

Relationships of ocular allergy, nasal allergy, sinusitis and asthma: an anatomic, physiologic and immunopathologic continuum

Alergia ocular, rinite, sinusite e asma: um continuum anatômico, fisiológico e imunopatológico

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Abstract

Objective: Allergic rhinoconjunctivitis, sinusitis and asthma are common diseases and often coexist in an interdependent nature in the same patient. They have similar anatomic, physiologic and immunopathologic features and share the same immune inflammatory triggers and modes of treatment. Mast cells, Th2 cells, eosinophils, cytokines, IgE and other inflammatory constituents contribute to the mechanisms associated with the allergic responses that link these clinical disorders. This article reviews the studies linking these clinical entities and examines the evidence suggesting a continuum.

Data Sources: A MEDLINE search of the last 10 years was conducted.

Allergic rhinitis for example is frequently associated with bronchial hyperresponsiveness and this inter-relationship is evident from epidemiologic, pathophysiologic, and clinical studies which are reviewed in this article.

Results: The recognition of the continuum of similarly-involved pathologic features present in the allergic ocular, nasal and sinus network and the lungs has led to the introduction of new terms such as rhinosinusitis and allergic rhinobronchitis. Rhinitis is therefore a risk factor for the development of asthma.

Conclusions: Upper and lower allergic respiratory diseases constitute an important global health problem and a progressive increase in their frequency in the modern world has been seen in recent years. Recognition of their commonality as different manifestations of one disease entity will ultimately improve the diagnosis and management of patients with these common disorders.

Rev. bras. alerg. imunopatol. 2003; 26(3):89-94 rhinoconjunctivitis, rhinosinusitis, allergic rhinobronchitis, immunopathology, atopic inflammation, bronchial hyperresponsiveness.

Resumo

Objetivo: A rinoconjuntivite alérgica, a sinusite e a asma são doenças comuns que frequentemente coexistem em um mesmo paciente. Elas compartilham características anatômicas, fisiológicas e imunopatológicas. Apresentam, também, fatores precipitantes e terapêutica semelhantes. Os mastócitos, células Th2, eosinófilos, citocinas, moléculas de adesão, quimiocinas, IgE, e outros elementos pró-inflamatórios contribuem para o estabelecimento do quadro imunopatológico que integra este continuum atópico. Esta revisão examina criteriosamente esta complexa rede inflamatória integrada.

Métodos: Foi realizado um levantamento na Med-line, dos últimos dez anos, relativo aos trabalhos de epidemiologia, fisiopatologia, imunopatologia e terapêutica da conexão observada entre a conjuntivite alérgica, rinite, sinusite e asma.

Resultados: O reconhecimento deste continuum envolvendo as mucosas conjuntival, nasal, sinusal e os brônquios levou à introdução na literatura médica de novos termos: a rinossinusite e a rinobronquite alérgica. A rinite é modernamente considerada um fator de risco para o aparecimento e o agravamento da hiper-responsividade brônquica e conseqüentemente da asma clínica.

Conclusões: *As doenças respiratórias das vias aéreas superiores e inferiores estão interconectadas e a sua incidência mundial aumenta progressivamente. O tratamento integrado da rinite, conjuntivite, sinusite e asma, levando em consideração as suas semelhanças e diferenças, melhorará definitivamente a qualidade de vida dos pacientes atópicos.*

Rev. bras. alerg. imunopatol. 2003; 26(3):89-94 rinoconjuntivite, rinossinusite, rinobronquite alérgica, imunopatologia, inflamação atópica, hiperresponsividade brônquica.

Introduction

Allergic rhinitis, conjunctivitis, sinusitis and asthma are among the most common clinical entities which present to the allergist-immunologist. Although at first impression they appear to be separate and distinct entities, there is increasing evidence to suggest that they may represent different manifestations of a single disease. Moreover, coexistent and interdependent anatomic, physiologic and immunopathologic features and mechanisms underlie these clinical disorders¹. For example, they not only have common immune inflammatory triggers and similar therapeutic approaches, but also epidemiologic and clinical studies have provided further evidence for an interrelationship. Histologically, the upper and lower airways are lined, and linked, by a common respiratory epithelium. Physiologically, they are joined by the nasobronchial reflex, pathologically, by similar early- and late-phase allergic responses throughout the airways and immunologically by a common systemic and mucosal immunologic response to aeroallergens characterized by IgE antibody production. Uncontrolled rhinitis may be associated with worsening of coexisting asthma, and effective treatment of allergic rhinitis usually improves the associated asthma. The key to managing both entities, therefore, is prevention and relief of chronic allergic inflammatory changes in both the upper and lower airways. A new term "allergic rhinobronchitis" has been proposed to describe this relationship². Allergic rhinitis and associated conditions such as chronic sinusitis and allergic asthma should be seen as a single condition affecting the entire airways that have a common IgE-mediated hypersensitivity response to a wide range of specific inhalant allergens³. Therefore a substantial proportion of patients with allergic asthma have comorbid allergic rhinitis, conjunctivitis and rhinosinusitis⁴.

Asthma, rhinosinusitis and rhinoconjunctivitis: evidence of linked immunopathogenesis

Sinusitis is a common chronic illness with a marked health care impact. Chronic hyperplastic sinusitis with nasal polyposis present significant inflammation which includes the presence of eosinophils and IL-5 producing T lymphocytes⁵. The coexistence of asthma and rhinosinusitis has been noted for more than 70 years⁶. Compiling evidence supports the relationship of sinusitis and asthma. Whether rhinosinusitis is a precipitating factor of asthma is still an issue of debate. Current data link rhinosinusitis and asthma by a common and complex inflammatory process. Eosinophils and the airway epithelium play a major role in this immunopathogenesis. Extensive sinonasal disease is a risk for the occurrence of allergic asthma¹. Peripheral eosinophilia in rhinosinusitis correlates with severe and extensive disease⁷. Corticosteroid-dependent asthmatics usually have abnormal sinus computed tomography. There is good correlation among abnormal sinus tomographic findings, clinical symptoms and the absolute number of blood eosinophils⁸. As previously described, upper and lower respiratory diseases, (asthma, sinusitis, and otitis media with effusion) frequently complicate allergic rhinitis (tables 1, 2, 3). The pathophysiologic link between allergic rhinitis and sinusitis includes inflammation caused by nasal allergy and/ or viral infections leading to obstruction, fluid accumulation and bacterial infection. Persistent inflammatory changes cause mucosal damage and a chronic state of associated obstruction and infection. Acute disease can then become chronic. Diagnosing and prophylactically treating nasal allergies may prevent recurrency and improve therapeutic responses⁹. An association between allergic rhinitis and conditions including asthma, sinusitis, otitis media, nasal polyposis, respiratory infections, and even orthodontic malocclusions has been documented. Shared pathogenic mechanisms, epidemiologic studies and clinical findings indicate that these conditions represent immunopathological consequences of the complex inflammation observed in allergic patients. Global antiallergic treatment affects both the upper and the lower airways. The use of nasal corticosteroids in subjects with rhinitis and asthma reduces not only rhinitis symptoms but also asthma symptoms and decreases the nonspecific bronchial airway reactivity to methacholine. Similarly antihistamines improve the pulmonary function tests of these patients. In the treatment of acute sinusitis, the combination of intranasal topical corticosteroids and antibiotics provides greater benefit than the use of antibiotics alone. The increased prevalence of IgE-mediated diseases requires effective and aggressive treatment including appropriate pharmaceuticals, allergen avoidance and specific and potent allergy immunotherapy¹⁰. There is a consistent observation in many patients that control of asthma remains difficult when their sinus disease is not treated and appropriate treatment of their sinuses frequently results in improvement of their asthma. The data of Blair *et al*¹¹ not only provides evidence supporting the relationship between atopy and infection but also that allergic inflammation enhances bacterial sinusitis explaining therefore the development of sinusitis in patients with allergic rhinitis (table 4). The radiographic abnormal findings observed in the sinuses of asthmatics probably are not artifacts but rather reflect pathologic changes. Eosinophilic infiltration with major basic protein deposition in the sinus tissues is commonly seen in patients with both sinusitis and asthma. Eosinophils may impair cilia, promoting stasis of secretions and sinus ostial obstruction, leading to secondary

bacterial infections. Medical and surgical treatments of sinusitis can improve coexistent asthma, suggesting that sinusitis can exacerbate asthma. Sinus inflammation exacerbates bronchial responsiveness through tri-geminal afferents and vagal efferents and may indirectly worsen asthma by enhancing nasal obstruction, causing loss of inspired air filtration, humidification, and warming¹².

Table 1 - Various Linkages of the “United Airways”

Clinical entity	Anatomic	Physiologic	Immuno-pathologic	Therapeutic
Allergic rhinitis	Respiratory epithelium	Inflammation, congestion and obstruction	IgE-mediated inflammation	Relief of inflammation and congestion
Conjunctivitis	Respiratory epithelium	Inflammation, congestion	IgE-mediated inflammation	Relief of inflammation
Sinusitis	Respiratory epithelium	Inflammation, congestion and obstruction	IgE-mediated inflammation	Relief of obstruction and treatment of infection
Asthma	Respiratory epithelium	Inflammation, congestion and obstruction	IgE-mediated inflammation	Control obstruction and relieve inflammation

Allergic ocular diseases are often associated with seasonal allergic rhinitis. Allergic conjunctivitis is part of the hay fever syndrome. Atopic subjects frequently present allergic rhinoconjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, giant papillary conjunctivitis and ocular contact allergy¹³. Mechanisms by which mast cells, T cells, eosinophils, cytokines, and other inflammatory mediators and constituents contribute to the unique features of the allergic eye diseases and their link to allergic responses of the airways, have been well documented¹⁴. Most of the allergic patients have also ocular involvement. The ocular component may be the most prominent and often the major disabling feature of their allergy. These symptoms may be seasonal or perennial. The spectrum of ocular allergy ranges from acute seasonal allergic rhinoconjunctivitis to chronic variants of atopic keratoconjunctivitis. IgE mediated allergy is the most frequent immunopathogenic mechanism present in allergic rhinoconjunctivitis and its comorbid disease link. Knowing the precise and actual immunologic pathogenesis will help assessing and treating the allergic ocular manifestations associated with rhinitis, sinusitis, serous otitis media, atopic dermatitis, and asthma¹⁵.

Table 2 - Similarities and Differences in Immunopathogenesis of Rhinitis and Asthma

Th2 cells and cytokines

Similar Features	Different Features	Sequelae
Genetics and IgE	Abundant vascular supply in nose	Nasal obstruction and rhinitis
Eosinophils and mast cells	Hyperresponsiveness of bronchial smooth muscle	Bronchospasm of asthma
Th2 cells and cytokines	Epithelial shedding; Remodelling and fibrosis in lung	Fixed airway obstruction in lung Leukotrienes and neuropeptides Release and upregulation of other pro-inflammatory mediators
----- - Leukotrienes and neuropeptides -----		

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Release and upregulation of other pro-inflammatory mediators		

Table 3 - Evidence Supporting the Rhinitis-Sinusitis-Asthma Connection

- About 80% of asthmatics have rhinitis
- 20-30% of patients with rhinitis have asthma
- Control of rhinitis reduces bronchial hyperresponsiveness
- Rhinitis usually precedes asthma
- Rhinitis is a risk factor for asthma
- Rhinosinusitis worsens asthma
- Patients with rhinitis may present hyperreactive airways
- Asthmatics without rhinitis may exhibit nasal eosinophilic inflammation
- Sinonasal inflammation is a risk for asthma
- Steroid-dependent asthmatics usually have abnormal sinus computed tomography
- Good correlation among abnormal sinus x-rays, blood eosinophilia and asthma symptoms
- Treatment of sinusitis improves asthma

Table 4 - Evidence Supporting the Atopy-Infection Connection*

- Atopy predisposes to viral upper respiratory infections
- Allergic inflammation enhances bacterial sinusitis
- Allergic rhinitis a risk factor for sinusitis

*(Blair C *et al.* Allergic inflammation enhances bacterial sinusitis in mice. *J Allergy Clin Immunol* 2001;108:424-9).

The unified airways disease concept and the understanding of the atopic inflammation as a systemic and *continuum* ongoing process has been previously discussed¹⁶. Recent documentation and evidence include the data showing that immunotherapy in children with seasonal allergic rhinitis reduced the subsequent development of asthma¹⁷ and the fact that treatment of allergic rhinitis decreased the number of asthma emergencies and hospitalizations¹⁸. Rhinitis is an independent risk factor for adult-onset asthma both among atopic and nonatopic patients and this risk is further increased if rhinitis is complicated with sinusitis¹⁹. Linkage of upper and lower airway disorders has been proved both in a murine model of allergic rhinitis²⁰ and in humans²¹ in whom anti-asthma medications were more frequently prescribed if rhinitis was comorbid²². Finally the inflammation of the small airways should also be addressed when treatment of the respiratory tract is contemplated²³.

Conclusions

Rhinitis, sinusitis, conjunctivitis, and asthma, constitute a comorbid continuum. These entities share linked immunopathogenesis as well as common genetic predisposition. IgE mediated reactions, mast cells, Th2 cells and its cytokines, eosinophils, and different pro-inflammatory mediators (adhesion molecules, chemokines, etc.), participate in this complex pathogenic process, definitely making these disorders a single disease entity, with different forms and degrees of clinical presentation. Many recent global epidemiologic, immunologic, clinical, and therapeutic studies indicate that rhinitis plays an etiologic role in the development of sinusitis and asthma. Allergic rhinitis also influences the clinical course of asthma. Rhinitis should therefore be considered a risk factor and a precursor of asthma. Ideally, treatment should be instituted early to control the inflammatory process of both the upper and lower airways, being justified by the current evidence of the concept of "one respiratory tract

disease entity”.

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