

Allergic and Immunologic Features of Ménière's Disease

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KEYWORDS

• Ménière's disease • Allergy • Endolymphatic hydrops • Vertigo

Key Points: ALLERGIC AND IMMUNOLOGIC FEATURES OF MÉNIÈRE'S DISEASE

- The endolymphatic sac is not only capable of processing antigen, but also producing its own antibody response to immune stimulation.
- The prevalence of confirmed allergy in patients with MD is 41%, as compared with 14% to 20% of the US population as a whole.
- A large subset of patients with MD also has migraine headaches. The vast majority of these also have allergy, which may play a triggering role in both entities.
- First-generation antihistamines, although having a beneficial anticholinergic effect on the symptom of vertigo, do not change the underlying pathophysiology of the allergic immune response.
- The allergic stimulation of symptoms seen in some patients with MD is more effectively managed with allergy immunotherapy for inhalant allergies, and dietary elimination of food allergies.

In 1861, Prosper Ménière's 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

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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(pp 181–5)} AAO-HNS guidelines further define the vertigo episodes as a “spontaneous rotational vertigo lasting at least 20 minutes.” **Box 1** lists the classification of MD based on the AAO-HNS criteria.

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.⁴ Although idiopathic, MD has been ascribed to various causes, including trauma, viral infections, metabolic disorders, allergies, and autoimmune factors. The author emphasizes that MD, at the time of this writing, is idiopathic. The author believes that there may be some genetic predisposition to the development of MD and/or endolymphatic hydrops, with the final “insult” resulting in disease development being either inflammatory or a dysregulation of ion channels. The author does not believe that MD, per se, is “caused” by allergies, but rather, in some patients who likely have a genetic predisposition, an allergic reaction produced by a food and/or inhalant allergen may stimulate an inflammatory reaction resulting in the development of symptoms. In this article, the author specifically looks at the evidence, both historical and current, linking some cases of MD to an underlying allergic state. Briefly addressed are other potential stimuli, such as viral antigen and autoimmune factors, in addition to the Type I Gel and Coombs reaction characterized as “allergy.”

First, the immunology of the inner ear is reviewed. Then, the literature from 2002 to 2010 regarding MD, allergy, and autoimmunity is reviewed.

Box 1

Classification of Ménière’s disease based on the AAO-HNS criteria

- *Certain Ménière’s disease*
 - Definite Ménière’s disease, plus histopathological confirmation
- *Definite Ménière’s disease*
 - Two or more definite spontaneous episodes of rotational vertigo for 20 minutes or longer
 - Audiometrically documented hearing loss (unilateral or bilateral) on at least one occasion
 - Tinnitus or aural fullness in the affected ear
 - Other causes excluded, such as vestibular schwannoma
- *Probable Ménière’s disease*
 - One definite episode of rotational vertigo
 - Audiometrically documented hearing loss (unilateral or bilateral) on at least one occasion
 - Tinnitus or aural fullness in the affected ear
 - Other causes excluded
- *Possible Ménière’s disease*
 - Episodic vertigo of the Ménière’s type without documented hearing loss, or
 - Sensorineural hearing loss (unilateral or bilateral, fluctuating or fixed, with disequilibrium but without definite episodes of vertigo)
 - Other causes excluded³

REVIEW OF IMMUNOLOGY

The inner ear demonstrates both cellular and humoral immunity. Most leukocytes enter the cochlea via the spiral modiolar vein.⁵ The innate immunity of the cochlea has been suggested to allow an adaptive local response to antigen challenge.⁶ Hashimoto and colleagues⁶ have suggested that the inner ear may be “primed” by lipopolysaccharides or other viral or bacterial antigens, resulting in the upregulation of interleukin (IL)-1C 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 and colleagues⁷ have suggested that the seat of immune activity in the inner ear appears to be the endolymphatic sac (ES) and duct. Immunoglobulin (Ig) G, IgM, IgA, and secretory components 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 peri connective tissue and, clinically, the production of endolymphatic hydrops.⁸

The ES is capable of both processing antigen and producing its own local antibody response.^{9,10} Surgical destruction of the ES results in decreased antigen and antibody responses.¹⁰ The highly vascular subepithelial space of the ES contains numerous fenestrated blood vessels,¹¹ with arterial branches of the posterior meningeal artery supplying the ES and duct.¹² 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.¹³ Tests of abnormal cell-mediated immunity are either inconsistent or normal, even in patients with known causes of inner ear autoimmune dysfunction, including Cogan syndrome.¹³ Despite increased understanding of labyrinthine immunoreactivity, a reliable laboratory marker to “prove” autoimmune or allergic causation in patients with suspected inflammatory hearing loss has not yet been developed.

The first published report of MD believed to be provoked by an allergic reaction was in 1923.¹⁴ Both inhalant and food allergies have been linked with MD symptoms.¹⁵ 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.^{16,17}

There are different possible mechanisms by which an allergic reaction produces MD symptoms.¹⁸ 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 and colleagues¹⁹ have shown that Waldeyer 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 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.^{20,21} 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 granulomatosis, a prototype immune-complex-mediated disease. Upon examining the temporal bones of patients with Wegener granulomatosis and unexplained sensorineural hearing loss, the cochlea is found to be normal; the pathology occurs in the ES.²²

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 ring, with subsequent T-cell homing to the ES,²³ 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. Gacek²⁴ recently published temporal bone evidence of viral particles enclosed in transport vesicles in a patient with a history of MD. He also noted that antiviral treatment controlled vertigo in most patients with both MD and viral neuronitis.

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 nonallergic persons to develop upper and lower respiratory viral infections.

The herpes virus family would appear to be the most likely candidate for a viral stimulus. Patients with MD have elevations in serum antibody against herpes simplex and enterovirus.²⁵ Additionally, Heat Shock Protein 70, an antibody frequently seen elevated in both MD and autoimmune inner ear disease (AIED), is often upregulated in viral infections.

EPIDEMIOLOGY OF MD

In a survey performed of 734 patients with Ménière's syndrome, the prevalence of skin test-confirmed concurrent allergic disease was 41%.²³ Although the prevalence of allergic rhinitis is often quoted as 20% or more, the recent Allergies in America report,²⁶ the largest survey to date regarding prevalence and disease burden of allergic rhinitis,

found that physician-diagnosed allergic rhinitis in patients with rhinitic symptoms is 14%. Hence, the prevalence of physician-diagnosed allergy in American patients diagnosed with MD is almost 3 times that of the general population.²³ In a more recent survey of patients with MD, Derebery and Berliner found that patients reported a 58% rate of allergy history and, again, a 41% rate of positive skin or in vitro test.¹⁷

In his original description, Prosper Ménière's suggested an association between migraine and MD.¹ Since then, many investigators have noted paroxysmal headache independently occurring in many patients with MD.^{27–29} Radtke and colleagues³⁰ 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 with a control group of age- and sex-matched patients without MD attending an otolaryngology clinic.³¹ Sen and colleagues³¹ 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 39.0% compared with 18.0% in the control group, whereas the prevalence of allergy in those with MD was 51.9%, compared with 23.0% 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 9 times more prevalent in the MD group.

The Sen and colleagues' study³¹ is interesting because it suggests that in that large subset of patients with MD who also have migraine, the vast majority report an additional diagnosis of allergy. 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 patients with MD—were asked the same question and gave such differing responses adds credence to the supposition that there is a much higher incidence of allergy and migraine in patients with MD.

Although the list of "causes" for migraine is quite extensive, it has long been noted that allergic reactions were a common trigger in many sufferers. There are striking similarities among MD, allergy, and migraines concerning both symptom presentation and vascular changes. All 3 tend to recur cyclically, and sufferers are often able to note a cause and effect between a particular suspected "exposure" or event and the subsequent development of symptoms. The entities all show similar vascular changes as well: vasoconstriction, vasodilatation, and plasma extravasations, during the course of symptom production. Ibekwe and colleagues³² reported that there is an elevation in IgG containing immune complexes in the meningeal vessels of patients with migraine, as well as in the subepithelial layer of the endolymphatic sac in patients with MD. They hypothesized that there may be a common defective ion channel in both disease states, with the predominant expression in the inner ear and brain, resulting in a local increase in extracellular potassium and the production of symptoms.

PATHOPHYSIOLOGY OF MD

Paparella and Djalilian³³ 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.

The author also believes that MD is likely multifactorial in etiology. It is not the author's contention that MD is "caused" by allergy. However, if we accept that most 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. Inflammatory stimulation by an inhaled or ingested allergen in a genetically predisposed individual should be considered as one possible trigger.

IMMUNOPATHOLOGY OF MD

Many investigators have looked at serologic evidence of immunopathology or changes in patients with MD. Savastano and colleagues³⁴ found more than half of 200 patients with MD had increased circulating immune complexes, as well as an increase in the number of IL-2 receptors and autoantibodies, compared with healthy controls. There were no elevations of IgG, IgM, IgA, erythrocyte sedimentation rate, C-reactive protein, complement factors, and cryoglobulins in most patients.

Of interest, Savastano and colleagues³⁴ 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 exhibits moderate disability with intermittent or continuous dizziness/unsteadiness requiring employment in a sedentary occupation; and grade III exhibits 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 Brookes²⁰ and by Derebery and Berliner.²³ It would have been interesting for Savastano and colleagues³⁴ to have done a subanalysis of patients with bilateral MD (not identified in the text). Derebery and Berliner²³ found a direct relationship between larger elevations in circulating immune complexes and disease bilaterality.

Keles and colleagues³⁵ 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 MD 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 measured lymphocyte subtypes, including CD4, CD8, CD23 antibodies, interferon (IFN)-H, 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 patients with MD and the controls in CD4, CD4/CD8, CD23, IFN-H, and IL-4 levels. Keles and colleagues³⁵ 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 MD group compared with only 19.5% of the control group. Additionally, 67.3% of the patients with MD gave a positive history of allergy, whereas the same was found in only 34.7% of the control group, leading Keles and colleagues³⁵ to suggest that potentially beneficial future therapies would be suppression of production of IL-4 and IL-1, or stimulation of a helper T1 (Th1) cell predominance with the application of Bacillus Calmette-Guérin (BCG) vaccination.

This interesting study does not change the current treatment parameters for MD³⁵, however, it documents that unselected patients with MD have serologic findings that correlate strongly with atopy.

Oral steroids have commonly been used for treatment of patients with MD as a "rescue" and are the only treatment shown to offer efficacy in the treatment of AIED, many of whom present with a rapidly progressive form of bilateral MD.³⁶ However, long-term use of steroids are fraught with potential side effects, including osteoporosis, cataracts, and hyperglycemia. Intratympanic (IT) dexamethasone is used increasingly in an attempt to obtain the anti-inflammatory benefits of steroids without the systemic side effects. Herraiz and colleagues³⁷ recently reported that IT dexamethasone gave excellent improvement in tinnitus and decreased vertigo, as well as good preservation in hearing in a group of 34 patients with MD treated with IT dexamethasone in an open-label study, with improvement persisting for up to 24 months. The reader is also encouraged to read a review by McCall and colleagues³⁸ regarding other potential forms of drug delivery that may be applicable to treating patients with MD.

TREATMENT OF MD

The standard therapy in the United States and many other areas in the world for treatment of MD are sodium restriction, diuretics, and rescue vestibular suppressants for vertigo attacks. Many if not most patients get good results with this treatment, which, although not curative, can offer acceptable relief from vertigo most of the time. There is no treatment for MD that has been shown to be effective at hearing stabilization, at the time of this writing. The patient with MD should never be told "nothing can be done for it." Should medications not work, progressively more aggressive management, including endolymphatic shunt surgery, intratympanic gentamicin, or ablative procedures, such as vestibular nerve section or labyrinthectomy in the case of nonserviceable hearing, can be effective. Some patients will benefit by the use of the Meniett pressure-regulating device.

In addition to these, the author reviews several studies related to treatment of MD on immunologic and allergic aspects of the disease. Jeck-Thole and Wagner³⁹ published a review of safety data on betahistine, which is often sold under the trade name Serc (Solvay Pharmaceuticals, Marietta, GA, USA). Betahistine contains a structural analog of histamine, and is prescribed in 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 3 times daily. The reader may see a patient with MD using betahistine and reporting good clinical results.

In the United States, the most commonly prescribed medications for treating symptoms of MD are antihistamines (eg, meclizine, diphenhydramine, and dimenhydrinate). These medications are felt to be effective by exerting an anticholinergic central suppressive effect on the symptom of vertigo. 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 H₁, H₂, H₃, and, eventually, H₄.^{40,41}

Betahistine acts as a neurotransmitter modulator of the complex histaminergic receptor system with no known affinity for any other receptors.⁴² Betahistine is a weak partial H₁ receptor agonist with a distinctly lower affinity than histamine. It has almost no affinity for the H₂ receptor, having extremely weak effects on gastric secretion.⁴³ In contrast, betahistine shows a potent antagonistic effect on the H₃ receptor. The H₃ heteroreceptor, belonging to a class of presynaptic receptors, is involved in the synthesis and release of histamine and other neurotransmitters, including dopamine, H-aminobutyric acid (GABA), acetylcholine, norepinephrine, and serotonin.⁴⁴ Actions that are mediated by the H₁ receptor are blocked by negative H₃ receptor feedback. Betahistine has an antagonistic effect on the H₃ receptor, followed by an increased histamine release. Betahistine's H₃ receptor antagonistic action is believed to be responsible for improvement in the inner ear microcirculation and subsequent reduction of endolymphatic pressure.^{45,46} 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. A recent meta-analysis of treatment with betahistine in treating vertigo in non-Ménière's patients has shown it to be efficacious.⁴⁷

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 H₁-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.⁴⁸

INDICATIONS FOR TESTING

How does one select which patient with MD should undergo diagnostic testing? Classically, Powers¹⁵ described suggestive history, including a seasonal relationship of symptoms (eg, hearing loss, vertigo attacks), as well as the presence of "other symptoms" suggesting allergy, such as rhinitis, as indicators. These are actually a useful guide. The author also feels other details of history are useful guides, including bilateral symptoms, strong family history of allergy, a history of childhood allergy that one has "outgrown," as well as obvious factors such as the production of MD symptoms within a short time after exposure to a food or inhaled antigen.

As for testing modalities, there are varying thoughts regarding the relative sensitivity versus specificity of various tests, including prick testing, intradermal, intradermal titration, intradermal dilutional provocative food testing, as well as *in vitro*. The reader is encouraged to perform his or her own review of the subject. The author suggests that, whatever testing type is selected, the patient be tested with both inhalants as well as food antigens, despite the acknowledged lesser sensitivity of food testing when compared with inhalant.

Our preferred method of testing is intradermal titration, or, less so, prick testing with single-dilution intradermal testing in the case of negative results with a prick test. The author has observed that the reactivity of patients with suspected inhalant allergic triggers to their MD symptoms are often relatively low, typically in the range of

1/500 wt/vol of antigen.⁴⁹ Likewise, Topuz and colleagues⁵⁰ also noted that there was a large increase of abnormal electrocochleography results before and/or after prick testing in patients with MD (29% of diseased ears vs 78% after testing), as well as that the inner ear did not appear to require a strong antigen dose to be objectively stimulated. Similar electrocochleography changes have also been noted in patients with MD who have been tested with dietary antigen stimulation by provocative food testing, nasal provocation with inhalant antigens, and prick testing.⁵¹ The reader is advised to recall that the purpose of testing for allergy is to establish objectively whether a patient is allergic to a particular allergen or not, rather than to infer that the amount of antigen that produces a positive skin test directly relates to what type or how severe those induced symptoms will be.

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 recommended²⁰ 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 with 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.⁵² 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 4 of 8 SF-36 Health Survey scales. Initial SF-36 scores indicated that patients with both MD 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 that 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. It has been 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.⁵³ 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 MD.

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 the author's experience, non-sedating 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 the author's clinical experience, the symptoms of MD are generally better controlled, with fewer vertigo attacks and more stable hearing, in those patients with allergy and MD whose underlying allergic disorder is downregulated 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 MD; however, realistically, recruiting patients for such a study would be a challenge because of the potentially disabling symptoms of MD.

SUMMARY

The prevalence of both migraine and atopy is much higher in patients with MD than in the healthy population. Unselected patients with MD have serologic findings that correlate both with underlying atopy and inflammation. Indications for testing for allergy in a patient with MD should include symptoms associated with a seasonal relationship or food ingestion to symptom production, a known history of allergy or clear allergic symptoms in a patient with MD, or a known past childhood history or a strong family history of allergy. Additional consideration should be given for testing in those patients with bilateral MD. 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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