

Complications of allergic rhinitis: Implications for sinusitis and asthma

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The relationship between infectious rhinitis and sinusitis is so clear that the suggestion has been made that the term "rhinosinusitis" might more precisely define the disease state.¹ Several considerations support this contention. Rhinitis typically precedes sinusitis, and sinusitis without rhinitis is rare. The mucosae of the nasal and sinus tissues are contiguous, and the symptoms of nasal obstruction and nasal discharge are prominent in sinusitis. In certain clinical situations, either rhinitis (i.e., allergic rhinitis) or sinusitis (i.e., acute frontal sinusitis) may occur alone, but in most instances there is some involvement of the contiguous secondary site. A recent study, using computerized tomography (CT), documented that radiographic changes do occur in the sinuses of otherwise healthy patients with uncomplicated viral upper respiratory infections of brief duration.² It is therefore clear that infectious rhinitis will predispose to the development of sinusitis. Before discussing the possibility that allergic rhinitis is associated with or is a cause of sinusitis, we will review some basic aspects of sinus anatomy and physiology.

PATHOPHYSIOLOGY OF SINUSITIS

A number of factors contribute to the defense of the sinuses against infection. These include ostial patency, gas exchange, mucociliary action, enzymatic defense, and immunoglobulins.³ The most important of these factors is ostial patency. It is vital that the ostia, the small openings on the lateral wall of the nose through which the sinuses communicate with the outside environment, be patent. If the ostia are closed off or narrowed by, for example, a viral-induced rhinitis, a resultant decline in emptying time and gas exchange occurs, thus leading to decreased oxygen tension, which in turn favors bacterial growth and purulence. Secretions produced by the sinus mucosa accumulate, stagnate, and become infected by relatively harmless opportunistic pyogenic bacteria normally found in the nose. In most instances of sinusitis, bacteria gain access to the sinuses via the ostia.

RELATIONSHIP BETWEEN ALLERGIC RHINITIS AND SINUSITIS

There are two ways of looking epidemiologically at the relationship between allergic rhinitis and sinusitis. The first is to examine the incidence of allergy in patients with sinusitis. In 1961, Van Dishoeck found that 40% of adults with chronic maxillary sinusitis had some kind of allergy. If the maxillary sinusitis was bilateral, the incidence of allergy went up to 80%.⁴ Savolainen examined 224 army recruits with acute maxillary sinusitis verified with radiography and sinus aspirates. He found a significant increase in positive skin tests in 32% of the recruits vs 19.5% in an age-matched control group.⁵ Among a group of children with chronic sinusitis refractory to prolonged medical therapy, 22 were clearly allergic and 15 were probably allergic.⁶ In another study of 90 children with chronic sinusitis, 51% had positive skin tests.⁷ In a sample of patients undergoing surgery for chronic sinus disease, only the group with extensive disease exhibited an association between chronic sinusitis and allergy.⁸

A second approach to looking at the relationship between allergic rhinitis and sinusitis is to examine the incidence of sinusitis in patients with allergic rhinitis. Both Rachelefsky et al.⁹ and Shapiro¹⁰ have described an increased incidence of sinusitis defined by history, physical examination, and imaging criteria in children referred to an allergist/immunologist for evaluation of rhinitis. A large proportion of children in both groups were proven to be atopic by skin testing, supporting a connection between allergic rhinitis and sinus disease. Taken together, these studies support a minimum concordance of allergy and sinusitis of 25%, with a maximum concordance of 70%. This clearly is above the general prevalence of allergy, and supports the impression that allergy is an important, associated, and probable predisposing factor in sinusitis. It seems reasonable to believe that narrowing or closure of the sinus ostia by nasal mucosal swelling causes sinusitis irrespective of whether the cause is infectious (viral) or allergic. There is a need for large prospective studies to better define the relationship between allergic rhinitis and sinusitis.

RELATIONSHIP BETWEEN SINUSITIS AND ASTHMA

The frequent association of paranasal sinus disease and bronchial asthma has been noted for a great many years. A number of clinical studies in the 1920s and 1930s emphasized the importance of sinusitis as a

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TABLE I. Disease characteristics before and after treatment for sinusitis in 48 children

Characteristic	% of Patients	
	Before	After
Cough	100	29
Wheeze	100	15
Normal pulmonary function test	0	67
Bronchodilator treatment	100	21

From Rachelefsky GS, et al. Chronic sinus disease with associated reactive airway disease in children. *Pediatrics* 1984;783:526-9. By permission.

trigger for asthma.¹¹⁻¹³ However, the relationship between sinusitis and asthma then seemed to fall into disrepute, and little was written about this relationship for the next several decades. One prevailing thought was that sinus changes simply reflected a disease of the entire respiratory membrane, and that management of sinusitis would therefore be expected to have little effect on the course of lower respiratory tract disease.

RADIOGRAPHIC EVIDENCE OF SINUSITIS IN ASTHMA

A high incidence of radiographic evidence of sinusitis is present in both children and adults with asthma. One study at Los Angeles Children's Hospital showed that 75% of patients with status asthmaticus had abnormal sinus x-ray films.¹⁴ A recent study in Finland reported abnormal sinus radiographs in 87% of patients with exacerbation of asthma.¹⁵ The overriding question is whether this association represents an epiphenomenon; that is, are sinusitis and asthma manifestations of the same underlying disease process in different parts of the respiratory tract, or is there a causal relationship? Can sinusitis trigger bronchial asthma?¹⁶

IMPACT OF SINUSITIS TREATMENT ON ASTHMA

Although more objective evidence is needed, data indicate that asthma that is difficult to control will abate when coexistent sinusitis is cleared by medical and/or surgical treatment. This can be considered as strong suggestive evidence for an etiologic role of sinusitis in lower airway disease.

RESULTS OF MEDICAL THERAPY

A study by Rachelefsky et al. demonstrated that children with combined sinusitis and lower airway hyperreactivity showed significant alleviation of the asthmatic state when they received appropriate medical and/or surgical (i.e., antral lavage) treatment for their sinusitis.¹⁷

Disease characteristics before and after treatment for sinusitis in 48 children with hyperreactive airway disease

are given in Table I.¹⁷ Only 7 of the children required sinus lavage; the remainder received appropriate medical therapy. As shown in the table, 79% of the children were able to discontinue bronchodilator therapy after resolution of their sinusitis. Pulmonary function tests showed normal results in 67% of those with pretreatment abnormalities. Similar results were reported in another group of children with asthma and sinusitis at the University of Pittsburgh.¹⁸

RESULTS OF SURGICAL THERAPY

At the Saint Louis University Health Sciences Center, we have had an opportunity to observe a large group of adult patients who had coexistent sinusitis and asthma and who also provided suggestive evidence that sinusitis plays an important role in the pathogenesis of asthma. More than 90% gave a history indicating that their sinusitis preceded the development of asthma symptoms.¹⁶ On the basis of a history and a battery of allergy skin tests to common Saint Louis aeroallergens, two thirds of the patients were judged to be nonatopic, and more than 50% gave a history of aspirin sensitivity. Most important was that more than 90% of these patients were receiving corticosteroid therapy.

Corticosteroid dependency furnishes an important clue to those patients in whom an underlying sinusitis may act as a trigger for the development of asthma. In the study at our health sciences center, these patients were uniformly medically resistant; that is, sinusitis either recurred or never sufficiently resolved despite aggressive medical management.¹⁶

Early results obtained with bilateral intranasal sphenoethmoidectomy showed that the asthmatic state abated significantly in 65% of patients.¹⁹ We found that patients who showed improvement within the 2 years following surgery were likely to experience continued improvement throughout a 5-year observation period. More than 80% of the patients reported that they had experienced moderately or greatly reduced nasal symptoms, and 60% felt that their asthma symptoms had eased.

Equally good results have been obtained with functional endoscopic sinus surgery (FESS). One study reported results of a trial involving 205 patients with the aspirin triad, all of whom were steroid dependent. After FESS, 40% of the patients were able to discontinue steroids; another 44% had their illness controlled with alternate-day steroid therapy or bursts of steroids.²⁰ Another study investigated chronic sinusitis and asthma in 20 patients aged 16 to 72 years. After FESS, 70% reported the frequency of their asthma to be much reduced; 65% reported significantly less severe asthma. Of particular interest was a reduction of 75% in hospitalizations and 81% in emergency department/urgent office visits in the year following FESS.²¹

The effect of FESS on chronic sinusitis and concomitant childhood asthma is also promising. Parsons et al. reported findings in 52 children (average age, 7.4 years; range, 7 months to 17 years). After FESS, there was a

reduction of 89% in chronic cough and a 96% decrease in asthma. The average number of exacerbations per month fell from 6.7 to 2.5, and emergency department visits decreased by 79%.²²

POSSIBLE MECHANISMS OF SINUSITIS AND CONCOMITANT ASTHMA

The eosinophil

It is well known that the eosinophil plays an important role in mediating injury to bronchial epithelium in chronic asthma. In one study, researchers assessed the role of the eosinophil in chronic inflammatory disease of the paranasal sinuses by examining tissue from patients who underwent surgery for chronic sinusitis.²³ Sinus tissue from patients with sinusitis and concomitant chronic asthma and/or allergic rhinitis was extensively infiltrated with eosinophils. In contrast, sinus tissue from patients with chronic sinusitis alone had no eosinophils.

Immunofluorescence studies have shown a striking association between the presence of extracellular deposition of major basic protein and damage to sinus mucosa. The histopathology of the paranasal respiratory epithelium also appeared similar to that described in bronchial asthma.

These studies suggest that the marked tissue eosinophilia associated with chronic hyperplastic sinusitis is strongly correlated with local cytokine production, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2). Interestingly, IL-5 messenger RNA (mRNA) expression was not a prominent feature of the sinusitis.²⁴

The studies also suggest that the eosinophil acts as an effector cell in chronic inflammatory disease in paranasal respiratory epithelium, and points to the possibility that sinus disease in patients with asthma is caused by the same mechanisms that damage bronchial epithelium.

Inflammatory mediators

Another proposed mechanism whereby sinusitis may act as an aggravator of asthma is local stimulation of irritant receptors by inflammatory mediators with resultant reflex bronchospasm. In a recent study utilizing a radionuclide technique, pulmonary aspiration of upper airway secretions could not be demonstrated. The authors concluded that seeding of the lower airways by mucopurulent secretions is unlikely to account for pulmonary disease coexistent with sinusitis. It also seemed unlikely that locally produced inflammatory mediators would be aspirated into the lung.²⁵

Inflammatory mediators—leukotrienes, prostaglandin D₂, and histamine—were measured in maxillary sinus lavage fluid obtained during surgery for chronic sinusitis. The findings were compared with levels of mediators in nasal lavage fluid from a group of subjects with allergic rhinitis. The results indicated that the levels of leukotrienes, prostaglandin D₂, and histamine in sinus fluid were significantly increased over those in the control nasal lavage fluid, and were in the range associated with local inflammation and irritant receptor stimulation.²⁶

Neural reflexes

The postulated neuroanatomic pathways that could reflexly connect the paranasal sinuses to the lungs are as follows: Receptors in the nose, pharynx, and presumably in the paranasal sinuses give rise to afferent fibers that, in turn, form part of the trigeminal nerve. The trigeminal nerve passes to the brain stem, where it can connect via the reticular formation with the dorsal vagal nucleus. From the vagal nucleus, parasympathetic efferent fibers travel in the vagus nerve to the bronchi. The cholinergic parasympathetic nervous system plays a role in maintaining resting bronchial muscle tone as well as in mediating acute bronchospastic responses. The vagus nerve provides the cholinergic motor supply to airway smooth muscle.

Studies done both in animals and in humans have shown that reflex bronchoconstriction can result from stimulation of receptors in the nose and nasopharynx. In 1870, Kratchmer showed that a variety of irritants, such as ether, sulfur dioxide, and cigarette smoke, applied to the nasal mucous membrane of cats and rabbits, produced bronchoconstriction.²⁷ Others reported that the bronchoconstriction caused by mechanical or electric stimulation of the nasal mucosa could be abolished by vagus-nerve resection.²⁸ Kaufman and Wright exposed to silica particles, the nose and nasopharynx of subjects with no evidence of pulmonary disease, which resulted in a significant increase in lower airway resistance that could be abolished by pretreatment with atropine.²⁹

Further insights have recently been gained into the mechanisms of sinusitis-induced asthma. In a study of 106 patients with chronic sinusitis, histamine challenges were given to the lower airway before and after medical treatment of sinusitis. FEV₁ was measured as an index of bronchial narrowing, and mid-inspiratory flow as an index of extrabronchial airway narrowing.³⁰ Both intrabronchial and extrabronchial hyperreactivity decreased, with the reduction in extrabronchial hyperreactivity being more pronounced, and preceding the intrabronchial decline in hyperreactivity. The changes in intrabronchial and extrabronchial reactivity were strongly associated with pharyngitis as determined by history, physical examination, and nasal lavage. The investigators who conducted the study propose that airway hyperresponsiveness in sinusitis might depend on pharyngobronchial reflexes triggered by seeding of the inflammatory process into the pharynx through postnasal drip of mediators and infected material from affected sinuses.

Animal models

A rabbit model of sinusitis has been developed.³¹ Rabbits positioned with their heads up and tested 16 hours after injection of chemotactic complement factor C5a des Arg into the maxillary sinuses showed a marked increase in airway responsiveness to histamine. When the rabbits were positioned head down or intubated to block the passage of cells or mediators from the nose to the lower airways, they failed to show lower airway hyperresponsiveness. The researchers concluded that

the mechanism of lower airway hyperresponsiveness occurring in rabbits with induced sinusitis can best be explained as postnasal drainage of cell products of inflammation into the lower airways.

CONCLUSION

Direct evidence of a mechanistic link between the processes of sinusitis and asthma is lacking³²; basic mechanisms for such an association need to be investigated further by establishing experimental animal models and by appropriate human studies. Strong clinical evidence in both children and adults suggests that sinusitis not only occurs in association with bronchial asthma, but that it may also play a role in the pathogenesis of the latter condition. These findings were based on studies indicating that proper treatment of sinusitis by medical and/or surgical means frequently results in a substantial reduction in asthma symptoms.

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