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Recent Developments in United Airways Disease

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The nose and lung are both part of the respiratory tract. Often the diseases affecting the nose and/or the bronchi are treated separately. However, in recent years, numerous studies have highlighted the fact that the respiratory system is a single entity and the concept of "united airway disease" has become more and more important. The unity of the respiratory tract is confirmed both from a morphological and from a functional point of view. Nevertheless, this concept is also confirmed for the respiratory immune system, innervation and vascularization interesting all along the tract, from the nose to the bronchioles. When treating rhinitis, it is often necessary to assess the presence of asthma. Patients with sinusitis should be evaluated for a possible concomitant asthma. Conversely, patients with asthma should always be evaluated for possible nasal disease. The medications that treat nasal diseases appear to be useful in improving control of asthma and in reducing bronchial hyperresponsiveness as well. Physicians should always keep these notions in mind, and evaluate and treat respiratory diseases taking into account the unity of the respiratory tract.

Key Words: Airways; allergic rhinitis; ARIA; asthma; rhinosinusitis; united airways

INTRODUCTION

The link existing between the upper and lower airways has been observed repeatedly in the past, but the concept of united airways disease (UAD) is a matter of recent years,[1] thanks to the increasingly detailed pathogenic knowledge acquired over the last 15 years. Nevertheless, in daily practice, the nose and lungs are treated as separate entities and by two different specialists.

Each portion of the respiratory tree has specific tasks, such as humidification, air filtration, warming, and perceiving perfumes and odors for the nose; phonation for the larynx; and gas exchange for the lungs. However, clinical signs and diseases affecting both nose and bronchi are often common, as asthma and rhinitis. In fact, nasal and bronchial diseases often coexist and Upper Respiratory Tract Infections (URTI) are capable of exacerbating asthma,[2] while rhinitis has been identified as an independent risk factor for asthma development.[3] The upper and lower respiratory tracts form a *continuum* and share many anatomical and histological properties and an important feature: the passage of air into and out of the lungs. In addition, the upper and lower airways also share a common susceptibility to different agents, such as allergens, infections, pollutants related to occupational exposures, certain drugs; and respond to these elements in a similar way. The surface of the whole tract is characterized by a ciliate epithelium with mucinous glands associated and by a dense network of vascularization and innervation.[4] Particularly considering innervation, it surely seems very similar all along the respiratory tract, supporting the hypothesis of the so-called sinu-nasal-bronchial reflex as a possible common pathogenetic mechanism.[5,6]

The natural progression of respiratory allergy commonly starts from the upper respiratory tract and later spreads to the lower tract.[7] Allergic patients suffer from a general inflammatory status interesting the whole respiratory tract and manifesting through several different diseases mainly affecting the nose, the paranasal sinuses and the bronchi.[8] Local inflammation may

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actually play a systemic role via soluble mediators that involve the bone marrow,[9] which responds in a rapid and specific way to nasal challenge, with an increased production of precursors and mature eosinophils.[10,11] Moreover, nasal allergen exposure in patients suffering from AR may rapidly lead to a significant pulmonary allergic inflammation, even subjects who don't have a history of asthma nor BHR.[12] It has been demonstrated that a segmental bronchial challenge may induce nasal symptoms and inflammation in patients suffering from AR, 24 hours after the test; on the other hand, even after a nasal challenge, a decline in respiratory function may be detected, 4-6 hours after the test.[13,14]

All these observations have therefore contributed to the genesis of the term UAD, and the respiratory tract is now considered as a single entity both morphologically and functionally.[15]

Anatomy of the respiratory tract

The respiratory tree is functionally divided between the conductive paths and the portion deputed for gas exchange. Anatomically, it is classically distinguished into nose, mouth, pharynx, larynx, trachea and bronchi, which, in turn, are dichotomically divided until the respiratory bronchioles. These lasts, with their air cells, correspond to the respiratory portion reserved for pulmonary gas exchange. Conventionally, the respiratory tree is divided into two parts: the upper airway and lower airway and the larynx is the portion that separates the two areas. The upper respiratory tract begins therefore with the nostrils and the mouth and ends with the larynx, while the lower tract goes from the larynx to the alveoli. The nasal cavity is limited by bones and divided into two areas by the nasal septum. These two portions form the anterior nasal passages or nostrils, and posteriorly they re join to form a single air cavity in the pharynx. A visible part, the vestibule, and an inner part, which represents the main portion of the nasal cavity, form the nose. In the main nasal cavity, three bones form the nasal choanae and they increase the inner surface of the nose, while reducing the lumen at the same time. This conformation allows a close contact between the inhaled air and the nasal mucosa, resulting in humidification and heating of the air. In addition, the turbulent flow of the air allows the deposition of particles on the nasal cavity, so that this area of the respiratory tract has an action of filtration as well.[16] The nasal sinuses, which communicate with the nasal cavity, are involved in thermal regulation of the inhaled air.[17]

After the nasal cavity, the pharynx communicates with the larynx, which is the organ of phonation, but it is also a valve that protects the airways and lungs from a possible passage of foreign bodies.[18] The larynx ends in the trachea, which is formed by regular cartilaginous rings without a back cartilaginous wall. This configuration allows the trachea both to prevent collapse in case of an abrupt rise in intrathoracic pressure and to decrease the pressure when it suddenly increases to efforts such as coughing. Distally, the trachea is divided into two bronchi, the right and the left one.

The main bronchi have a cartilage structure as well. They divide dichotomically into bronchioles, in successive generations. As the bronchi become smaller, even the cartilage becomes thinner until it disappears in the bronchioles. After the terminal bronchioles, there are the respiratory bronchioles and the air cells that constitute the area of the lungs deputed to gas exchange.

Reactions triggers

Several factors may trigger reflex airways reactions. Viruses and bacteria are responsible for infectious rhinitis, rhinosinusitis, bronchiolitis and pneumonia. They may even cause exacerbations in patients suffering from Chronic Obstructive Pulmunary Disease (COPD) and asthma.[19] Cigarette smoke and pollutants, atmospheric or professional, may damage the epithelium as well, and they may be responsible for a chronic inflammation such as chronic bronchitis and induce metaplasia and cancerous lesions in the upper and lower respiratory tract. Tobacco smoke is the most important risk factor of COPD,[20] cancer of the larynx, bronchial cancer, but also of rhinitis.[21] Inhalation of cadmium smoke from an occupational exposure to can lead to emphysema,[22] while exposure to asbestos can lead to cancer. These are just some examples of stimuli that can lead to a high or low respiratory morbidity. Air pollutants such as nitric dioxide, sulfuric dioxide or particles may be responsible for exacerbations of COPD.[23]

Allergens are potent stimuli of allergic rhinitis and asthma. The rates of indoor allergens such as dust mites or animal proteins, are highly correlated with asthma.[24] The rates of outdoor allergens such as pollen are more often associated with rhinitis.[25] Pollen particles are generally too large to penetrate the lower respiratory tract, but it has been shown that pollen grains can be found in bronchial secretions and lung parenchyma.[25] Asthma and rhinitis are hypersensitivity reactions, which can also be triggered by drugs such as beta-blockers or aspirin, cold dry air exposure, physical exercise or different professions.[26,27]

The molecular weight of particles and substances that lead to nasal reactions is higher in the nose than in the bronchi, because the nose acts as a filter that receives and modifies the composition of the air. However, in case of nasal obstruction, the inspired air, which penetrates the bronchi, is neither heated nor purified and can therefore damage the bronchial epithelium. An upper airways alteration may lead to clinical manifestations of nasal disease, but it may also lead to lower respiratory tract morbidities.[28] Particles are rapidly removed from the nasal lumen, thanks to the important vascularization, while the elimination of the same needs much more time in the lower respiratory tract. Low molecular weight antigens produce therefore much more intense inflammatory reactions in the bronchial district.

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Allergic rhinitis and asthma

Allergic rhinitis is considered a risk factor for developing asthma, but it is possible that this term is not totally correct in the sense that this condition may represent an early stage of UAD that can progress to full-blown asthma.[4]

Allergic rhinitis (AR) is the most common of all atopic diseases and it can develop at any age; nevertheless, most patients report the onset of symptoms before 30 years of age, during some of the most productive years of life.[29]

AR was initially subdivided on the basis of the time of exposure, into seasonal, perennial and occupational diseases. Since the publication of the Allergic Rhinitis and its Impact on Asthma (ARIA) project, the terms intermittent and persistent were introduced and a new grading of severity (mild and moderate/severe) was proposed too; with such a classification, the persistent type describes a distinct group with characteristics that differentiate them from intermittent allergic rhinitis.[30]

AR is now recognized to be characterized by more than the classic symptoms of sneezing, rhinorrhea, and nasal obstruction. In fact, it is well known that it is associated with impairments in how patients function in day-to-day life at home, at work, and in school.[30] Patients may also be bothered by sleep disorders, emotional problems, impairment in activities, and social functioning.[30]

Asthma is defined as a disease of reversible airway obstruction and is diagnosed by using measures of lung function and bronchial hyperreactivity.[31] Clinical manifestations include dry cough, expiratory wheezing, chest tightness and dyspnoea, which are intermittently triggered by allergens, infections and airways irritants.[32]

The natural history of asthma is still poorly characterized; however, we know that a small proportion of asthmatic patients have a most severe form that requires, despite new and improved inhalation therapies, a continuous and long-term treatment with oral corticosteroids to control symptoms.[33] Since difficult asthma is rare in childhood, when an asthma is difficult to treat and poorly controlled, a special evaluation should include the review of diagnosis with accurate lung function and the evaluation of possible comorbidities.

Allergic rhinitis (AR) is frequently associated with asthma and it often precedes bronchial hyper-reactivity.[4] Approximately 19%-38% of patients with AR have concomitant asthma and 30%-80% of asthmatics have AR, although these figures probably underestimate the phenomenon, as recent surveys found symptoms of rhinitis in 98.9% of allergic asthmatics and in 78.4% of non-allergic asthmatics.[34] A large proportion of patients with AR (up to 80% of cases) show bronchial hyperreactivity (BHR), even though they do not present any clinical sign of lung function impairment nor of asthma[35,36] and such a finding may represent a prognostic factor for further progression to asthma.[37] In fact, BHR, which is a paramount feature of asthma, may be considered as a strong risk factor for the onset of asthma in patients presenting with AR.[38,39]

Small airway disease (SAD), defined as a reduction in forced expiratory flow (FEF) at 25%-75% of the pulmonary volume and a normal spirometry, is suggested to be a marker of early allergic or inflammatory involvement of the small airways in subjects with allergic diseases and no asthma.[4] FEF25-75 seems to be significantly associated with BHR, and it has been proposed as an early marker of bronchial involvement in patients with AR who perceive only nasal symptoms.[40]

In those patients concomitantly presenting with both AR and asthma, a significantly higher number of aeroallergen sensitizations may be detected than in those without asthma, and patients suffering from perennial rhinitis present an increased risk to develop asthma.[41]

Rhinosinusitis and asthma

The coexistence of sinusitis and asthma, particularly in children, has been known for several years; the involvement of paranasal sinuses is considered to be very important for the development of lower respiratory tract diseases.[42,43] However, whether rhinosinusitis is actually a precipitating factor for bronchial asthma is still debated.[33] Rhinosinusitis and asthma seem to be two different expressions of a common pathological process, not always affected by allergy, in which eosinophils and the airway epithelium play a central role.[33] Recent progress in understanding the biology of airway disease has identified inflammation as the key to understand these diseases. Nevertheless, several other mechanisms that link the upper (nose, sinuses, larynx, pharynx, and trachea) and lower (bronchi and lungs) airway segments may be involved too.[44]

Rhinosinusitis is a common disease that may be present in the pediatric population and may influence the clinical course of asthma by a variety of mechanisms.[45] In facts, sinonasal pathology is recognized to be one of the most common comorbidity among asthmatic patients.[46] Symptoms include nasal congestion, nasal discharge, nasal purulence, postnasal drip, facial pressure, hyposmia, cough, fever, halitosis, dental pain, ear fullness, and headache. The diagnosis and management of sinusitis are often challenging, but generally unsatisfactory.[47]

The term sinusitis refers to the presence of inflammation within any of the four pairs of paranasal sinuses. The pathogenesis of this disease is poorly understood. The long-term consequences of chronic sinusitis may include lose of mucociliary clearance and of other physiologic mechanisms that normally maintain the relative sterility of the sinuses.[47]

In facts, rhinosinusitis coexists with asthma in 34%-50% of patients.[48] Nevertheless, in patients presenting with asthma, the incidence of concomitant rhinosinusitis rise up to 84%, especially during asthma exacerbations.[48] The observation that asthma and rhinosinusitis coexist in patients at a higher frequency than would be expected from the prevalence of each in the general population provides a strong connection between the up-

per and lower airways.[45] Sinonasal disease in asthmatics appears to differ somewhat from that of the general population and the temporal sequence of disease and parallel inflammatory pathways involved suggest that they may be progressive manifestations of a common disease process.[46] Precipitants of asthma are generally also precipitants of sinusitis, and, therefore, the association of sinusitis with asthma exacerbations may be an epiphenomenon.[47]

It is not clear whether rhinosinusitis is a direct trigger for asthma or if the two conditions are just manifestations of a common underlying process. Possible explanations for the observed association of rhinosinusitis and asthma may include the nasobronchial reflex, pharyngobronchial reflex, postnasal drainage of inflammatory mediators from the upper to lower airway, inhalation of dry, cold air and environmental pollutants, and the "shared pathogenesis" of rhinosinusitis and asthma.[31] Even the bone marrow may provide this link between the upper and lower airways in creating a common disease: blood eosinophil count is often increased in asthma and correlates with severity of asthma, while IL-5 may be a key cytokine for orchestrating the systemic interaction.[31,48]

Current evidence suggests that rhinosinusitis without either polyps or eosinophilic inflammation is a direct trigger for asthma, whereas rhinosinusitis with both polyps and eosinophilic inflammation shares underlying mechanisms with asthma.[32] There is also evidence that markers of bronchial inflammation, typically monitored in asthmatics, correlate with the severity of sinusitis.[49]

The two diseases are inflammatory processes in which eosinophils and the airway epithelium play a central role: eosinophils are thought to damage the epithelium by releasing cytokines and other pro-inflammatory proteins. The damaged epithelium then react by releasing cytokines and chemokines that further attract eosinophils, thus starting a vicious circle of actions and reactions that activates and sustains inflammation.[33]

Treating the nose and the lungs

Nasal and inhaled steroids

Nasal steroids are a great tool for controlling symptoms in patients with AR and treating patients suffering from rhinosinusitis. These drugs, especially when combined with inhaled steroids, are capable of reducing both bronchial hyper-reactivity in asthmatic patients and recurrence to the emergency department for exacerbation and hospitalization.[50,51]

Nowadays, treating rhinitis is essential to manage asthma symptoms as well, meaning that asthma and rhinitis, in some patients, may be controlled by the exclusive use of nasal medication.[52] The hypothesis that nasal inhalation of a corticosteroid can be effective both for rhinitis and asthma was examined with positive findings in several studies where budesonide had been nasally administered, resulting in both upper and lower airways deposition.[53] Alternatively, exhaling a budesonide inhaler through the nose results in a significant reduction in dose requirement of budesonide nasal spray in patients who have asthma with rhinitis.[54]

Nevertheless, the definition of a realistic extent of effect of nasal steroids on asthma control appears rather uncertain and further researches should be performed to evaluate the effects of intranasal corticosteroids on asthma control; a combination of intranasal and intrabronchial corticosteroids should continue to be used in clinical practice until more research is carried out.

Antihistamines

Antihistamines are very helpful in controlling symptoms of AR or of allergic rhino-conjunctivitis, mainly in association with nasal steroids. During the pollen season, antihistamine treatment reduces the symptoms of asthma.[55] Nevertheless, it is clear that they do not affect asthma, even though their beneficial action on the upper airway contributes to improve the overall management of the *one airway disease*.[56]

In children, the occurrence of respiratory infections and exacerbations of asthma may be reduced by continuous antihistamine treatment.[57,58]

Leukotriene receptor antagonists (LTRAs)

The purpose of prescribing an antileukotriene treatment in patients with both AR and asthma is to reduce the inflammation of both the nasal and bronchial mucosae, and to improve the total symptoms score of both conditions. Several studies have actually showed that LTRAs are effective in treating both the upper and lower airways in patients with asthma and AR.[59,60]

Specific immunotherapy

Specific immunotherapy, either sublingual or subcutaneous, is prescribed in patients suffering from AR or asthma or both. Such a treatment results in lower asthma symptoms and reduced use of medication during the second and third years of therapy, associated with a reduction in asthma development and in nonspecific BHR.[61] The apparent success of specific immunotherapy in children with AR in preventing the development of asthma and BHR provides a powerful argument supporting a common pathogenetic mechanism in allergic respiratory disease.[62]

Nevertheless, further investigations are needed in order to confirm the preventative role of specific immunotherapy.

CONCLUSIONS

The idea of a *one airway disease* is the key concept of the ARIA document, and has relevant implications for the diagnostic and therapeutic management of respiratory allergy. Several studies have shown that in patients with asthma who have a seasonal

rhinitis, an increase in bronchial hyper-reactivity may be outlined. There is also an infiltration of the bronchial mucosa by neutrophils. Furthermore, in patients with asthma and rhinitis, the treatment of rhinitis leads to an improvement of respiratory symptoms.

ARIA document has clearly underlined, throughout these last 10 years, the role of AR as a risk factor for asthma and suggests to always consider bronchial involvement in patients presenting with AR.[2] On the other hand, even the Global Initiative for Asthma (GINA) advises to evaluate asthmatic patients for nasal involvement as well.[63] In clinical practice, therefore, it should be now clear that, when evaluating a patient presenting with AR, doctors should perform respiratory function test or at least pose questions to evaluate a possible concomitant bronchial involvement; on the other hand, patients suffering from asthma should always receive a nasal treatment as well.

The role played by sinus disease in asthma is only partly understood, largely owing to deficits in the clinical classification and in basic knowledge of pathophysiological pathways. Nevertheless, it is now clear the existence of a causal relationship between sinusitis and asthma. If, on one hand, the treatment of sinusitis leads to a symptoms improvement in asthmatic patients, on the other hand, sinusitis seems to induce a worsening of asthma. Thus, it seems clear that rhinosinusitis and asthma represent a range of overlapping diseases with a similar pathophysiological mechanism, where chronic airway mucosal inflammation and remodeling are playing a critical and integrating role in these diseases.[48]

It can be suggested that rigorous treatment of comorbid factors, such as rhinosinusitis, could result in less asthma exacerbations, which will greatly improve the quality of life of these difficult-to-control patients with asthma.[64]

In general, there is a strong interaction between the upper and lower respiratory tract which may be due to a loss of power filtering and protection functions of the nose, an interaction of neurotransmitters or the spread of inflammation of the lower respiratory tract.[65-68] There is also an infiltration of the nasal mucosa by eosinophils in asthmatic patients without rhinitis and bronchial segmental challenge with allergen leads to an increase in nasal airways resistance. In general, therefore, not only URTI lead to lower airways inflammation, but even the other way is true. All these considerations reinforce the theory that there is one and unique respiratory system that reacts as a single body at the same time.

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