

Allergy and Ménière's Disease

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Ménière's disease (MD), which by definition is idiopathic, has been ascribed to various causes, including both inhalant and food allergies. Patients with MD report higher rates of allergy history and positive skin or in vitro tests compared to a control group of patients with other otologic diseases and to the general public. Recent immunologic studies have shown higher rates of circulating immune complexes, CD4, and other immunologic components in patients with MD compared to normal controls. Published treatment results have shown benefit from immunotherapy and/or dietary restriction for symptoms of MD in patients with both allergy and MD.

Introduction

In 1861, Prosper Ménière first associated dizziness with the inner ear [1]. Later, the syndrome of fluctuating sensorineural hearing loss, episodic vertigo, and tinnitus was named for him. Since then, the pathogenesis of Ménière's disease (MD) was found to be a hydropic distension of the endolymphatic system. In its guidelines for MD diagnosis and evaluation of treatment, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) describes MD as a "clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops . . . For clinical purposes (treatment and reporting), the presence of endolymphatic hydrops can be inferred during life by the presence of the syndrome of endolymphatic hydrops. This syndrome is defined as the presence of . . . recurrent, spontaneous episodic vertigo; hearing loss; aural fullness; and tinnitus" [2]. AAO-HNS guidelines further define the vertigo episodes as a "spontaneous rotational vertigo lasting at least 20 minutes." The initial vertigo attack—the feeling of intense motion when sitting or standing still—can cause the subject to fall to the ground and is accompanied by nausea and vomiting. An incidence rate of 15 per 100,000 and a prevalence rate of 218 per 100,000 have been reported for MD in the United States [3].

Although idiopathic, MD has been ascribed to various causes, including trauma, viral infections, metabolic disorders, and autoimmune factors. The first published report of MD believed to be provoked by an allergic reaction was in 1923 [4]. Both inhalant and food allergies have been linked with MD symptoms [5]. Many of MD's clinical characteristics suggest an underlying inflammatory, if not autoimmune, etiology such as its propensity to wax and wane, with periods of remission. It is also bilateral in a significant number of cases [6,7].

In this article, we first review the immunology of the inner ear. We then review literature from the years 2002 to 2007 regarding MD, allergy, and autoimmunity.

Review of Immunology

The inner ear has little exposure to pathogens and few resident cells that are associated with immunologic function. In the past, this led to assumptions that it was immunologically privileged, similar to the brain. More recent research indicates that the inner ear is actually more immunoresponsive than the brain [8]. The labyrinth exhibits a blood-labyrinthine barrier analogous to the blood-brain barrier, which maintains the cochlea's unique ionic characteristics. There is no lymphatic drainage from the inner ear, and, although immunoglobulins are present in the perilymph, the amount is only 1/1000 of that in the serum [9].

The inner ear demonstrates both cellular and humoral immunity. Most leukocytes enter the cochlea via the spiral modiolar vein [10]. The innate immunity of the cochlea has been suggested to allow an adaptive local response to antigen challenge [11]. Hashimoto et al. [11] have suggested that the inner ear may be "primed" by lipopolysaccharides or other viral or bacterial antigens, resulting in the upregulation of interleukin (IL)-1 β in the spiral ligament fibrocytes, permitting leukocytes to enter. Subsequently, in those having lymphocytes primed to react against inner-ear antigens, an initiated immune response may result in local inflammation. Altermatt et al. [12] have suggested that the seat of immunoactivity in the inner ear appears to be the endolymphatic sac (ES) and duct. Immunoglobulin (Ig) G, IgM, IgA, and secretory component are found in the ES, and numerous plasma cells and macrophages reside in the perisaccular connective tissue.

Additionally, the labyrinth exhibits active components of allergic reactivity. Mast cells have been

identified in the perisaccular connective tissue. Following sensitization, IgE-mediated degranulation of mast cells has resulted in eosinophilic infiltration of the perisaccular connective tissue, and clinically, the production of endolymphatic hydrops [13].

The ES is capable of both processing antigen and producing its own local antibody response [14,15]. Surgical destruction of the ES results in decreased antigen and antibody responses [15]. The highly vascular subepithelial space of the ES contains numerous fenestrated blood vessels [16], with arterial branches of the posterior meningeal artery supplying the ES and duct [17]. Although the labyrinth is protected by the blood-labyrinthine barrier, the posterior meningeal artery is fenestrated, offering a peripheral portal of circulation. Fenestrated vessels supplying organs involved in absorption (eg, kidney, choroid) are especially susceptible to damage by immune complex deposition.

Despite evidence of immune activity, only 30% of patients with MD show a true autoantibody response on Western blot assay to specific antiochlear antibody [18]. Tests of abnormal cell-mediated immunity are either inconsistent or normal, even in patients with known causes of inner ear autoimmune dysfunction, including Cogan's syndrome [18]. Despite our increased understanding of labyrinthine immunoreactivity, we have not yet developed a reliable laboratory marker to "prove" autoimmune or allergic causation in patients with suspected inflammatory hearing loss.

Possible Mechanisms

There are different possible mechanisms by which an allergic reaction produces MD symptoms [19]. First, the ES itself could be a target organ of the allergic reaction. The sac's peripheral and fenestrated blood vessels could allow antigen entry, stimulating mast cell degranulation in the perisaccular connective tissue. The resulting inflammatory mediator release could affect the sac's filtering capability, resulting in a toxic accumulation of metabolic products, and interfering with hair cell function. Also, the fenestrated blood vessels to the ES could be pharmacologically vulnerable to the effects of vasoactive mediators such as histamine, which are released in a distal allergic reaction. The unique blood supply of the interosseous ES would serve as a portal for these mediators to exert a direct pharmacologic effect. The potent vasodilating effects of histamine or other mediators could affect the resorptive capacity of the ES. Yan et al. [20] have shown that Waldeyer's ring in the nasopharynx is the anatomic site of T-cell homing to the ES. In systemically sensitized rodents, intranasal antigen stimulation with keyhole limpet hemocyanin (KLH) in Waldeyer's ring resulted in an antigen-specific reaction in the ES and perilymphatic vessels, suggesting that viral or allergic antigen could be processed in the nasopharynx, with the resulting specific immune reaction occurring at the ES.

A second possible mechanism involves the production of a circulating immune complex, such as a food antigen, which is then deposited through the fenestrated blood vessels of the ES, producing inflammation. An increased incidence of circulating immune complexes in the serum has been described in both MD and allergic rhinitis [21,22]. The inflammatory response resulting from the deposition of immune complexes along vascular basement membranes is the hallmark of an immune complex disease. Although the binding of the complexes to the cell membranes facilitates their phagocytosis, it also results in the release of tissue-damaging enzymes. This is believed to be the mechanism of unexplained sensorineural hearing loss in patients with Wegener's granulomatosis, a prototype immune-complex mediated disease. Upon examining the temporal bones of patients with Wegener's granulomatosis and unexplained sensorineural hearing loss, the cochlea is found to be normal; the pathology occurs in the ES [23]. Alternatively, circulating immune complexes may be deposited in the stria, causing the normally intact blood-labyrinthine barrier to leak as a result of increased vascular permeability. In addition to disrupting normal ionic and fluid balance in the extracapillary spaces, this could facilitate the entry of autoantibodies into the inner ear.

A third possible mechanism is a viral antigen-allergic interaction. A predisposing viral upper respiratory infection in childhood (eg, mumps, herpes) antigenically stimulates Waldeyer's ring, with subsequent T-cell homing to the ES [20], resulting in a chronic low-grade inflammation. This is not enough initially to result in hearing loss or vertigo, but it does produce mild impairment of ES absorption. Later in adult life, "something" in the system then stimulates excess fluid production. Several investigators have assumed that viral infections play a direct or indirect role in the etiology of MD. Viruses are also capable of exacerbating allergic symptoms by several mechanisms. Both live and ultraviolet light-inactivated viruses have been shown to enhance histamine release, an effect believed to be mediated by interferon. Viruses can also damage epithelial surfaces, thereby enhancing antigen entry and increasing the responsiveness of target organs to histamine. It has long been noted that patients with poorly controlled allergy are more likely than non-allergic persons to develop upper and lower respiratory viral infections.

Epidemiology

In a survey we performed of 734 patients with Ménière's syndrome, the prevalence of test-confirmed concurrent allergic disease was 41%, twice that of the general population [24]. In a more recent survey, we found that patients reported a 58% rate of allergy history, and again, a 41% rate of positive skin or in vitro test [7].

In his original description, Prosper Ménière suggested an association between migraine and MD [1]. Since then,

many authors have noted paroxysmal headache independently occurring in many patients with MD [25–27]. Radtke et al. [28] published a well-designed prospective trial based on strict diagnostic criteria, which clearly established an increased lifetime prevalence of migraine in patients diagnosed with MD.

A recent study reported both an increased incidence of self-reported migraine and allergic rhinitis in patients with MD as compared to a control group of age- and sex-matched patients without MD attending an otolaryngology clinic [29••]. Sen et al. [29••] used a web-based questionnaire to recruit 108 patients with MD, and a control group of 100 patients attending the otolaryngology clinic for other problems. The migraine prevalence in MD sufferers was 39% compared to 18% in the control group, whereas the prevalence of allergy in those with MD was 51.9%, compared to 23% in the control group. In the MD group, a history of allergy was significantly more prevalent in patients with migraine (71%) than in those without migraine (39%). There was no such link between allergy and migraine in the control group, with the combination of allergy and migraine nine times more prevalent in the MD group (OR 9.23; 95% CI 3.11–27.32).

The Sen et al. [29••] study is interesting because it suggests that migraine is almost ubiquitous in patients with MD. In reviewing their web-based questionnaire, one weakness would be that the allergy history is obtained by simply asking the subjects whether they or family members suffer from any allergy, without confirmatory skin or in vitro testing. However, the fact that all patients—control group and Ménière's—were asked the same question and gave such differing responses does add credence to the supposition that there is a much higher incidence of allergy and migraine in patients with MD.

Pathophysiology

Paparella and Djalilian [30] provide an excellent review for the practitioner of the temporal bone correlates of the clinical symptoms of MD. They review various theorized “causes” of MD symptoms, including allergy. They conclude that the fundamental etiology of MD is likely a multifactorial inheritance, suggesting that the most likely predisposing factors are hypoplasia of the mastoid air cell system, vestibular aqueduct, and ES, and the other physical abnormalities that have been frequently reported in patients with MD.

We also believe that MD is likely multifactorial in etiology. It is not our contention that MD is “caused” by allergy. However, if we accept that the majority of patients with MD do have an anatomic abnormality, including a smaller than average ES size, factors that may affect either excessive endolymph production or reduction of endolymph absorption may promote MD symptoms. Allergy should be considered as one such factor.

Immunopathology

Savastano et al. [31••] recently studied the validity of serologic nonspecific immune tests in determining a possible role of immunopathology in a series of 200 patients with MD compared to a control group of 50 healthy blood donors. All patients and controls had no known diagnosis of autoimmune disease or steroid treatment. Results indicated negative or insignificant levels of IgG, IgM, and IgA, erythrocyte sedimentation rate, C-reactive protein, complement factors, and cryoglobulins in most patients. However, more than half had significant elevations in levels of circulating immune complexes. Rates of elevation of circulating immune complexes, lymphocyte subpopulations (especially IL-2 receptor), and autoantibodies were higher in the Ménière's group than in controls.

Savastano et al. [31••] also attempted to relate immunologic findings to disease severity, using the 1985 AAO-HNS Pearson and Brackmann classification of disability for reporting results in MD treatment. (It is unclear why they did not use the currently accepted AAO-HNS functional disability scale from the 1995 guidelines.) In the 1985 system, grade I exhibits no or mild disability with intermittent or continuous dizziness precluding work in a hazardous environment; grade II, moderate disability with intermittent or continuous dizziness/unsteadiness requiring employment in a sedentary occupation; and grade III, severe disability/disabling symptoms precluding gainful employment. There was a significant relationship between disease severity and test abnormalities for circulating immune complexes, CD4, and CD4 to CD8 ratio, with the highest rate of serologic abnormalities found in group III with disabling symptoms and the lowest rate in group I. A trend was also found for differences in C-reactive protein, C3 complement, and early T-activation.

Elevated circulating immune complexes in patients with MD have been reported by Brookes [21] and by Derebery et al. [22]. It would have been interesting for Savastano et al. [31••] to have done a subanalysis of patients with bilateral Ménière's (not identified in the text). Derebery et al. [22] have found a direct relationship between larger elevations in circulating immune complexes and disease bilaterality.

The Savastano et al. [31••] study adds credence to a possible underlying inflammatory etiology in most patients with MD. The study authors suggest that monitoring serum levels of circulating immune complexes, CD4, and CD4 to CD8 ratios may be useful as prognostic markers of disease progression. However, they did not elaborate on possible treatments, either immune-suppressive or allergic, resulting from their conclusions.

Keles et al. [32••] performed another study of MD immunopathology; they attempted to evaluate the possible role of allergy in producing Ménière's symptoms by examining the cytokine profiles, allergic parameters, and lymphocyte subgroups of patients with MD versus controls.

Forty-six adult patients with classic Ménière's were compared with an identical number of healthy volunteers in the same age group and socioeconomic class, living in the same region of Turkey. These researchers performed an extensive immune profile, measuring monoclonal CD4, CD8, CD23 antibodies, interferon (IFN)- γ , IL-4, total serum IgE, and antigen-specific IgE to regionally important tree pollens, molds, and common foods in the local diet.

Significant differences were found between the Ménière's patients and the controls in CD4, CD4/CD8, CD23, IFN- γ , and IL-4 levels. Keles et al. [32••] also found significant positive correlations between levels of CD23 and total serum IgE, CD8 and total serum IgE, CD4/CD8 and IgE, and CD23 and CD8, although correlation coefficients were not provided for the reader to determine strength of the relationships. Elevation of total serum IgE was found in 43.3% of the Ménière's group compared to only 19.5% of the control group. Additionally, 67.3% of the MD patients gave a positive history of allergy, whereas the same was found in only 34.7% of the control group. Significant elevations of antigen-specific IgE in the patients with MD were not present in the control group.

Keles et al. [32••] suggest that future therapies could potentially be beneficial, such as suppressing production of IL-4 and IL-1, or stimulating a helper T1 (Th1) cell predominance by the application of BCG vaccine. This interesting study does not change the current treatment parameters for MD. However, it documents that unselected patients with Ménière's have serologic findings that correlate strongly with atopy. The authors perform a large literature review, and reiterate well the published theories about how an underlying atopic state may provoke the symptoms of MD.

Treatment

We review several studies related to treatment of MD on immunologic aspects of the disease. Jeck-Thole and Wagner [33•] published a review of safety data on betahistine, which is often sold under the trade name Serc (Solvay Pharmaceuticals, Marietta, GA). Betahistine has a structural analog of histamine that is prescribed for the treatment of vestibular disorders, such as MD, for symptomatic treatment of vertigo. Betahistine is said to be the most commonly prescribed medication for MD in the world. Although not currently available in the United States, it can be obtained by compounding pharmacies or through sources in Canada or Europe. The typical adult dose is 16 mg three times daily. The reader occasionally may see a patient with MD using betahistine and reporting good clinical results. We include this article simply for the educational review of a medication that is commonly used for Ménière's worldwide.

In the United States, the most commonly prescribed medications for treating symptoms of Ménière's are antihis-

tamines (eg, meclizine, diphenhydramine, dimenhydrinate). Therefore, it might appear to be counterintuitive to prescribe a histamine analog to treat these same symptoms. In tissue, histamine is primarily stored in mast cells and may be released by various drugs, venoms, or allergens, resulting in hypersensitivity reactions, gastric acid secretion, and increased capillary permeability. In association with the peripheral actions of histamine, its function as a central neurotransmitter was postulated. Subsequently, various receptor subtypes were described, including histamine H_1 , H_2 , H_3 and, eventually, H_4 [34,35].

Betahistine acts as a neurotransmitter modulator of the complex histaminergic receptor system with no known affinity for any other receptors [36]. Betahistine is a weak partial H_1 receptor agonist with a distinctly lower affinity than histamine. It has almost no affinity for the H_2 receptor, having extremely weak effects on gastric secretion [37]. In contrast, betahistine shows a potent antagonistic effect on the H_3 receptor. The H_3 heteroreceptor, belonging to a class of presynaptic receptors, is involved in the synthesis and release of histamine and other neurotransmitters, including dopamine, γ -aminobutyric acid (GABA), acetylcholine, norepinephrine, and serotonin [38]. Actions that are mediated by the H_1 receptor are blocked by negative H_3 receptor feedback. Betahistine has an antagonistic effect on the H_3 receptor, followed by an increased histamine release. Betahistine's H_3 receptor antagonistic action is believed to be responsible for improvement in the inner ear microcirculation and subsequent reduction of endolymphatic pressure [39,40]. Betahistine has also been shown to inhibit the basal spike generation of the vestibular neurons in the lateral and medial vestibular nuclei, both crucial for controlling posture.

In terms of side effects or drug interaction, betahistine is nonsedating and free from psychomotor impairment. Theoretically, because betahistine and histamine are similar, betahistine could interact with an antihistaminic agent such as diphenhydramine or cetirizine, or even induce or support hypersensitivity reactions with regard to the H_1 -agonistic quality. However, betahistine affinity at the receptor site has been shown to be significantly weaker than histamine affinity. In addition, betahistine-induced histamine release from mast cells has not been described [41].

Treatment outcome studies

We evaluated the effect of specific allergy immunotherapy and food elimination of suspected food allergens on patients with MD for whom allergy treatment had been recommended [19] via a questionnaire regarding their symptoms. The 113 patients treated by desensitization and diet showed a significant improvement after treatment, both in allergy symptoms and in Ménière's symptoms. The patient ratings of frequency, severity, and interference with daily activities of their Ménière's symptoms also appeared

better after allergy treatment, compared to ratings from the control group of 24 untreated patients. Results indicated that patients with MD can show improvement in tinnitus and vertigo symptoms when receiving specific allergy therapy, suggesting the inner ear may also be a direct or indirect target of an allergic reaction.

Because the first study asked patients to retrospectively rate their pretreatment symptoms, a prospective study was undertaken in which 68 patients completed the questionnaire before allergy treatment and at an average of 23 months after treatment [42]. Severity of vertigo, tinnitus, and unsteadiness improved significantly, as did frequency of vertigo, frequency and interference of unsteadiness, and ratings on the AAO-HNS disability scale. Quality of life improved significantly on four of eight SF-36 Health Survey scales. Initial SF-36 scores indicated that patients with both Ménière's disease and allergy score more poorly than the general US adult population on several quality-of-life aspects. Paired comparisons between SF-36 scale scores at initial and follow-up intervals identified significant improvements in subtests that were below normal initially. Statistical analyses strongly suggested that these improvements were independent of natural history and of other medical treatment for MD the patients may have received during the immunotherapy period.

A weakness of these and other studies is that there are no control groups receiving saline injections or given diets eliminating foods that were negative on testing. We have observed that patients with MD are reluctant to commit to months or a year of possible placebo injections to "prove" that immunotherapy may help improve symptoms of vertigo, hearing loss, and/or tinnitus. Presently, we rely on using statistical control as well as research that clearly demonstrates the ability of allergy immunotherapy to downregulate Th2 cell-driven inflammatory responses in patients with allergic rhinitis and asthma [43]. If MD is believed to be a chronic condition with an inflammatory component, it is logical that downregulating the production and release of both proinflammatory and vasoactive mediators promoting fluid extravasation and/or retention could help lessen symptoms. This is the rationale for using steroids and restricting dietary salt in patients with Ménière's.

The classic first-generation antihistamines commonly used for their desired anticholinergic effects to lessen vertigo severity do not change the underlying pathology of hydropic distention of the endolymphatic space. Pharmacologically, these agents have limited effect, and do not block the effects of other inflammatory mediators, such as leukotrienes, released with mast cell degranulation. In our experience, nonsedating antihistamines have limited benefit in treating vertigo and/or dizziness. Effective immunotherapy, with its induced immunologic changes, can prevent mast cell degranulation. Additionally, an appropriate

elimination diet for documented food allergies can prevent an immune-mediated reaction.

In our clinical experience, the symptoms of MD are generally better controlled, with fewer vertigo attacks and more stable hearing, in those patients with allergy and Ménière's whose underlying allergic disorder is down-regulated with immunotherapy and/or dietary avoidance of reactive food allergens. The ideal "proof" of the role of allergy in a large subset of patients who develop MD would be a double-blind, placebo-controlled trial of immunotherapy, for the minimum of 2 years as required by AAO-HNS for evaluating the effects of surgical procedures for Ménière's; however, realistically, recruiting patients for such a study would be a challenge due to the potentially disabling symptoms of MD.

Conclusions

The prevalence of both migraine and atopy is much higher in patients with MD than in the normal population. Unselected patients with MD have serologic findings that correlate both with underlying atopy and inflammation. Although there are no double-blind, placebo-controlled trials comparing outcomes of patients with MD treated with specific allergy immunotherapy, clinical case reports strongly suggest that such treatment lessens severity and frequency of vertigo and results in more stable hearing. Objective outcomes of successful medical and surgical treatment of MD symptoms have been established and published, and may be used as a reference for assessing treatment response by specific allergy immunotherapy, or dietary elimination of food allergy.

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