International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 2; February 2017; Page No. 170-174

A clinical study of effects and implication of allergic rhinosinusitis

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Abstract

Dysfunction of the upper and lower airways frequently coexist, and they appear to share key elements of pathogenesis. Data from epidemiologic studies indicate that nasal symptoms are experienced by as many as 78% of patients with asthma and that asthma is experienced by as many as 38% of patients with allergic rhinitis. Studies also have identified a temporal relation between the onset of rhinitis and asthma, with rhinitis frequently preceding the development of asthma.

Patients with allergic rhinitis and no clinical evidence of asthma commonly exhibit nonspeeific bronchial hyperresponsiveness. The observation that management of allergic rhinitis also relieves symptoms of asthma has heightened interest in the link between these diseases. Intranasal corticosteroids can prevent increases in nonspecific bronchial reactivity and asthma symptoms associated with seasonal pollen exposure.

Similarly, among patients with perennial rhinitis, daily asthma symptoms, exercise-induced bronchospasm, and bronchial responsiveness to methacholine are reduced after admmistratio n of intranasal corticosteroids. Antihistamines, with or without decongestants, reduce seasonal rhinitis symptoms, asthma symptoms, and objective measurements of pulmonary function among patients with rhinitis and asthma.

The mechanisms that connect upper and lower airway dysfunction are under investigation. They include a nasal-bronchial reflex, mouth breathing caused by nasal obstruction, and pulmonary aspiration of nasal contents.

Nasal allergen challenge results m increases in lower airway reactivity within 30 minutes, suggesting a neural reflex. Improvements in asthma associated with increased nasal breathing may be the result of superior humidification, warming of inspired air, and decreased inhalation of airborne allergens. Postnasal drainage of inflammatory cells during sleep also may affect lower airway responsiveness. A link between allergic rhinitis and asthma is evident from epidemiologic, pathophysiologic, and clinical studies. Future research, however, is needed to determine whether nasal therapy can alter the natural history of asthma.

Keywords: allergic rhinitis, asthma, bronchial hyperresponsiveness, intranasal corticosteroids, antihistamines, decongestants

Introduction

The apertures of the nose, how marvelously they come next after the sponge like (ethmoid) bone.., and how the connection was cut through into the mouth at the palate in order that inspiration may not begin in a straight line with the trachea and that the air entering it may first be bent and convoluted, so to speak. For I think this should be double advantageous: the parts of the lung will never be chilled when oftentimes the air surrounding us is very cold. and the particles of dust.... will not penetrate as far as the trachea.

Galen, 2nd century AD, "On the Usefulness of the Parts of the Body." Practicing physicians and clinical investigators have long noted a relation between allergic rhinitis and bronchial asthma.

Dysfunction of the upper and lower airways frequently occur together and appear to share key elements of pathogenesis. Despite the strong clinical association between these diseases, it remains controversial whether rhinitis serves as a risk factor for the development of asthma and whether active nasal disease can affect lower airway symptoms and function. These and other issues have practical implications for clinicians who treat patients with chronic respiratory allergy. In this review, the association between allergic rhinitis and bronchial asthma is examined through a review of data from epidemiologic, clinical, and laboratory studies. Potential areas of future research to aid understanding of this relation are highlighted.

A large number of cross-sectional studies have demonstrated that rhinitis and asthma commonly occur together. Nasal symptoms have been reported among 28% to 78% of patients with asthma, [1-3] compared with approximately 20% of the general population [4] Similarly, as many as 19% to 38% of patients with allergic rhinitis may have asthma, 1, 3 much more than the 3% to 5% prevalence among the general population? In a survey of 6563 residents, new diagnoses of probable allergic rhinitis or asthma were two- to fourfold higher among persons who previously had one of these diseases compared with persons who had no history of either disease [6].

The onset of rhinitis and asthma may be temporally related. In a study involving children 13 to 17 years old with both rhinitis and asthma, 59% either had nasal symptoms first or had symptoms of both diseases appear during the same year [7]. A similar study involving college students revealed that 64% had rhinitis before the onset of asthma and that 21% had both upper and lower airway disease at the same time [8]. In a study involving 7662 patients with a broad range of ages, 49% of patients with both rhinitis and asthma had nasal symptoms first, and 25% had both diseases within I year of each other [3]. These studies suggest that rhinitis frequently precedes asthma and that upper airway dysfunction may be a predictive factor for subsequent development of lower airway disease. However, because these are cross-sectional studies based on patient recall, the data cannot be considered conclusive.

Multiple investigations have shown that patients with allergic rhinitis and no clinical evidence of asthma commonly exhibit nonspecific bronchial hyperresponsiveness. Comparisons of these data are difficult because the studies were performed with a variety of methods for bronchial provocation and used different definitions of hyperresponsiveness.

One early report suggested that as many as 73% of patients with nasal allergies demonstrated increased airway responsiveness to methacholine or histamine. Data collected more recently show that between approximately 11% and 32% of patients with rhinitis have positive bronchoconstrictor responses to histamine, methacholine, or carbachol that are in the range of responses Observed in patients with asthma.

H43 Among patients with seasonal hay fever and no asthma, airway responsiveness may increase markedly during seasonal periods of pollen exposure. Madonini *et al*. examined 27 patients with seasonal rhinitis before and during the pollen season. The investigators documented that the incidence of bronchia hyper responsiveness rose from 11% before to 48% during the pollen season, n In addition, patients with perennial allergic rhinitis appear to have higher levels of lower airway responsiveness than patients with seasonal nasal allergy [14].

It is difficult to determine whether rhinitis is the first manifestation of respiratory allergy for a patient who may eventually have asthma or whether nasal disease is playing a direct role in causing asthma. Long-term epidemiologic studies of patients with allergic rhinitis, including assessments of bronchial responsiveness, will be critical in answering this question. In addition, results from therapeutic and laboratory research studies will help to provide insights into this question.

Clinical Trials: The Effects of Nasal Therapy on Asthma

In anecdotal experience, physicians have often noted improvements in asthma after successful treatment of rhinitis. Until recently, however, few controlled clinical trials have been attempted to measure this effect. Since the mid 1980s, several investigators have begun to evaluate carefully the impact of rhinitis therapy on asthma symptoms, pulmonary function, and airway responsiveness.

Studies have demonstrated minimal deposition of intranasal corticosteroids into the lungs, restricting the therapeutic effects of these agents to the upper airway [13]. Therapeutic trials of these rhinitis-specific medications, therefore, are useful in assessing the effects of nasal dysfunction on asthma. A number of trials have been conducted to examine the efficacy of intranasal corticosteroids for patients with both seasonal and perennial allergic disease of the upper and lower airways.

Welsh *et al*. compared use of intranasal flunisolide, beclomethasone dipropionate, cromolyn, and placebo in patients with ragweed hay fever [11]. In addition to measuring nasal symptoms, the investigators also assessed chest symPtoms in a small subgroup of patients who had seasonal asthma. Rhinitis scores improved among patients receiving active treatment (i.e., either of the two corticosteroids or cromolyn); however both of the intranasal corticosteroids were more effective than cromolyn.

In addition, asthma symptoms were virtually eliminated in the two groups receiving intranasal steroids compared with subjects taking cromolyn and placebo (Fig. 1). My coworkers and I later sought to confirm these findings in a study of the use of intranasal beclomethasone dipropionate by patients with seasonal allergic rhinitis and asthma [17].

Bronchial responsiveness to inhaled methacholine, measured before and at the peak of the fall pollen season, increased in a statistically significant way among patient s receiving placebo but did not change among patients receiving active treatment. However, there were no differences in asthma symptoms, peak expiratory flow rates, or spirometric indices between the active therapy and placebo groups. Although both these trials involved small numbers of patients the results suggest that prophylactic treatment with intranasal corticosteroids can prevent increases in nonspecific bronchial reactivity and asthma symptoms associated with seasonal pollen exposure.

Similar investigations have focused on patients with perennial nasal allergy and asthma [17]. In a 4-week trial of use of intranasal budesonide by patients with perennial rhinitis and asthma, chronic nasal obstruction improved and mouth breathing decreased with active therapy [20]. With these changes in nasal function, daily asthma symptoms were reduced and exercise-induced broncho-spasm, assessed by means of treadmill testing, was markedly attenuated. In a subsequent study involving patients with mite-induced rhinitis and asthma, Watson *et al*. evaluated the effects of intranasal become tha sone dipropionate on asthma, including an assessment of bronchial responsiveness to methacholine [17].

After 4 weeks of active treatment, airway responsiveness was reduced by approximately a twofold dilution compared with baseline. The investigators also performed a radiolabeled deposition study of the corticosteroid aerosol and found that less than 2% of the drug was deposited into the chest area. These two trials demonstrated that intranasal corticosteroids are effective in improving chest symptoms and nonspecific airway responsiveness in patients with established, chronic nasal inflammation. The results of the study by Watson *et al*. also suggested that the reduction in asthma is due to improvement in nasal function rather than direct effects on the lower airways.

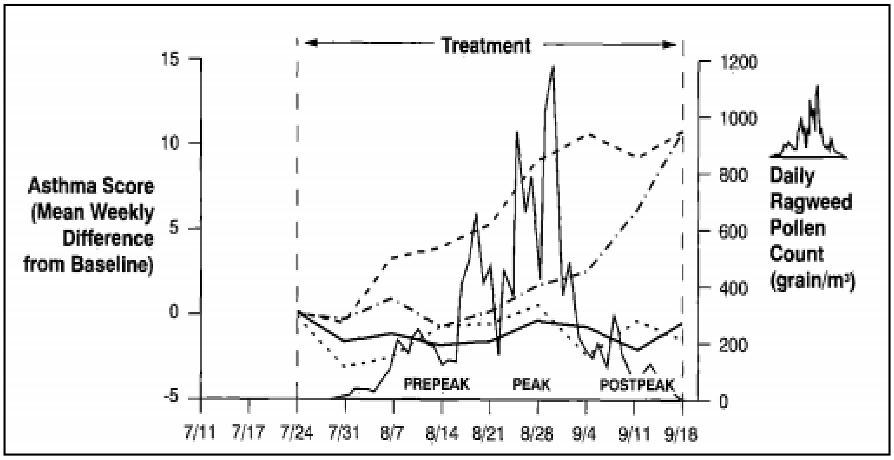

Fig 1: Mean weekly scores for symPtoms of asthma, adjusted for baseline values among 58 patients with seasonal asthma

Another study that requires comment compared the effects of intranasal versus intrabronchial (by means of oral inhalation) administration of beclomethasone dipropionate 400 ~g/day on lower airway reactivity in patients with rhinitis and no asthma. After 2 weeks of therapy, intranasal delivery of the corticosteroid caused marked improvement in bronchial responsiveness, whereas oral inhalation had no effect on reactivity.

Because intranasal administration was far more effective than oral inhalation of the corticosteroid, these data suggest that nasal inflammation plays a key role in modulating lower airway responsiveness associated with allergic rhinitis. Long-term studies involving patients with perennial rhinitis and bronchial hyperreactivity will help determine whether asthma can be prevented among some persons by means of early treatment with intranasal corticosteroids.

Histamine has been identified as a mediator of potential importance in allergic asthma? ~ Histamine type 1-receptor antagonists have been shown to have direct effects on lung function. Clinical trials with these drugs have demonstrated variable improvement in lower airway symptoms and function. Therefore, unlike those of intranasal corticosteroids, the salutary effects of antihistamines on asthma cannot be ascribed solely to improvements in upper airway function. Studies of first-generation antihistamines demonstrated minimal improvement in bronchial asthma? ° Initial small-scale trials of second-generation drugs included small numbers of patients and yielded mixed results?

In general, reductions in lower airway symptoms were observed only when larger than approved doses of antihistamines were used (e.g., terfenadine 240 to 540 mg per day 24'25 and cetirizine 15 to 20 mg per dayaT, 28). Two muldcenter trials have been conducted with antihistamines in approved doses; the results indicated improvement in asthma symptoms? 9,31 Grant *et al*. demonstrated that cetirizine, 10 mg once a day, reduced the severity of seasonal rhinitis and asthma symptoms; however, objective measures of pulmonary function were not statistically different from those of placebo? In a study in which loratadine 5 mg plus pseudoephedrine 120 mg was administered twice a day to patients with seasonal rhinitis and asthma, my coworkers and I demonstrated that asthma symptoms, peak expiratory flow rates, spirometry, and asthmaspecific quality of life all improved in a statistically significan t way among patients taking active therapy? 1 The inclusion of decongestant therapy in this trial may have had clinically significant effects on asthma by restoring the filtration function of the nose. Antihistamines, with and without decongestants, appear to be useful adjuncts in treating patients with seasonal allergic rhinitis and concomitant asthma.

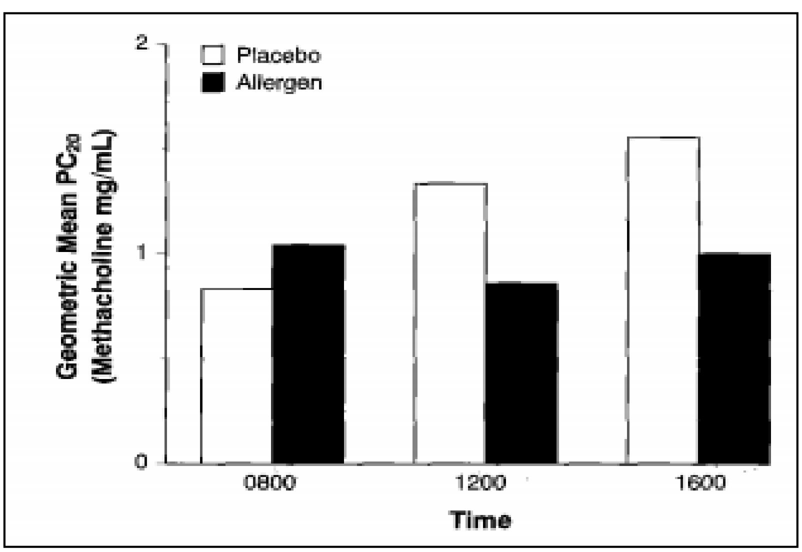

Fig 2: Effect of nasal challenge on bronchial responsiveness, expressed as the geometric means of PC2o to inhaled methacholine; p = 0.011 at 1200

Pulmonary aspiration of nasal contents

Galen noted an association between nasal disease and asthma and postulated that secretions dripped from the skull into the lungs. Studies from the 1920s and 1930s suggested that substances placed in the uppe r respiratory tract were recoverable later from the tracheobronchial treeg, Huxley *et al* in 1978 investigated pharyngeal aspiration during sleep among both healthy persons and in patients with depressed sensorium? With a radiolabeled marker that was intermittently released into the nose, pulmonary aspiration was detected in a substantial number of both healthy and ill persons. Bardin *et al*., however, were unable to document marked aspiration of radionuclide in a study involving 13 patients with chronic rhinosinusitis and asthmaY To help define the relation between upper airway inflammation and asthma, Brugman *et al*. performed a series of experiments using a rabbit model of rhinosinusitis and lower airway responsiveness? [4]

After inducing granulocytic rhinosinusitis, with the use of complement component C5a des arg, lung mechanics and bronchial reactivity to inhaled histamine were measured. Although there were no changes in baseline pulmonary function, histamine responsiveness increased with the presence of upper airway inflammation. These changes in reactivity were blocked by strategies that prevented the exudate from draining beyond the larynx. Observations from this animal model suggest that upper airway inflammation augments nonspecific bronchial responsiveness by means of aspiration of nasal drainage.

After injection of the maxillary sinuses with C5a des arg, neutrophils and eosinophils were notably absent from the nasal-sinus exudate, and bronchial responsiveness was unchanged. Granulocytes, therefore, appear to be required for the changes in reactivity in this model. Combining these experimental findings with those of prior studies of pharyngeal aspiration in human subjects, it can be speculated that postnasal drainage of inflammatory cells during sleep may affect lower airway responsiveness. It is dilficult to determine which of these experimental mechanisms is most important in linking the nose to the lower airways. In all likelihood, all three phenomena contribute in some way to alterations in lung function in patients with allergic rhinitis and asthma.

Summary and Future Directions

Epidemiologic surveys have shown that allergic rhinitis and asthma commonly coexist and that an important minority of patients with nasal allergy demonstrate nonspecific bronchial hyperresponsiveness in the absence of overt asthma. A limited number of studies suggest that allergic rhinitis is a risk factor for asthma and that asymptomatic bronchial hyperresponsiveness may influence this process. Among patients who have both rhinitis and asthma, intranasal corticosteroids and antihistamines, with or without decongestants, reduce asthma symptoms and in some instances improve pulmonary function and bronchial hyperresponsiveness.

Although pathophysiologic connections between the nose and lungs are not entirely understood, laboratory studies with both animal and human subjects suggest that a nasal-bronchial reflex, shifts in breathing patterns, and pulmonary aspiration of nasal contents may contribute to lower airway dysfunction among patients with rhinitis. Although treatment of allergic rhinitis appears to have beneficial effects on concomitant asthma, it is unclear whether nasal therapy can alter the natural history of respiratory allergy. Long-term controlled studies with rhinitis therapy or allergy immunotherapy will be of great importance in determining whether the development of asthma can be prevented among patients with rhinitis alone.

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