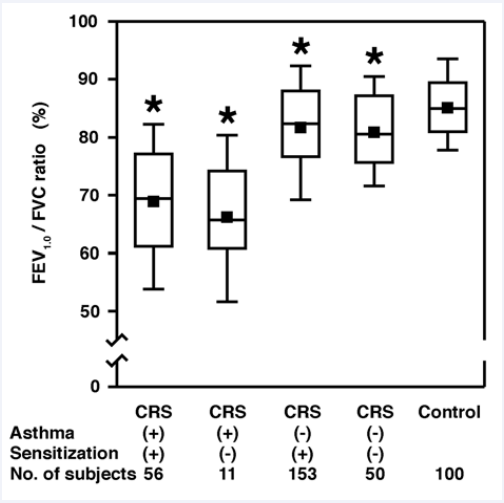

Figure 1 Pulmonary function (forced expiratory volume in one second / forced vital capacity ratio ($FEV_{1.0}$ / FVC ratio)) in patients with chronic rhinosinusitis (CRS). The chronic rhinosinusitis patients were divided into four groups based on the presence of asthma and sensitization to thirteen commonly inhaled allergens (*Dermatophagoides pteronyssinus*, *Felis domesticus*, *Canis familiaris*, *Dactylis glomerata*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Trichophyton rubrum*, *Alnus incana*, *Cupressus japonica*, *Chamaecyparis obtusa*, *Ambrosia elatior*, and *Artemisia vulgaris*). The chronic rhinosinusitis patients show significantly affected lung function. An asterisk (*) indicates $P<0.05$ by unpaired t-tests as compared with normal controls. A rectangle includes the range from the 25th to the 75th percentiles, a horizontal line indicates the median, and a vertical line indicates the range from the 10th to the 90th percentiles. The black square indicates the mean value.

Numerous studies have shown the relationship between asthma and chronic rhinosinusitis. However, differing opinions have also been published [23-25]. The co-existence of asthma and chronic rhinosinusitis is well recognized [26]. An early study showed that patients with mild-to-moderate asthma had an 88% incidence of abnormal sinus computed tomography (CT) findings, while patients with severe steroid-dependent asthma showed 100% abnormal sinus findings on CT-scans [27]. In addition, a

cohort study investigating the impact of self-reported sinusitis on lower airway disease showed that the participants with sinusitis had increased asthma exacerbations [28]. Medications that treat nasal diseases appear to be useful in improving asthma control and in reducing bronchial hypersensitivity [29]. Improvement of chronic rhinosinusitis by successful endoscopic sinus surgery can improve pulmonary dysfunction in patients with asthma [30].

CRSwNP has been considered as a Th2 cytokine-dependent disease, and shows a significant relationship to IgE production [31, 32]. A significant production of Th2 cytokines (Interleukin (IL)-5, IL-13) as well as chemokines, growth factors, and lipid mediators is observed in asthmatic patients [33]. Because of the complexity of the pathophysiology involved, the interaction between asthma and chronic rhinosinusitis has not been well understood [34-36]. Recent studies show that chronic rhinosinusitis patients without asthma and chronic obstructive pulmonary disease (COPD) have an asymptomatic decreased lung function, and the presence of Th2 cytokine in the nasal discharge positively correlates with the obstructive lung function changes [37, 38]. Although a specific causal relationship has not been established, particular attention is required for the onset or disease progression of asthma under the management of chronic rhinosinusitis.

COPD

COPD is a long-term lung disease frequently caused by smoking. It is characterized by a persistent blockage of airflow from the lungs. COPD has an extremely complicated pathogenesis, and multiple factors including inflammatory and/or immunological components of the respiratory system are responsible for the unpredictability of COPD exacerbations [39]. Recently, some studies have demonstrated the possible role that upper airway diseases play on the pathophysiology of COPD [40]. Hurst et al. reported that the nasal patency evaluated by acoustic rhinometry correlates significantly with the pulmonary airflow obstruction and disease severity in COPD. However, debate remains as to whether COPD is associated with sinonasal involvement [40-42].

A few studies were found in the literature concerning the link between rhinitis and COPD [43, 44]. Common colds can cause deteriorations of preexisting COPD, and rhinoviruses are the most frequently detected pathogens [45]. Rhinovirus infection induces numerous inflammatory cytokines and chemokines including IL-6, IL-8, IL-16, and chemokine (C-C motif) ligand 5 (CCL5), also known as regulated on activation, normal T-cell expressed, and secreted (RANTES), which may lead to increased lower airway inflammation [46]. Inflammatory cytokines and chemokines also have a critical effect in the onset and development of COPD [47]. Acute infectious rhinitis is associated with more than 40% of COPD exacerbations [45]. Although there is a high incidence of atopy in patients with COPD as confirmed by a skin prick test, and COPD patients have higher nasal levels of eotaxin, granulocyte-colony stimulating factor (G-CSF), and interferon gamma (IFN-γ), a large population-based epidemiologic survey shows that allergic rhinitis is not significantly associated with COPD [48-50]. In addition, a recent study with 3,471 subjects reported that non-allergic rhinitis (rhinitis without serum specific IgE) showed no significant association with COPD [51].

A possible relationship between chronic rhinosinusitis and COPD has been reported. Chronic rhinosinusitis was present in 53% of patients with COPD, and severe COPD patients have a higher Lund-Mackay staging score [52]. Another study shows that chronic rhinosinusitis is not strictly related to COPD severity, although the high prevalence of chronic rhinosinusitis in COPD is observed [53]. Post-nasal drip with an increased nasal concentration of IL-8 and higher nasal bacterial load likely causes COPD, and significant correlation between the degree of upper and lower airway inflammation in COPD patients has been reported [54]. Because the number of studies regarding the role of chronic rhinosinusitis on COPD is limited, a causal relationship between chronic rhinosinusitis and COPD has not been established.

DISCUSSION AND CONCLUSION

Distinctive remodeling of the upper airway has been reported in patients with chronic rhinosinusitis; the remodeling features are related to the inflammation patterns of chronic rhinosinusitis. Eosinophilic inflammation may contribute to the pronounced edema in eosinophilic CRSwNP. Hypoxia, possibly secondary to blockage of the drainage channel, may lead to neutrophilic inflammation with overproduction of TGF-β2 and subsequent fibrosis in CRSsNP and non-eosinophilic CRSwNP [55]. Obstructive lung function change due to remodeled airway structure is a characteristic feature of asthma and COPD [39]. Common molecular and cellular aspects of these diseases have been reported. A particular phenotype of chronic rhinosinusitis, allergic rhinitis, and asthma may share the pathogenesis. Although numerous clinical and basic findings of upper and lower airway diseases have been reported, the ideal management of united airway diseases has not been achieved. Several studies in the last decade showed a possible association between genetics and chronic rhinosinusitis [56]. Genes encoding the chloride ion transportchannel and human leukocyte antigens (*HLA*), as well as genes involved in innate and adaptive immune responses (*CD14*, *NOS*, *TLR2*, *IL-4*, *IL-13*, *IL-33*, *TNF*, and others), tissue remodeling (*MMP9*, *POSTN*, and others), and arachidonic acid metabolism (*LTC4S*, *PTGDR*, *PTGS2*, and others) may be linked to the onset and/or development of allergic rhinitis, chronic rhinosinusitis, and lower respiratory diseases [57-60]. One of the therapeutic applications of new technologies may be gene therapy using genetic engineering techniques. Molecular therapy is a promising treatment for airway diseases. The recombinant humanized anti-IgE antibody (Omalizumab) has a clinically significant effect in the treatment of patients with both allergic rhinitis and asthma [61]. Combining creative approaches with recent advances in these technologies may provide some novel therapeutic options for treating united airway diseases.

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