

Complications of allergic rhinitis

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Upper and lower respiratory diseases, including asthma, sinusitis, and otitis media with effusion, frequently complicate allergic rhinitis. The close association of nasal allergies with these conditions has been supported by extensive epidemiologic evidence. Similar models have been proposed to explain the pathophysiologic links between allergic rhinitis and both sinusitis and otitis media with effusion. In these models, inflammation caused by nasal allergy and/or viral infection leads to obstruction, fluid accumulation, bacterial infection, and acute disease. If these diseases are unsuccessfully treated, a chronic state of inflammation, obstruction, and infection develops that can cause mucosal damage and, ultimately, chronic disease. A number of studies have investigated the roles and interactions of viruses and allergens in the development of otitis media with effusion. Diagnosing and prophylactically treating nasal allergies in patients with this condition may help prevent recurrent episodes and improve the response to therapy. (*J Allergy Clin Immunol* 2000;105:S605-9.)

Key words: Allergic rhinitis, eustachian tube obstruction, middle ears underpressure, otitis media with effusion, sinusitis

Approximately 20% of adults and children have seasonal or perennial allergic rhinitis.¹ Despite its prevalence, the condition is often treated inadequately and becomes chronic. A chronic state of nasal inflammation and obstruction develops, frequently leading to more serious complications in both the upper and the lower airways. Retrospective and prospective epidemiologic surveys have shown that allergic rhinitis is closely associated with, and may be a causative factor in, asthma, sinusitis, and otitis media with effusion (OME).

Models have been developed to explain the pathogenesis of both sinusitis and OME. The precipitating events in both these models are not bacterial infections but nasal inflammation and obstruction caused by nasal allergy and/or virus infection. With regard to OME, nasal challenges with histamine and allergens have been shown to cause nasal obstruction that results in eustachian tube obstruction. Experimental infection with certain viruses not only causes eustachian tube obstruction but also middle ear under pressure and middle ear disease. Viral upper respiratory tract infection (URTI) in patients with nasal allergy (especially to perennial allergens) may serve to enhance inflammatory responses in the nose and

Abbreviations used

OME: Otitis media with effusion
URTI: Upper respiratory tract infection

eustachian tube that provoke eustachian tube obstruction and lead to OME.

EPIDEMIOLOGIC LINKS BETWEEN ALLERGIC RHINITIS AND OTHER AIRWAY DISEASES

Cross-sectional epidemiologic studies demonstrate that up to 78% of patients with asthma are diagnosed with allergic rhinitis.² A more recent study documented that 99% of adults and 93% of adolescents with allergic asthma also have allergic rhinitis.³ Conversely, asthma is diagnosed in up to 37% of patients with seasonal rhinitis.⁴ In patients with both allergic diseases, rhinitis precedes asthma in 43% to 64% of the cases.³ A prospective 23-year study reported a 3-fold increase in the incidence of asthma in patients who previously had allergic rhinitis (without apparent asthma) compared with those patients who had not had rhinitis (10.5% compared with 3.6%).⁵

The coexistence of allergic rhinitis and sinusitis has been well documented. An early study demonstrated that 53% of children with allergic rhinitis had abnormal sinus radiographs,⁶ whereas, in a more recent study, up to 70% of children with allergy and chronic rhinitis had abnormal findings on sinus radiographs.⁷ Numerous studies of children and adults have documented the prevalence of allergic rhinitis and/or atopy in patients with both acute and chronic sinusitis.⁸⁻¹⁰ In patients with recurrent sinus infections, extensive sinus disease was associated with allergy in 78% of patients.¹¹ In children with chronic OME, 40% to 50% have allergic rhinitis confirmed with positive allergy skin tests or increased serum IgE antibodies to specific allergens.¹²

MODEL FOR THE DEVELOPMENT OF SINUSITIS AND OTITIS MEDIA

A cyclic model has been proposed to explain the progression of sinusitis from an acute to a chronic condition.¹³ This model assumes that the initial event in sinusitis is not bacterial infection but, rather, the obstruction of the osteomeatal complex, which impedes the normal movement of air and secretions in and out of the sinuses. Nasal inflammation primarily caused by viral URTI and allergic rhinitis contribute to the obstruction of the sinus passages. The results of 1 study showed that approximate-

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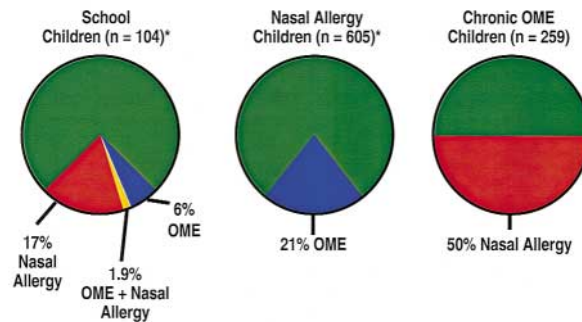


FIG 1. Nasal allergy and chronic OME in various pediatric populations. *Control group. (Adapted from Tomonaga K, Kurono Y, Mogi G. The role of nasal allergy in otitis media with effusion. *Acta Otolaryngol* [Stockh] 1988;458[suppl]:41-7. With permission.)

TABLE I. Early- and late-phase allergic reactions after intranasal allergen challenge

Obstruction	Response (n/N)		
	Early	Persistent	Late
Eustachian tube			
Patients	7/10	2/10	6/10
Ears	12/20	4/20	10/20
Nasal	9/10	2/10	7/10
Bronchial	2/10	0/10	3/10

Adapted from Skoner DP, Doyle WJ, Boehm S, Fireman P. Late phase eustachian tube and nasal allergic responses associated with inflammatory mediator elaboration. *Am J Rhinol* 1988;2:155-61. With permission.

ly one third of subjects who were inoculated with rhinovirus experienced the development of sinus abnormalities and typical sinus disease symptoms.¹⁴ In another study, 87% of healthy adult volunteers with self-diagnosed colds had abnormalities of 1 or both maxillary sinuses.¹⁵

Thickened secretions develop that are unable to pass through narrowed ostia; and the accumulation of these secretions leads to further obstruction, mucosal swelling, and, possibly, thickening of the sinus mucosa. An anaerobic environment develops in the sinus that favors bacterial growth, leading to infection. Impaired ciliary function and an increase in thickened mucus further obstruct drainage. Unless the cycle is broken, obstruction continues to increase and unresolved or new infections flare up, leading to recurrent acute episodes and eventually to chronic disease. This model offers an explanation of why chronic sinusitis is often resistant to treatment with antimicrobials alone and a rationale for treating the cause of inflammation (eg, with antihistamines and corticosteroids).

A similar model has been developed to explain the pathogenesis of OME. Acute otitis media and OME are the most common childhood illnesses that require physician care.¹² By the time children reach 3 years of age, 83% have

had at least 1 episode of acute otitis media.¹⁶ However, acute otitis media also affects a substantial number of adults.

The OME model hypothesizes that nasal inflammation because of allergens and/or viral URTIs leads to inflammatory swelling and obstruction of the eustachian tube, which in turn leads to increased negative pressure in the middle ear and improper ventilation. Middle ear under pressure allows fluids into the middle ear. Transient eustachian tube opening can occur in the middle ear with an effusion, which results in insufflation or aspiration into the middle ear cavity of nasopharyngeal secretions that contain bacteria, virus, and/or allergens. Bacteria in the middle ear fluid can cause acute bacterial otitis media. Sustained obstruction and dysfunction of the eustachian tube (eg, because of inflammation caused by perennial allergic rhinitis), persistent effusion, and unresolved bacterial infections can lead to chronic OME. This model has been extensively tested because of the accessibility of the middle ear to assessment of function. A number of studies on the pathogenesis of otitis media have described the interactions among viral URTIs, nasal allergic reactions, eustachian tube dysfunction, and middle ear disease.

Figure available in print only.

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FIG 2. Changes in environment (A) pollen and (B) eustachian tube obstruction before (week 1), during (weeks 2 to 9), and after (weeks 10 and 11) grass pollen season. * $P < .05$ versus baseline. (Modified with permission from Skoner DP, Lee L, Doyle WJ, Boehn S, Fireman P. Nasal physiology and inflammatory mediators during natural pollen exposure. *Ann Allergy* 1990;65:206-10. Copyright ACAAI.)

THE ROLE OF ALLERGENS IN MIDDLE EAR DISEASE

The high prevalence of chronic OME among patients with allergic rhinitis strongly suggests that IgE-mediated allergies are involved in the pathogenesis of middle ear disease. Of the children with allergy, 21% have OME, whereas 50% of children with chronic OME have nasal allergy (Fig 1).¹⁷

Several studies have examined the effects of seasonal allergic rhinitis on eustachian tube function and middle ear pressure in subjects with allergic rhinitis. The results of these studies demonstrate that during peak pollen season in untreated pollen-allergic individuals, eustachian tube obstruction increases from 15% at baseline to 60% at peak pollen exposure (Fig 2).¹⁸ In addition, negative middle ear pressure develops in 24% to 48% of pollen-allergic adults during natural peak pollen exposures.¹⁹

Intranasal pollen challenges in subjects with allergy have been shown to promote nasal symptoms, nasal obstruction, and eustachian tube obstruction.²⁰ Both early- and late-phase immune reactions in the eustachian

FIG 3. The distribution of nasal- and eustachian tube-obstructing antigen doses for study subjects. *Open bar*, nasal obstruction; *filled bar*, eustachian tube obstruction. (Adapted from Skoner DP, Doyle WJ, Chamovitz AH, Fireman P. Eustachian tube obstruction after intranasal challenge with house dust mite. *Arch Otolaryngol Head Neck Surg* 1986;112:840-2. Copyright 1986, American Medical Association.)

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FIG 4. Incidence of eustachian tube obstruction in patients who were sensitized to ragweed and who were challenged with antigen after pretreatment with either placebo or antihistamine plus decongestant. (Modified with permission from Stillwagon PK, Doyle WJ, Fireman P. Effect of an antihistamine/decongestant on nasal and eustachian tube function following intranasal pollen challenge. *Ann Allergy* 1987;58:442-6. Copyright ACAAI.)

tube and the nose have been reported after intranasal challenge with ragweed pollen (Table I).²¹ Intranasal challenge with a perennial allergen (house-dust mite) also leads to eustachian tube obstruction (Fig 3).²² Fifty-five percent of adults with nasal allergy experienced the development of eustachian tube dysfunction in response to challenge with house-dust mite.²² Eustachian tube obstruction has also been reported to develop more frequently in subjects with allergic rhinitis than subjects without allergy after a single intranasal histamine challenge and at relatively low histamine doses.²³ In allergen-provocation studies, nasal obstruction usually preceded the development of eustachian tube obstruction, which

TABLE II. Specific micro-organisms in the 43 samples of middle ear fluid that contained both bacteria and viruses*

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was not the case after histamine challenge.²³ In addition, a variety of potent inflammatory mediators, including histamine, have been detected in middle ear effusions of children with OME.²⁴

It has been proposed that prolonged eustachian tube obstruction, which could result from perennial exposure to an allergen (eg, house-dust mite), could precipitate middle ear disease, if the "priming" phenomenon occurs in the eustachian tube (ie, the mucosa responds to lower doses of allergen with repeated exposure) as it does in the nose. Seasonal priming has been demonstrated to increase the physiologic responsiveness of the eustachian tube both to ragweed pollen and histamine, with the observed hyperresponsiveness extending beyond the ragweed season.²¹

THE ROLE OF VIRUS INFECTION IN MIDDLE EAR DISEASE

Epidemiologic studies show that one half of all new episodes of otitis media are diagnosed immediately after or concurrent with a viral URTI.¹² In the past, viruses have been isolated rarely from middle ear effusions in patients with otitis media with the use of standard culture techniques. However, recent studies with PCR-based molecular analysis have shown that 53% of middle ear effusions are positive for viruses.²⁵

Experimental infection with rhinovirus-39 in humans has shown substantial increases in eustachian tube dysfunction in most subjects and abnormal middle ear pressures in approximately 30% of infected subjects, but the development of otitis media was rare (0% to 3%).²⁶ However, in a study of intranasal inoculation with influenza A virus, 59% of subjects experienced the development of middle ear under pressure, and 25% of subjects experienced the development of otitis media.²⁵ This study was unique because 1 subject experience the development of middle ear under pressure followed by purulent otitis media. PCR analysis of the patient's middle ear effusion was positive for both influenza A and *Streptococcus pneumoniae*.²⁵ More than 80% of infected subjects experienced the develop-

ment of eustachian tube dysfunction, and approximately 80% had middle ear under pressure.²⁶ Five of 21 infected subjects had otoscopic evidence of OME beginning as early as 4 days after viral exposure. One subject experienced symptoms of dizziness and vertigo, which suggested transient inner ear involvement.²⁶ This supports a causal role for viral URTIs in the pathogenesis of otitis media through the early development of eustachian tube obstruction and abnormal middle ear pressure.

In a recently published study of children with acute otitis media, investigators isolated micro-organisms from the fluids in their subjects' middle ears.²⁷ Sixty-five percent of the fluid samples contained both bacteria and viruses. Of these samples, 100% of those samples that were infected with influenza virus also contained *S pneumoniae*, 25% contained *Haemophilus influenzae*, and 38% *Moraxella catarrhalis* (Table II).²⁷ These results suggest the possibility that virus infection sets the stage for bacterial infection.

VIRAL/ALLERGEN INTERACTION

The relationship between viral infection and nasal allergens in provoking OME is not clearly understood. However, there is evidence that their interaction enhances certain immune responses. Infection with rhinovirus-39 induces significant increases from baseline ($P = .000008$) in serum IgE antibodies in subjects with allergic rhinitis.²⁸ URTI also intensifies the release of a variety of inflammatory substances, some of which have been shown to provoke eustachian tube obstruction. For example, experimental infection with influenza A increases the release of histamine from peripheral blood basophils of patients with allergic rhinitis.¹² It has been reported that patients with allergic rhinitis and rhinovirus URTI have enhanced lower airway responsiveness and basophil histamine release to ragweed challenge,²⁹ which suggests that patients with allergic rhinitis may be hyperresponsive to inflammatory mediators elaborated during a viral URTI, which can be potentiated by the priming of a preceding allergy season or URTI.

SUMMARY

Numerous studies have supported the involvement and interaction of virus infection and allergic rhinitis in the pathogenesis of OME. Further clarification of the nature of the interactions between viruses and allergens in middle ear disease may help describe populations at risk for OME that would benefit from preventative therapies (eg, influenza inoculations, allergen avoidance, antihistamines). A small study investigated the prevention of eustachian tube obstruction by pretreatment with an antihistamine plus decongestant in a group of subjects who were ragweed-sensitive and who underwent nasal provocation with allergen. As the dose of ragweed was increased, actively treated patients showed a substantially lower incidence of eustachian tube obstruction (Fig 4).³⁰

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