

The Role of Allergy in Otologic Disease

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KEYWORDS

- Allergy • Atopy • Eustachian tube • Otitis media with effusion • Ménière's disease
- Endolymphatic hydrops • Eosinophilic otitis media • Immunotherapy

KEY POINTS

- The current medical evidence supports the relationship between allergic disease, eustachian tube dysfunction, and otitis media with effusion.
- Atopic disease may play a role in the pathogenesis of eosinophilic otitis media.
- The association of allergy and Ménière's disease is well-documented, and certain patients may benefit from allergy immunotherapy.

INTRODUCTION

Allergic disease is one of the most common conditions for which patients seek treatment in the United States. The prevalence of allergy has been estimated at around 30% to 40%,¹ and the economic burden of allergic rhinitis has been estimated to be between \$5.5 and \$9.7 billion per year.² Allergy is commonly associated with conditions such as rhinitis, sinusitis, and asthma, but the relationship between allergy and otologic disease is less clear. In this article, the authors examine the evidence for a relationship between allergic disease and several common otologic conditions, including otitis media, eosinophilic otitis media (EOM), and Ménière's disease (MD).

THE ROLE OF ALLERGY IN EUSTACHIAN TUBE DYSFUNCTION AND OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME) is a clinical disease characterized by the presence of nonpurulent fluid in the middle ear behind an intact tympanic membrane. The symptoms of OME usually involve hearing loss and aural fullness; in children, it can be associated with delayed speech and language development and may cause permanent middle ear damage with mucosal changes.³ Although it is generally agreed that

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OME is a multifactorial disease arising from various factors including viral or bacterial pathogens, environmental risks such as firsthand or secondhand smoking, and patient-specific anatomy, the relationship between allergy and OME has been historically controversial.

Epidemiology

Many recent studies have established that the prevalence of allergic rhinitis in patients with OME is higher than that in the general population, although the degree of difference in these studies varies greatly. In Korea, the incidence of allergic rhinitis was significantly higher in children with OME (33.8%) than without OME (16%).⁴ In Japan, it was estimated that 6% to 20% of the general population is atopic and, among atopic patients, only 21% have OME; however, more than 87% of patients with OME were found to be atopic and/or have allergy symptoms.⁵ In other studies, allergy is estimated to confer anywhere from a 2.0- to a 4.5-fold increased incidence of OME compared with that of nonsensitized people.^{6,7} The wide range of prevalence may be attributed to uncontrolled study designs, including varying criteria used for diagnosing allergic sensitization and the different populations being studied.^{8,9}

Pathophysiology

The accumulation of fluid in the middle ear cavity in OME involves 2 different mechanisms at the level of the middle ear mucosa: the first involves transduction from the mucosa capillaries, and the second involves active secretion, or exudation, from mucosal glands.¹⁰ The eustachian tube (ET) also plays a role and is a structure that facilitates communication between the middle ear cavity with the nasopharynx. Its basic functions are (1) ventilating the middle ear cavity to regulate middle ear air pressure with atmospheric pressure, replenishing oxygen that has been absorbed and allowing gases produced in the middle ear to escape, (2) draining middle ear secretions into the nasopharynx, and (3) protecting the middle ear from nasopharyngeal secretions and sound pressure.¹¹ The respiratory epithelium lining the ET mucosa has several types of defense mechanisms, including mechanical (eg, mucociliary apparatus), innate (eg, inflammatory mediators), and acquired (eg, antigen specific).¹² It has been established that OME is related to ET dysfunction, because suboptimal opening and closing of the ET affects the basic functions of ventilating and draining the middle ear space.^{9,13,14} The proposed mechanisms explain that ET dysfunction is due to an inflammatory process that includes intrinsic mechanical obstruction from the inflammatory swelling of the ET mucosa, altered mucociliary activity, and hypersecretion by seromucous glands. Several double-blind protocols have demonstrated intranasal allergen challenges result in ET obstruction, with allergic reaction inhibiting even transient dilations of the ET during swallowing.^{15–18} Histologic studies have also shown that levels of eosinophils, CD3 T cells, interleukin (IL)-4 levels, and messenger RNA levels for IL-5 are increased at both ends of the ET. All these studies suggest that the ET may become dysfunctional owing to allergic inflammation causing intrinsic mucosal edema and obstruction.

The adenoidal tissues are part of the mucosal-associated lymphoid tissue of the upper airway as well, joining the palatine, torus tubarius, and lingual tonsils to form the circle of lymphoid tissue around the pharyngeal wall known as Waldeyer's ring. The adenoids are organized in deep crypts, and contain germinal centers and interfollicular areas, which play an important role in the generation of both T helper cells (Th1, Th2), and immunoglobulin A (IgA)-committed B cells.¹⁹ Adenoids have been proposed to cause ET dysfunction both by physical obstruction as well as by the release of chemical mediators. The proportions of CD4⁺, CD8⁺, and CD19⁺ associated with Bcl-2 (an

antiapoptotic protein) were found to be lower in children with hypertrophic adenoids with OME than the levels in children with hypertrophic adenoids without OME, which indicates there is enhanced apoptosis of the naïve and effector T cells in adenoid tissue, suggesting the adenoids play a role in lymphocyte regulation in local immunologic disorders.²⁰ Another study reported that lymphocytes from the adenoids showed decreased Th1 cytokine but normal Th2 cytokine secretions compared with peripheral blood lymphocytes among children with recurrent otitis media, which suggests the underlying Th2 immune profile associated with atopy may play a role in determining the risk of recurrent OME.²¹

The middle ear mucosa evolves from the same ectoderm as the rest of the upper respiratory tract epithelium, and has been found in animal studies to have the same active intrinsic immunologic responsiveness to antigenic stimulus as the nasal tract, sinuses, and bronchi.²² Inflammatory cells and molecules found in the fluid of middle ear effusions (MEEs) have been used to evaluate the pathogenesis of OME. Several studies have reported increased eosinophil mediators and increased Th2 cytokine levels in MEEs and mucosal biopsies.^{23–27} One such study in adults revealed that levels of IL-4 were higher in MEEs of adults with allergic rhinitis than in those without allergic rhinitis, suggesting that Th2 cytokines may be related to the pathogenesis of OME in allergic rhinitis-positive adults, whereas Th1 cytokines potentially affect MEEs in OME regardless of the presence of allergic rhinitis.²⁸ Multiple other studies have demonstrated the association of serum and middle ear immunoglobulins with Th2 response in the middle ear.^{29–31} These studies suggest that inflammation of the middle ear can indeed be allergic in nature, and the middle ear may be included with the rest of the upper respiratory tract in the concept of the single “unified airway.”^{29,32}

Immunotherapy for Otitis Media with Effusion

There are studies investigating immunotherapy and OME that have demonstrated that some patients' effusions resolve when allergies are treated with immunotherapy and/or diet elimination, although these trials are uncontrolled or nonrandomized.^{33–40} In 2008, Hurst⁴¹ conducted a study comparing immunotherapy treatment patients with a control cohort of allergic patients not receiving immunotherapy, showing resolution of 89% of OME in treated patients versus 0% of controls. This study suggested that, in this select population, immunotherapy was efficacious in preventing or limiting the duration of OME; however, this study was not randomized, and a possibility of a strong selection bias exists without randomization, limiting the ability to come to a scientific conclusion based on these data alone.⁴¹

Summary

The current medical evidence supports the relationship between allergic disease, ET dysfunction, and OME. The majority of studies that have been performed on this subject suggest that a large percentage of patients with OME are atopic, and that the middle ear is capable of an allergic response and can be considered a part of the unified airway. Definitive randomized studies on resolution of effusions with immunotherapy are lacking, and future randomized, controlled trials are needed to determine the exact role of allergen immunotherapy in the OME population.

EOSINOPHILIC OTITIS MEDIA

EOM is a form of intractable otitis media that occurs primarily in patients with bronchial asthma and was first reported in 1994.⁴² The diagnostic criteria for EOM were established in 2011, and since then the pathophysiology and clinical characteristics of the

disease are continuing to be elucidated.^{43–47} The major criteria are identification of eosinophils from MEE or middle ear mucosa by histologic or cytologic examination. Minor diagnostic criteria include association with adult-onset bronchial asthma and nasal polyposis, highly viscous MEE, and resistance to conventional treatment for otitis media. A definitive case meets the major criteria plus 2 or more minor criteria.⁴³

Epidemiology

The majority of first-time EOM patients have been found to be aged 50 to 60 years, with a 2:1 female to male ratio.⁴³ On average, these patients showed an 83% rate of bilateral disease a 50% rate of superimposed progressive sensorineural hearing loss, and a 6% rate of hearing loss progression to complete deafness in the involved ears.⁴³ Approximately 75% displayed sinusitis or multiple nasal polyps and adult-onset bronchial asthma.⁴³

Clinical Features

EOM is generally considered to be a bilateral process. Regardless of the existence of tympanic membrane perforation, the effusion of EOM is yellowish and highly viscous. When a tympanostomy tube is placed in EOM, the lumen of the tube is easily blocked by the viscous effusion.⁴⁸ In a study of 190 EOM patients, approximately one-half showed conductive hearing loss and 6% became completely deaf.⁴³ It is proposed that eosinophilic and bacterial inflammatory products of the middle ear may invade the inner ear via the round window to cause inner ear damage.⁴⁸ Risk factors associated with the severity of EOM include body mass index and duration of bronchial asthma.⁴⁹ The prevalence of eosinophilic rhinosinusitis has been found to be increased in patients with EOM at approximately 75%,⁴⁸ another disease often associated with an atopic Th2 inflammatory pattern.

Pathophysiology

ET dysfunction, specifically insufficient closing of the ET as evaluated by sonotubometry, has been observed in EOM patients and may lead to pathogenic EOM by allowing foreign materials to enter the middle ear and cause eosinophilic inflammation.^{50,51} Histologic examination of the MEEs in EOM patients have shown the level of IgE as well as the concentration of eosinophil cationic protein are significantly higher in the MEE than the serum of EOM patients.⁵² Eosinophilic granule 2-positive cells and the eosinophil chemoattractants IL-5 and eotaxin have been found to be significantly higher in the MEE and middle ear mucosa of EOM patients than in the corresponding control group.^{53,54} Another study examined a population of 26 patients with EOM and found that there were a high number of positive sensitizations in serum testing (16 of 26 had positive testing to perennial allergens), and that the rate of detection of specific IgE locally within the ear was significantly higher than in control patients. They found that antigen-specific IgE within the middle ear was present in 16 of 26 patients versus 1 of 9 control patients ($P \leq .01$), and that middle ear-specific IgE presence correlated with the severity of EOM, suggesting a role for atopic disease in the pathogenesis of EOM and perhaps presenting a therapeutic target.⁵⁵

Treatment

Standard treatment for EOM differs around the world. In some places, steroids are injected into the middle ears, and supplanted with antibiotics as indicated by infection. The anti-IgE agent omalizumab has also been shown to improve the severity of EOM with resolution of MEE; however, the clinical application of omalizumab may be limited

by its cost and need for prolonged use.^{49,56} A recent study showed promise in weekly injections of pegylated interferon in the treatment of refractory cases of EOM.⁵¹

In the United States, EOM treatment still seems to focus on surgical intervention. Surgical treatment with tympanostomy tubes as mentioned does not effectively solve the clinical symptoms of EOM. Tympanoplasty is aimed at controlling otorrhea or treating hearing impairment owing to EOM, and tympanomastoidectomy facilitates middle ear and mastoid ventilation, and the delivery of topical steroids. There have also been cases reported in which cochlear implantation was performed to treat deafness associated with EOM.^{57,58}

Future study will be needed to determine the role for allergy treatment and immunotherapy in this challenging disease. It stands to reason that, a Th2-driven disease with high levels of local specific IgE, may benefit from immunotherapy, but at this time the question remains unanswered.

Summary

EOM is a recently described entity, the pathophysiology of which seems to be related to chronic allergic or immune response, likely through antigen presentation via a dysfunctional ET. The clinical features of this disease are still being defined through case reports and series, and further research is needed in identifying the role of allergy in the pathophysiology and treatment.

ALLERGY AND ENDOLYMPHATIC HYDROPS

The symptoms of MD were first described by Prosper Ménière in 1861, when he associated episodes of vertigo with the inner ear. The syndrome is described by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) as the presence of recurrent, spontaneous episodic vertigo (rotational and lasting at least 20 minutes), hearing loss, aural fullness, and tinnitus ([Table 1](#)).⁵⁹ It is generally agreed that the pathogenesis of MD involves the hydropic distension of the endolymphatic system, and the AAO-HNS also describes MD as the “idiopathic syndrome of endolymphatic

Table 1
Criteria for diagnosis of Ménière’s disease

Diagnostic Certainty	Criteria
Certain	Definite Ménière’s disease, plus histopathologic confirmation of hydrops
Definite	Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h Audiometrically documented low-frequency to midfrequency sensorineural hearing loss in 1 ear, defining the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear not better accounted for by another vestibular diagnosis
Probable	Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h; fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear not better accounted for by another vestibular diagnosis
Possible	Episodic vertigo of the Ménière’s type without documented hearing loss or sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definite episodes Other causes excluded

From Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS guidelines for the definition of Ménière’s disease. *Otolaryngol Head Neck Surg* 2016;154(3):404; with permission.

hydrops.” Although by definition idiopathic, MD has previously been attributed to a variety of etiologies including trauma, viral infections, metabolic disorders, autoimmune factors, and allergies. Although there is not yet any evidence to prove causation between allergy and MD, there has been a recognized association between the 2 entities for nearly a century; the first published report of MD thought to be related to allergy appeared in the literature in 1923, when 2 cases were described of patients with symptoms consistent with MD whose symptoms resolved with epinephrine treatment.⁶⁰ An association between allergy and MD has been shown in various cross-sectional and observational studies over time.

Epidemiology

In the United States, MD has been reported as having an incidence rate of 15 per 100,000 and a prevalence rate of 190 per 100,000.^{61,62} The prevalence in Japan and Finland have been reported as 17 per 100,000 and 43 per 100,000, respectively.⁶³ In a survey of 734 patients with Ménière’s syndrome, the prevalence of skin test–confirmed concurrent allergic disease was 41%, roughly 3 times the prevalence of physician-diagnosed allergy in the general population.^{64,65}

Pathophysiology

The exact pathophysiology of MD is poorly understood, although it is generally believed to be related to distortion of the membranous labyrinth resulting from an overaccumulation of endolymph. The inner ear fluids endolymph and perilymph are separated by thin membranes that support the neural apparatus of hearing and balance. Attacks of hydrops are proposed to be due to an increase in endolymphatic pressure, which causes a rupture in Reissner’s membrane separating the perilymph from endolymph. The resulting chemical mixture leads to depolarization blockade and transient loss of function of the vestibular nerve. This sudden change in the firing rate of the vestibular nerve creates an acute vestibular imbalance, or vertigo.⁶⁶

It has been suggested that the endolymphatic sac and duct are the sites of immune activity in the inner ear. The endolymphatic sac has been found to be capable of both processing antigens and producing its own local antibody response.^{67,68} IgG, IgM, IgA, and secretory components are found in the endolymphatic sac, and the perisaccular connective tissue houses numerous plasma cells, macrophages, as well as mast cells.^{69,70}

A few mechanisms by which allergy could produce MD have been proposed, with a focus on the theme of inflammation within the endolymphatic sac⁷¹ are as follows:

1. The endolymphatic sac contains fenestrated blood vessels that allow for antigen entry, subsequently leading to mast cell degranulation and inflammation in the perisaccular connective tissue. This could then result in a toxic accumulation of metabolic products, which may interfere with hair cell function, and the histamine release could cause vasodilation and affect the resorptive capacity of the endolymphatic sac.
2. Circulating immune complexes enter the endolymphatic sac circulation through the fenestrated blood vessels or are deposited in the stria, resulting in inflammation and possibly increased vascular permeability, disrupting the normal fluid balance in the inner ear.
3. A viral antigen–allergic interaction stimulates Waldeyer’s ring, triggering T-cell migration to the endolymphatic sac, which results in a chronic low-grade inflammation and, over time, can stimulate excess fluid production.

Treatment

The aim of medical treatment of MD is symptomatic relief. The standard therapy for MD involves a sodium-restricted diet, diuretic medication, and vestibulosuppressants as needed, which for the majority of patients offers acceptable relief from vertigo. No treatment has been found thus far for stabilization of the hearing loss resulting from MD. In MD that has failed medical therapy, further interventions can be trialed including use of a Meniette pressure-regulating device, intratympanic gentamicin, endolymphatic shunt surgery, or ablative procedures such as vestibular nerve section or labyrinthectomy.^{71,72}

Betahistine is a medication commonly prescribed for the treatment of MD. It is a histamine analogue medication that acts as a weak H1 receptor agonist and strong H3 receptor antagonist. Its proposed mechanism is decreasing the release of histamine, dopamine, gamma-aminobutyric acid, acetylcholine, norepinephrine, and serotonin, improving microcirculation in the inner ear.⁷³ Although it is one of the most frequently prescribed medications for MD in Europe, it is not currently available in the United States, although can be obtained by compounding pharmacies or through sources in Canada or Europe.^{74,75} Prior observational studies and randomized, controlled trials produced contradictory results on the treatment efficacy of betahistine; however, a recent large double-blind randomized placebo controlled trial provided no clear evidence that betahistine produces a significant decrease in the number of vertigo attacks.⁷⁶

The most commonly prescribed medications for the treatment of MD in the United States are antihistamines, including meclizine, diphenhydramine, and dimenhydrinate. It is thought that these medications exert an anticholinergic central suppressive effect on vertigo. These medications ultimately do not alter the underlying pathology of hydroptic distention of the endolymphatic space.

The effect of allergen immunotherapy and elimination of suspected food allergens in MD patients has been studied. There was a significant improvement from before to after treatment in both allergy and MD symptoms in those treated with allergen immunotherapy and dietary avoidance in one retrospective study.⁷⁷ A subsequent prospective questionnaire-based study demonstrated a significant decrease of vertigo, tinnitus, and unsteadiness, and improvement of ratings on AAO-HNS disability scale after immunotherapy, suggesting a role for allergen immunotherapy in this disease.⁷¹

Summary

Although MD is accepted to be a multifactorial disease, the association of allergy and MD is well-documented, and allergy may be involved in the final inflammatory pathway in certain patients with MD.⁷⁸ The research on MD and allergy treatment is largely made up of clinical case reports, with a lack of any randomized, double-blind, placebo-controlled trials comparing MD patient outcomes with immunotherapy; however, it is suggested that immunotherapy and dietary avoidance of allergens do lessen the severity of MD symptoms. The available evidence is in the form of prospective cohort studies, which suggest possible symptomatic improvement with allergy immunotherapy. These suppositions are made with uncontrolled studies, and one must take into consideration that MD often has a fluctuating course with periods of quiescence. Continued research is needed to more definitively demonstrate the benefits of these treatments; however, in the right patients, the risk of immunotherapy and dietary avoidance is low and can be considered in patients with MD who demonstrate allergic symptoms or have positive allergy testing.

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