

Asthma and sinusitis

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Important relationships exist between the upper and lower airways. It is well known that sinusitis and asthma coexist in many patients, and evidence is accumulating that there may be a cause-and-effect relationship, that is, that sinusitis is an important trigger for asthma. Studies in children and adults indicate that appropriate medical and/or surgical therapy of sinusitis frequently leads to improvement in the asthmatic state. Possible mechanisms for this relationship include the eosinophil acting as an effector cell, inflammatory mediators, and a vagal reflex. Further investigations need to examine both prospective studies of the effect of medical therapy for sinusitis on asthma and basic mechanisms relating the upper and lower airways. (J ALLERGY CLIN IMMUNOL 1992;90:534-7.)

Key words: Upper and low airway, sinusitis, asthma

The human airway has been traditionally divided into upper and lower segments with clear structural and functional distinctions. Diseases of the upper and lower airway may, however, coexist; rhinitis and bronchial asthma are good examples. As many as 80% of patients with asthma have rhinitis symptoms, whereas 5% to 15% of patients with perennial rhinitis have asthma. Much attention has been paid recently to the possibility that the upper airway may play an important role in the pathogenesis of bronchial asthma. Data from both experimental animal and human studies will be reviewed indicating that the distinctions between upper and lower airways are not as great as previously imagined and that in particular sinusitis may be an important triggering factor for bronchial asthma.

RELATIONSHIP OF SINUSITIS AND ASTHMA

The frequent association of paranasal sinus disease and bronchial asthma has been noted for a great many years. Several clinical studies in the 1920s and 1930s emphasized the importance of sinusitis as a trigger for asthma in many patients.¹⁻³ However, the relationship between asthma and sinusitis then fell into disrepute. It was thought that the sinus changes simply reflected a disease of the entire respiratory membrane; therefore management of sinusitis per se would be expected to have little effect on the course of lower respiratory tract disease.

There is no question of a high incidence of radiographic evidence of sinusitis, on the order of 40% to 60%, in asthmatic patients.^{4, 5} A recent study from Los Angeles Children's Hospital⁶ indicated that 75% of patients admitted to that institution with status asthmaticus had abnormal sinus x-ray films. The overriding question is, does this association represent 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, for example, can sinusitis trigger bronchial asthma?⁷

Although more objective evidence that sinusitis triggers or exacerbates asthma is needed, data indicate that patients who have asthma that is difficult to control will improve 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.

Studies by Rachelefsky et al.⁸ have demonstrated that children with combined sinusitis and lower airway hyperreactivity show significant improvement of the asthmatic state when they receive appropriate medical treatment for their sinusitis. Table I shows the disease characteristics before and after treatment for sinusitis in 48 children with hyperreactive airway disease. Only seven of these children needed sinus lavage; the rest received appropriate medical therapy. As can be seen from the table, 79% of these children were able to discontinue bronchodilators with resolution of their sinusitis. Pulmonary function tests showed normal results in 67% of those children with pretreatment abnormalities. Similar results were reported in another group of children with asthma and sinusitis from the University of Pittsburgh.⁹

At the St. Louis University Medical Center, we

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

Characteristic	Before (%)	After (%)
Cough	100	29
Wheeze	100	15
Normal PFT	0	67
Bronchodilator treatment	100	21

PFT, Pulmonary function test.

have had the opportunity to observe a large group of adult patients who had coexistent sinusitis and asthma and who also had suggestive evidence that the sinusitis played an important role in the pathogenesis of asthma (Table II). More than 90% gave a history indicating that their sinusitis preceded the development of asthma symptoms. Based on history and a battery of allergy tests to common St. Louis aeroallergens, two thirds of the patients were judged to be nonatopic, and more than 50% had a history of aspirin sensitivity. Most importantly, more than 90% of these patients were receiving corticosteroids. Corticosteroid dependency furnishes an important clue to those patients in whom an underlying sinus disease may act as a trigger for the development of asthma. These patients were uniformly medical resistant; that is, sinusitis either recurred or never sufficiently resolved with aggressive medical management.¹⁰ Our early results obtained with bilateral intranasal sphenoethmoidectomy (Table III) revealed that 65% of our patients showed significant improvement in their asthmatic state.⁷ We have found that patients who showed improvement within 2 years after 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 improved nasal symptoms, and 60% felt that asthma symptoms had improved.¹¹

POSSIBLE MECHANISMS EXPLAINING THE RELATIONSHIP OF SINUSITIS AND ASTHMA
The eosinophil

Evidence suggests that the eosinophil plays an important role in mediating injury to bronchial epithelium in chronic asthma. In a recent study (Table IV), the role of the eosinophil in chronic inflammatory disease of the paranasal sinuses was investigated with sinus tissue from patients who underwent surgery for chronic sinusitis. Sinus tissue from patients with sinusitis who also had chronic asthma and/or allergic rhinitis was extensively infiltrated with eosinophils. In contrast, sinus tissue from patients with chronic

TABLE II. Characteristics of patients with sinus disease and asthma

- Sinusitis preceded asthma in more than 90% of patients
- Two thirds were nonatopic based on history and skin tests
- More than half were aspirin sensitive
- More than 90% received corticosteroids

TABLE III. Effects of bilateral intranasal sphenoethmoidectomy on clinical symptoms in patients with combined sinusitis and asthma: Long-term follow-up

Time after surgery (yr)	Symptom improvement		Decrease in medications (% in patients)
	Asthma (% of patients)	Nasal	
2	65	85	60
5	60	81	60

sinusitis alone had no eosinophils. Immunofluorescence studies demonstrated a striking association between the presence of extracellular deposition of major basic protein and damage to sinus mucosa. In addition, the histopathologic findings of the paranasal respiratory epithelium appeared similar to those described in bronchial asthma. The findings suggest that the eosinophil acts as an effector cell in chronic inflammatory disease in paranasal respiratory epithelium. This points to the fact that the sinus disease in patients with asthma may be caused by the same mechanisms that cause damage to bronchial epithelium.¹²

INFLAMMATORY MEDIATORS

Another proposed mechanism for sinusitis as an aggravator of asthma is production of inflammatory mediators that could either be aspirated into the lower airways or locally stimulate irritant receptors in the sinuses with resultant reflex bronchospasm. In a recent study that used a radionuclide technique, pulmonary aspiration of upper airway secretions could not be demonstrated. The authors conclude that seeding of the lower airways by mucopurulent secretions is unlikely to account for coexistent pulmonary disease.¹³ It also seems unlikely that locally produced inflammatory mediators would be aspirated into the lung.

In another study investigating inflammatory mediators, the levels of leukotrienes, prostaglandin D₂, and

TABLE IV. Tissue eosinophilia in 26 patients with chronic sinusitis

Group 1: Chronic sinusitis and bronchial asthma (5); marked in all
Group 2: Chronic sinusitis, bronchial asthma, and allergic rhinitis (8); marked in all
Group 3: Chronic sinusitis and allergic rhinitis (7); marked in 6
Group 4: Chronic sinusitis; marked in 0

histamine were measured in maxillary sinus lavage fluid obtained during surgery for chronic sinusitis. These results were compared with levels of mediators in nasal lavage fluid from a group of subjects with atopic rhinitis. The results seen in Table V indicated that the levels of leukotrienes, histamine, and prostaglandin D₂ were significantly elevated over the control lavage fluid and were in the range associated with local inflammation and irritant receptor stimulation.¹⁴

NASAL-SINUS-BRONCHIAL REFLEX

Several studies relating the upper and lower airways are predicated on the fact that there are receptors in the nose, the nasopharynx, and presumably the sinuses that, on proper stimulation, result in bronchoconstriction. Kratchmer, a French physiologist, demonstrated a substantial increase in lower airway resistance in cats by stimulating the nose with either sulfur dioxide or ether.¹⁵ In 1903 Dixon showed that electrical stimulation of the nose can also result in increased lower airway resistance in cats. He subsequently extended these observations to demonstrate that section of the vagus nerve blocked the changes in lower airway resistance.¹⁶

Ogura and Harvey¹⁷ conducted a series of experiments in both animals and human subjects in their search for an association between nasal resistance and bronchial asthma. They were able to restore the lower airway to normal in some patients simply by correcting a nasal septal deviation. Speizer and Frank¹⁸ exposed healthy human volunteers to sulfur dioxide intranasally and showed an increase in lower airway reactivity.

In a well-controlled study, Kaufman and Wright¹⁹ obtained uniform increases in lower airway resistance by blowing silica particles into the nasopharynx in 10 nonsmoking adults who had no chest complaints and normal pulmonary function tests. Repeating the experiments after the injection of atropine, they demonstrated that the lower airway response was totally obviated.

TABLE V. Inflammatory mediators in lavage fluid

	LTC ₄ /D ₄ /E ₄	Histamine	PGD ₂
Sinus lavage in chronic sinusitis	1110	258	84
Nasal lavage in atopic patients	73	6	12

LTC, Leukotriene; PGD₂, prostaglandin D₂.

Could allergy-inducing particles deposited in the nose lead to a bronchial reflex? No such connection was found in several studies. When patients with grass- or ragweed-induced allergic rhinitis were subjected to intranasal challenge with specific allergens, no effect on lower airway performance could be demonstrated.²⁰ Schumacher et al.,²¹ who used histamine for intranasal challenge in patients with allergic rhinitis, were similarly unable to show any effect on lower airway responsiveness. Yan and Salome²² performed similar studies on patients with perennial rhinitis. When these patients with active rhinitis were challenged intranasally with histamine, half of the patients showed a significant fall in forced expiratory volume in 1 second (FEV₁). This suggests that a certain threshold of nasal disease severity may be necessary to provoke reflex changes in the lower airway as a response to nasal challenge.

One can postulate neuroanatomic pathways that could reflexly connect the paranasal sinuses to the lungs. Receptors in the nose, and presumably the paranasal sinuses, lead to afferent fibers that in turn form part of the trigeminal nerve. The trigeminal nerve then passes to the brain stem, where it can connect by way of 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 an integral part in maintaining resting bronchial muscle tone as well as in mediating acute bronchospastic responses.

SUMMARY

It appears that sinusitis occurs not only in association with bronchial asthma but may also play a role in its pathogenesis. The basic mechanisms underlying the relationship of sinusitis and asthma need to be investigated, and neurophysiologic studies exploring the nature of sinus reflexes should be designed with experimental animal models. Data certainly suggest that proper treatment of sinusitis by medical and/or

surgical means will frequently result in significant improvement of asthma symptoms.

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DISCUSSION

Dr. Druce. You change nasal physiology when you change posture. If you look at the patient in the erect position, there is a marked change in nasal airway resistance, which suggests some type of reflex activity in the blood vessels within the nose.

Dr. Irvin. It is very difficult for me to think that our data are explained either by posture or reflex. All the procedures occur the afternoon before the animal being studied.

Dr. Kaliner. I personally have to reject the concept that mucus can drain down into the airways. Rats are different from humans in many ways as are rabbits. If I stimulate rat airway epithelium with specific allergens, I find that the serosal mast cells degranulate within 30 seconds. That is about 1000 to 1500 μ m of mucosal tissue that the antigen could not possibly penetrate to degranulate those mast cells, and it occurs within 30 to 60 seconds. I believe that this must be a reflex response.

This reflex originates in the nasal mucosa and stimulates both the sinus and bronchial mucosa to become hypersecretory, which is why so many people have bronchitis and sinusitis simultaneously, and those who are predisposed to asthma have asthma. What we are treating is an ill-defined, nasalbronchial reflex.

Dr. Rachelefsky. A large spectrum of children have sinusitis as we have talked about but not persistent sinusitis, and when their sinusitis flares, their asthma worsens. When they contract their upper respiratory tract infections complicated by sinusitis, it triggers their asthma. When the sinusitis improves, the asthma clinically resolves. I think we agree that sinusitis can trigger asthma, but we do not know how, period.

Dr. Evans. I concur with Dr. Rachelefsky that sinusitis, certainly in a referral practice, is a major trigger of chronic asthma in children. We looked at asthma in the emergency room. We took radiographs of the sinuses and found evidence of sinusitis in 64% of those children who were admitted with asthma.