ALLERGIC RHINITIS AND ASTHMA – EVIDENCE FOR AN ASSOCIATION

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ABSTRACT

Asthma and allergic rhinitis (AR) are thought to be a reflection of the same disease process occurring in varying degrees along *one continuous airway*, and are often coexistent in the same individual. The evidence supporting this 'one airway' hypothesis is reviewed. Cohort and case-control studies of adults and children reviewed show that AR frequently precedes asthma, conferring a 3-7-fold increased risk for incident asthma. Cross-sectional studies reveal that rhinitis is highly prevalent among asthmatics ranging from 55% to 79%, and severity of rhinitis is positively associated with asthma severity. Pathophysiological interactions between upper and lower airways are appreciated from studies that demonstrate that following exposure to allergens or other triggers (such as histamine, cold dry air) in the nasal mucosa and bronchiolar airways, symptoms may manifest in both upper and lower airways in some individuals, or in only one site in others, despite the presence of pathological reactions along the whole airway. Treatments for AR such as topical corticosteroids and leukotriene modifiers result in improvement of asthma. Randomised trials of immunotherapy for AR have demonstrated a reduction in asthma incidence sustained at 10-year follow-up, and immunotherapy for concurrent asthma/AR has resulted in marked reduction in asthma as well as AR exacerbations.

Epidemiological, pathophysiological and therapeutic evidence supports the hypothesis that AR and asthma actually represent a spectrum of the same disease affecting one continuous airway.

INTRODUCTION

Asthma is a chronic lower airway disease characterised by recurrent cough and/or wheeze, with or without chest tightness or shortness of breath, alleviated by bronchodilator therapy. Allergic rhinitis (AR) is a chronic upper airway disease characterised by recurrent or persistent rhinorrhoea, nasal congestion, sneezing and/or nasal itchiness due to irritation and inflammation of the nasal passages. Asthma and AR are thought to be a reflection of the same disease process occurring in varying degrees along *one continuous airway*, and are often coexistent in the same individual. The evidence supporting the 'one airway' hypothesis explaining association between these two clinical conditions is reviewed.

EPIDEMIOLOGICAL EVIDENCE

Cohort studies

Cohort studies provide evidence that the natural history of allergic respiratory disease starts with allergic rhinitis (AR) and frequently progresses to asthma. A recent large retrospective cohort study[1] investigated association between physician-diagnosed AR and asthma in a large primary care population. The incidence of asthma was prospectively determined among 6 491 subjects age ranging from 0 to 88 years who had versus did not have AR. Excluding patients who had asthma at baseline, the study found that asthma developed more frequently among patients with AR (7.6%) than those without AR (1.6%) during a median follow-up period of 8.4 years. After adjusting for effect of age at enrolment, gender, eczema and socio-economic status, AR conferred a 5-fold increased risk for asthma independent of those factors (hazard ratio (HR) 4.86, 95% confidence interval (CI) 3.50-6.73).[1]

A longitudinal population-based cohort study[2] spanning 14 western European countries evaluated 6 461 participants aged 20-44 years for incidence and risk factors for adult-onset asthma. Over 8.8 years the cumulative incidence of asthma was 2.2%, and adjusted relative risk for asthma was higher among those with AR (3.53, 95% CI 2.11-5.91 than those with non-allergic rhinitis (2.71, 95% CI 1.64-4.46).[2]

One cohort of 747 children followed from birth to age 6 years[3] found that by the age of 6 years 42% had AR and that onset of rhinitis in the first year of life was a risk factor for asthma by age 6 years.[3] Another population birth cohort study[4] reviewed 1 456 10-year-old children for rhinitis, atopy (through skin-prick testing and serum inhalant immunoglobulin E (IgE) antibody screening) and bronchial hyper-responsiveness (through methacholine challenge). Recurrent nasal symptoms were prevalent in 22.6% of children, and asthma diagnosis was higher among those with rhinitis than those without. Rhinitis was also associated with more frequent bronchial hyper-responsiveness, even among children who did not wheeze.[4]

Among 1 021 individuals enrolled as college students and followed up for 23 years AR and/or positive allergy skin tests were associated with a 3-fold increased likelihood of developing incident new asthma.[5]

Case control study

A case control study[6] nested in a large longitudinal community population study examined 73 incident patients with physician-confirmed asthma (cases) against 2 177 controls without asthma, wheeze or shortness of breath, for various risk factors for asthma, including rhinitis. Adjusted multivariate analysis revealed that rhinitis conferred a 3-fold increased risk for asthma (odds ratio (OR) 3.21, 95% CI 2.19-4.71). On stratification, this 3-fold increased risk remained present among both atopic and non-atopic patients; however among atopic patients in the highest IgE tertile there was a 5-fold increased risk for asthma.[6]

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Cross-sectional studies

Strong evidence is provided by an international cross-sectional study[7] of 90 478 young adults from the USA, Europe and Australia-New Zealand which demonstrated that asthma was 7 times more frequent and bronchial hyper-reactivity (BHR) 3 times more frequent among subjects with rhinitis than those without (OR 6.63, 5.44-8.08, and 3.02, 2.66-3.43 respectively). In the same study among a randomly selected subset of 10 210 participants, 74-81% of subjects with asthma reported rhinitis, and asthma was present among 11.9% of subjects with pollen- and animal-sensitive rhinitis versus 2.0% of those without rhinitis.[7]

Among 3 000 randomly selected British schoolchildren evaluated through questionnaire, rhinitis symptoms were present in 61% of girls and 53% of boys with asthma.[8] When 2 005 Greek children were evaluated cross-sectionally through questionnaire, clinical evaluation and provocation testing, rhinitis was highly prevalent among children with asthma (69%), and asthma was prevalent in 33% of those with rhinitis.[9]

Recently in a survey of 813 adults and 806 children with asthma from four Asia-Pacific region countries and four European countries 69% of adults and 79% of children had concomitant AR, and most patients (79%) reported that flare-up of AR symptoms was associated with worsening of their asthma symptoms.[10] Similarly a French national survey conducted among 1 906 French general practitioners reported that among 4 335 asthmatic patients 55.2% had concomitant AR and that frequency and severity of AR increased with the severity of asthma.[11] The Swiss LARA survey[12] found a high prevalence of AR (76%) among asthma patients; however AR did not appear to impact on asthma control, with poor control observed among 53% and 57% of patients with and without AR respectively.[12]

All of these epidemiological cohort, case control and cross-sectional studies provide evidence supporting a clear association between AR and asthma, and suggest that AR frequently precedes asthma.

ANATOMICAL SIMILARITIES BETWEEN UPPER AND LOWER AIRWAYS

Various *anatomical similarities* exist between upper and lower airways which give indication of the continuity in function and structure of this organ lending evidence to the 'one continuous airway' theory. Both upper and lower airways are lined with mucosa from the walls of the nasal fossa through to the bronchioles. The histological structure of the mucosa transitions from stratified squamous in the nose to pseudostratified ciliated epithelium in the trachea and bronchi, thinning into cuboidal epithelium at the bronchioles and squamous in the alveoli. Cartilage is present in the nasal septum, and also in the larynx, trachea and bronchi. Muscular cells are present throughout the airway, with skeletal muscle predominating in the nasopharynx and larynx, and smooth muscle in the airways below. Glandular and secretory cells are present throughout most of the airway and are responsible for continuous mucosal secretions required for normal airway physiology. The nose has extensive vascular networks which are important for the humidification and warming of inspired air, and similarly the alveoli are lined by an extensive vascular capillary network necessary for rapid gaseous exchange.[13]

PHYSIOLOGICAL INTERACTIONS BETWEEN UPPER AND LOWER AIRWAYS

Physiological functions and interactions between nasal passage, nasopharynx and lower airways suggest much interdependence to maintain normal physiology. The nose conditions incoming air by warming and humidifying it, so that air reaching the lower airways does not cause irritation through drying and cooling. Similarly, as air is exhaled via the nose, heat is transferred back to the nasal mucosa.

There are neural communications linking the upper and lower airways: afferent sensory impulses from the nose via trigeminal nerve, from nasopharynx via glossopharyngeal nerve, and efferent impulses to the bronchi via the vagal nerve mediate bronchoconstriction, and contribute to reflex interactions between the upper and lower airways. Earlier studies have demonstrated that nasal irritation by silica particles induces increased airway resistance, and that atropine premedication prevents the reaction. Nasal insufflations with histamine similarly produce bronchospasm evidenced by a rapid significant drop in forced expiratory volume at one second (FEV_1) within minutes to hours.[14]

There is conflicting evidence regarding aspiration of secretions from the upper airways into the lower airways. Bardin *et al.*[15] evaluated patients with sinusitis with or without asthma for aspiration of radionuclide placed in their maxillary sinuses during therapeutic puncture into the lower airways. Radionuclide was demonstrable in their nasopharynx and oesophagus, but absent in their lower airways over a 24-hour period.[15] Beal *et al.*[16] demonstrated that patients with obstructive sleep apnoea appeared to have increased risk of aspiration into their lower airways compared to healthy controls.[16]

PATHOPHYSIOLOGICAL INTERACTIONS

There is evidence that allergens or triggers that induce allergic reactions in the nasal mucosa also trigger allergic responses in the bronchiolar airways in the same individual, and the patient may manifest symptoms at both sites (AR and asthma symptoms) or only one site (rhinitis only, or asthma only), despite having evidence of pathological reactions in both upper and lower airways. Some of the supportive research is reviewed.

A Danish study[17] evaluated 734 subjects (age 15-69 years) for association between rhinitis and asthma triggered by specific pollen, animal or mite allergens. All 52 patients with pollen-allergic asthma also had pollen-specific AR (in 28 cases the AR preceded the asthma); similarly all subjects with asthma triggered by animal or mite allergen universally had AR sensitive to the same allergens.[17]

Pelikan[18] demonstrated that an initial allergic reaction in the nasal mucosa may frequently induce a secondary asthmatic response; 82 asthmatics who demonstrated negative asthmatic responses to bronchial allergen challenge were given nasal challenges with various inhalant allergens through rhinomanometry, and spirometry was then applied to evaluate for secondary asthmatic responses. Among 69 patients who had positive nasal challenge response, 58 experienced a secondary asthmatic response.[18]

Bonay *et al.*[19] conducted a randomised cross-over double-blinded trial in which they gave grass pollen or placebo nasal challenge (outside the pollen season) and analysed nasal changes and airway responsiveness by methacholine challenge. Nasal lavage and induced sputum specimens were analysed for eosinophil activation (cytological and eosinophil-cationic protein expression). Airway responsiveness was increased in the grass pollen group compared to placebo, as were total eosinophils and eosinophil-cationic protein in induced sputum, and levels were positively correlated to methacholine responsiveness.[19]

One well-known trigger of asthma exacerbations – rhinovirus infection – infects the nasal tissues; however it frequently results in increased bronchial reactivity and asthma exacerbation. In adult studies viral nasal infections are associated with risk of exacerbation severe enough to warrant hospitalisation.[20] Similarly rhinosinusitis is frequently coexistent with asthma, with up to three-quarters of asthmatic children having abnormal sinus radiographs, 70% of asthmatic adults exhibiting symptomatic rhinosinusitis, and 88% abnormal sinuses on computed tomography (CT) scan in one study.[21]

Drugs that inhibit cyclo-oxygenase enzymes such as aspirin (acetyl salicylic acid (ASA)) and non-steroidal anti-inflammatory agents trigger asthmatic attacks and nasal reactions in aspirin-sensitive asthmatics. Ingestion of ASA in these individuals leads to eosinophilic inflammation of nasal and bronchial tissues, and overproduction of cysteinyl-leukotrienes. The underlying pathogenesis is genetically determined overtranscription of leukotriene synthase enzyme in eosinophils and mast cells of these individuals.[22]

An Italian study of 342 patients with moderate-severe persistent AR but no asthma were evaluated for presence of BHR. After methacholine challenge, 84.2% of them manifested BHR, and BHR was associated with tree and house-dust mite sensitisation (adjusted (adj) OR 8.1) and long duration of rhinitis >5 years (adj OR 5.4).[23] In another Italian cohort of 375 patients with moderate-severe persistent AR, exposure to bronchodilators led to increase in FEV_1 compared to baseline and to controls. Bronchodilation was seen more commonly in those with longer rhinitis duration, and with mite and tree allergies.[24]

If the nose fails to humidify and warm incoming air, the cold dry air causes BHR in the lower airways, a factor that explains exercise-induced asthma, and emphasises the interdependence between the upper and lower airways. Mild asthmatics were asked to breathe nasally only (tape over lips), and then orally only (nose clip) for 1 hour each on separate days; then lung function was measured over a period of 1 hour. FEV_1 was significantly lower after oral breathing than after nasal breathing, and oral breathing led to difficulty in breathing, and coughing/wheezing in some.[25]

Systemic spread of inflammatory mediators is thought to be a major contributor to the interaction between upper and lower airways in patients with allergic respiratory disease. Patients with AR and asthma both have similar cellular infiltrates and pro-inflammatory mediators in their nasal and bronchial mucosa, but also in the bone marrow, in duodenal tissues, and increased circulating eosinophils.[26,27] This evidence suggests that after allergic challenge, inflammatory cells and mediators enter the systemic circulation and may travel to lower airway respiratory mucosa not exposed to the allergen and cause inflammation. In subjects with pollen-sensitive AR and asthma, and in controls, blood eosinophil and neutrophil activity was tested first during the pollen season, then after nasal allergen challenge, and again after bronchial allergen challenge. Both AR and asthmatic groups demonstrated the same pattern of degranulation in systemic circulating eosinophils and neutrophils, specifically increased release of eosinophil-cationic protein and myeloperoxidase after nasal as well as bronchial site allergen challenge.[28]

EVIDENCE FROM TREATMENT OF AIRWAY DISEASE

Several therapies for AR may improve asthma, and vice versa.

In a nested case-control study hospital admissions for asthma were reduced when patients were treated with nasal corticosteroids alone (adj OR 0.56, 0.42-0.76) or corticosteroids combined with oral H_1 antihistamines (adj OR 0.27, 0.07-0.63), but not with antihistamines alone (0.68, 0.40-1.14).[29] Similar findings were reported in a large retrospective cohort study conducted on children and adults with use of nasal steroids and antihistamines associated with decreased risk for asthma exacerbations requiring acute healthcare utilisation.[30]

Control of symptoms of both mild to moderate asthma and seasonal AR improved with leukotriene modifiers.[31]

Children with chronic sinusitis were treated with antibiotics or nasal saline irrigation for 6 weeks, then the treatment order was reversed, and controls (no sinusitis) received nasal saline irrigation for 12 weeks. Antibiotic treatment resulted in significant improvement of clinical symptoms and signs of sinusitis, but not FEV_1. However the provocative concentration required to cause a 20% fall in FEV_1 was significantly higher after antibiotic treatment.[32]

Randomised controlled trials have shown that use of subcutaneous immunotherapy or sublingual immunotherapy in children or adults with AR can prevent asthma. In the PAT study, children with seasonal rhinoconjunctivitis and grass and/or birch pollen allergy but no other allergy were randomised to receive pollen immunotherapy or no immunotherapy. After 3 years of therapy, significantly fewer children in the intervention group developed asthma, and this effect persisted at 5-year and 10-year follow-up.[33,34,35] Similarly, 39 Turkish children with concomitant AR and asthma mono-sensitised to house-dust mite were given 3 years of sublingual immunotherapy against house-dust mite. They experienced reduction of acute asthma attacks from a mean of 8.2 to 0.4 attacks per year, and 82% of children experienced complete clinical remission of AR.[36] Both allergic asthma and AR may be effectively treated using anti-IgE.[37]

CONCLUSION

Evidence has been reviewed supporting the 'one airway hypothesis' that rhinitis and asthma, which frequently coexist, actually represent a spectrum of the same disease affecting one continuous airway. Epidemiological studies provide strong evidence of association and time-causal relationships; anatomical structural similarities and physiological interactions between upper and lower airways support this theory. Similarity between pathophysiological effects, triggers and airway hyper-responsiveness between upper and lower airways, as well as the beneficial therapeutic effect of various treatments of the upper airway on asthma further confirm that there is much interaction between AR and asthma.

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