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Office-based Meniere's disease management

Loren J. Bartels, MD, FACS,[a] Christopher J. Danner, MD, FACS,[b] Kyle P. Allen, MD[b]

From the [a]University of South Florida College of Medicine, Department of Otolaryngology, Tampa, Florida; and the [b]The Tampa Bay Hearing and Balance Center 5, Tampa, Florida

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Office management of Meniere's disease (MD) is highly varied in the published literature with relatively little of its management established by double-blind, randomized, cross-over studies. Guidelines for diagnosis have been updated to a degree of recent and standards for reporting outcomes continue to be the AAO-HNS 1995 criteria. Low-salt diet, diuretics, allergy management, antivirals, migraine management, increased water intake, sedatives, and psychoactive medications have at least some evidence of benefit. Imaging is important as tumor can present as MD, but imaging can also be used to affirm the diagnosis of MD, as well.

Introduction

For the office management of Meniere's disease (MD), a variety of treatments over a period of many years have been reported. An accurate diagnosis is the first step and involves a thorough history, physical examination, audiometry, often vestibular studies of various types, and magnetic resonance imaging to assess for pathology that can mimic MD. The history of MD provides context and the current diagnostic criteria and reporting standards are pertinent (Tables 1-5). A literature search found "Meniere's disease" in 2,835 articles with the term in their titles so that reviewing all of them is not feasible, but, among the more widely known office-based interventions, much can be reviewed.

Recently, the Barany Society formed a group to develop the international classification of vestibular disorders to standardize terminology for reporting and research purposes. For MD, a multinational group consisting of the Equilibrium Committee of the AAO-HNS, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology, the Korean Balance Society, and the Barany Society refined the definition of MD (Table 1).[1,2] However, as of now, no international consensus on the etiology or treatment of MD has been approved by the AAO-HNS or the Barany Society.[3] This communication, then, represents a compilation of published information on which strategies for managing MD are based.

In 1861, Prosper Meniere's published the notion that attacks of vertigo, tinnitus, and hearing loss originated in the inner ear rather than from the brain, contrary to what was then the general opinion.[4,5] The incidence of MD in Sweden was assessed for 1973 as one case per population of 2,163, or an overall incidence of 46/100,000. With a 2014 estimated population in the United States of 318 million, the current prevalence of MD in the United States should be approximately 128,000 people.[6] Although no specific etiology for MD has been proven, an association of clinical symptoms during life with a postmortem finding of endolymphatic hydrops is a common finding, although it is not exclusive to MD.[7] No clinical tests for MD are definitive, which means the diagnosis is made by identification of key clinical features in both the history and audio-vestibular testing.[3] Traditionally, the presumption summarized by Paparella suggested that MD occurs in a

Address reprint requests and correspondence: Loren J Bartels, MD, FACS.
E-mail address: lbartels@tampabayhearing.com

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Table 1 International Amended 2015 Criteria for Diagnosis of Meniere's disease[3]

Definite	2 or more spontaneous episodes Vertigo, each lasting 20 min to 12 h. Audiometrically documented lowfrequency to midfrequency sensorineural hearing loss in single ear defining this as the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo. Fluctuating aural symptoms home (hearing, tinnitus, or fullness or all of these) in the affected ear. Not better accounted for by another vestibular diagnosis.
Probable	2 or more episodes of vertigo or dizziness, each lasting 20 min or as long as 24 h. Fluctuating aural symptoms (hearing, tenderness, or fullness closed in the affected ear. Not better accounted for by another vestibular diagnosis (audiometric data not necessarily documented).

Table 2 1995 AAO-HNS Criteria for the diagnosis of Meniere's disease[93]

Certain diagnosis
Definite clinical Meniere's disease plus histopathologic confirmation
Definite Meniere's disease
2 or more definitive spontaneous episodes of vertigo 20 min or longer
Audiometrically documented hearing loss on at least 1 occasion
Tinnitus or aural fullness in the ear of concern
Probable Meniere's disease
A definitive episode of vertigo
Audiometrically documented hearing loss on at least 1 occasion
Tinnitus or aural fullness in the suspect ear
Possible Meniere's disease
Episodic vertigo of the Meniere's type without documented hearing loss
Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes
Other causes excluded
1995 AAO-HNS criteria for Hearing loss qualifying as Meniere's disease related
Average of hearing thresholds at 0.25, 0.5, 1 kHz is 15 dB or more higher than the average of 1-3 kHz.
In unilateral cases, the average threshold values at 0.5 and 1-3 kHz is higher than 20 dB or more poorer in the ear in question than on the opposite side
In bilateral cases, the average threshold values at 0.5 and 1-3 kHz is higher than 25 dB in the studied ear
In the judgement of the investigator, the patient's hearing loss meets reasonable audiometric criteria for hearing loss characteristic of Meniere's disease. The rationale for using this criterion should be stated and justified for each case.

milieu of endolymphatic hydrops, with altered endolymph homeostasis and a speculative variety of inherited factors. Playing roles, he wrote, potentially, are "allergic tendencies, autoimmunity, and viral disorders."[8] More recently, Gacek and Linthicum, separately in 2001, provided substantial evidence that a viral etiology is a likely cause in at least ¾ of postmortem cases evaluated.[9-12] Gacek, in 2009, found postmortem evidence supporting a viral neuropathy for MD. From a qualitative examination of 11 sectioned temporal bones from 8 patients with a history of MD, a significant loss of vestibular ganglion cells was found in both the affected and nonaffected ears. From that, Gacek opined that the viral neuropathy was related to the MD, but viral neuropathy may not be the singular factor. Rauch defined Meniere as a degenerative inner ear process in which impairment of one or more homeostatic systems causes instability.[13]

Theories of MD

Altered inner ear homeostasis

Takeda et al[14] reported that endolymph homeostasis may be mediated by the vasopressin-aquaporin-2 (VP-AQP2) system, proposing that endolymphatic hydrops may be caused by altered regulation of that system. (http://faculty.swosu.edu/scott.long/phcl/diuretic.htm). The heart and the kidney specifically exert an endogenous control of its fluid volumes. Release of renin causes formation of angiotensin II, which prompts the release of aldosterone, which causes the release of antidiuretic hormone (ADH), conserving fluid. Atrial natriuretic peptide [atriopeptin], secreted from the atrium of the heart in response to stretch receptors stimulated by overfilling of the chamber, indicating high blood volume, prompts the kidney to stop the conservation of Na resulting in increased Na excretion so that water would follow osmotically, thus reducing blood volume). Studies in mice suggest that administration of desmopressin [vasopressin type 2 receptor agonist] can exacerbate endolymphatic hydrops through vasopressin type 2 receptor-mediated effects, and can cause temporary vestibular abnormalities that are similar to the vertiginous attacks in patients with MD.[15] Mice treated with vasopressin for 8 weeks showed severe endolymphatic hydrops with partial loss of outer hair cells and spiral ganglion cells. (http://www.medicinenet.com/latanoprost/article.htm: Latanoprost is a derivative of the chemical, prostaglandin F2-alpha, used for the treatment of glaucoma. Latanoprost, by binding to a specific receptor for prosta-

Table 3 1995 AAO-HNS Staging of definite and certain Meniere's disease[93]

Stage 1	4-tone average dB (0.5 and 1-3 kHz)
1	< 25 dB
2	26-40 dB
3	41-70 dB
4	> 70 dB

Table 4 1995 AAO-HNS functional level scale[93]

Regarding my current state of overall function, not just during attacks, (check the ONE that best applies)
My dizziness has no effect on my activities at all
When I am dizzy, I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budge my energies. I am barely making it.
I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.
I have been disabled for 1 year or longer or I receive compensation (money) or both because of my dizziness or balance problem.

glandin, increases the flow of aqueous humor out of the eye) inhibited the development of endolymphatic hydrops caused by vasopressin.[16] The proteins and mRNAs of aquaporin-2 and vasopressin type 2 receptor [vasopressin-aquaporin-2 {VP-AQP2} system] are expressed in the stria vascularis of the cochlea and the epithelium of the endolymphatic sac, and the volume of the endolymphatic compartment is controlled by the VP-AQP2 system in the inner ear. Elevation of plasma vasopressin (p-VP) level has been observed in MD and that has been thought possibly to be evidence of dysregulation of the VP-AQP2 system in MD. In an analysis of the role of the VP-AQP2 system in inner ear fluid homeostasis, an increase in the plasma vasopressin level was closely linked to vertigo attacks in MD.[14] Aoki found that ADH levels in patients with MD were elevated compared with other patients with vertigo.[17] Other researchers have shown no elevation of ADH in patients with MD[18,19] Steinbach and associates studied ADH during food and fluid intake in patients with MD and controls, finding slightly higher plasma ADH level and plasma osmolality in patients with MD. The more significant finding was that at the end of a 12-hour thirst challenge in patients with MD compared with controls, no significant change in ADH level was found in patients with MD but, remarkably, urine osmolality was significantly higher ($P < 0.001$) in controls vs patients with MD. The result was an almost stable urine osmolality in patients with MD after a thirst challenge, although normal controls had an increase in urine osmolality implying that the vasopressin-driven water balance in patients with MD is likely different than normal. ADH and its target aquaporin-2 may be key players in the pathophysiological events leading to the development of MD.[20] Perhaps related, increased free water intake and water retention have a salutary effect on MD.[21,22] After endolymphatic surgery, it has been demonstrated that vasopressin levels may decrease.[23] Natriuretic peptides have also been demonstrated to exist in human endolymphatic sac tissue harvested during translabyrinthine surgery.[24] Natriuretic peptides are known to play a role in fluid homeostasis in extracardiac tissues, such as the ciliary process of the eye. This represents another system of receptors that could be disordered in the development of MD.

Table 5 1995 AAO-HNS Summary of reporting guidelines[93]

Numerical value	Class
0	A (complete control)
1-40	B
41-80	C
81-120	D
>120	E
Secondary treatment initiated owing to disability from vertigo	F

Numerical value = $(X/Y) \times 100$, rounded to the nearest whole number. Where X is the average number of definitive spells per month for 6 months, 18-24 months after therapy and *Y* is the average number of definitive spells per month for the 6 months before therapy.

Allergy

Allergy is a commonly present in patients with MD and in the general population with more than 30% of the general population having some history consistent with allergies and approximately 17% having IgE evidence of allergies.[8,25-31] When migraine is present, the odds of having significant allergies is even higher.[29] Allergy management can be helpful in the control of MD.[26]

Migraine

Migraine and MD commonly overlap. A most illustrative study from Mayo Clinic evaluated 147 patients with diagnoses of MD, vestibular migraine or a combination of MD, and vestibular migraine. Some also had chronic subjective dizziness (now called persisting perceptual postural dizziness syndrome http://id.who.int/icd/entity/2005792829). Approximately one-third had only MD, approximately 14% had both MD and vestibular migraine. Of 57 thought to have only MD, 27 (49%) had also headaches with migraine features that did not meet full International Headache Society diagnostic criteria for migraine (photophobia, headache with vomiting, or first-degree relative with migraine). Including patients with MD-vestibular migraine, 59% (45/76) of all patients with MD had migrainous features. Of 32 patients with chronic subjective dizziness, 29 (91%) also had vestibular migraine. MD and vestibular migraine symptoms overlap. These data also suggest that when a patient with MD also has chronic subjective dizziness, vestibular migraine is also highly likely to be present.[32] It is commonly noted that patients with

uncontrolled MD often have features of vestibular migraine.[33-35] Prevalence data indicate that the rate for Meniere's disease is 0.12%-0.5% of the population and the rate for vestibular migraine is approximately double, 0.98%.[36]

Viral association in MD

Evidence of HSV in patients with MD

Gacek found that viral vestibular neuritis accompanies MD in postmortem studies suggesting that MD commonly has an underlying viral etiology.[10,11] Linthicum found evidence of herpes simplex viral glycoprotein in the inner ear of 12 of 16 temporal bones of patients who had had clinical MD, when compared with 2 of 26 temporal bone controls.[12] Vrabec in 2003, analyzed the prevalence of viral DNA using a nested polymerase chain reaction designed to amplify the herpes simplex virus (HSV) DNA polymerase gene and found HSV DNA in vestibular neurectomy specimens in 6 of 6 specimens of MD patients compared with 81% of controls, $P = 0.02$.[37] However, Welling in 1997 studied the vestibular ganglia in 11 patients with MD compared with patients with ganglia of acoustic neuroma and found no evidence of HSV in any specimen by polymerase chain reaction (PCR).[38] Gartner, similarly, was unable to find HSV in the vestibular ganglia.[39] The rate of HSV-1 in patients with non-MD, as discussed later, draws questions as to reliability of these HSV negative results.

Prevalence of HSV in the vestibular nerve

If MD may represent a viral vestibulopathy, it must be demonstrated that HSV can affect the vestibular nerve. Furata in 1993 studied human vestibular ganglia for evidence of HSV colonization. His team examined 26 vestibular ganglia from autopsied adults in search of HSV type-1 (HSV-1) using (PCR), in situ hybridization (ISH), and immune-histochemical staining. HSV DNA was found in 6 of 10 vestibular ganglia using the PCR method. However, the latency-associated transcript (LAT) of HSV-1 was negative in all of the 16 vestibular ganglia examined. They concluded that HSV-1 is commonly latent in human vestibular ganglia.[40] In 1999, looking at the general presence of HSV-1 in vestibular and geniculate ganglia, Arbusow found HSV-1 in 66% of geniculate ganglia and 60% of vestibular ganglia of 35 human temporal bones.[41] In 2000, he studied patients with unselected, non-MD for prevalence of virus in the both the vestibular ganglia and vestibular nuclei, finding HSV-1 in 3 of 10 of both vestibular ganglia and vestibular nuclei. He thought that the patterns of HSV-1 infection of vestibular structures were compatible with virus migration from the vestibular ganglia to the vestibular nuclei.[42] Again, the sensitivity of the assays for virus remains a question, but the prevalence of virus in asymptomatic patients at least establishes that HSV is commonly present in vestibular nerves.

Vestibular neuritis induced by HSV

Based on the earlier described work of Arbusow and colleagues, among others, Strupp and Brandt[43] opined that acute vestibular neuritis is HSV related.

Pollack investigated evidence of HSV in saliva and serum IgM evidence of viral activation of patients with vestibular neuritis. HSV-1 was detected the saliva of 14% of symptomatic patients, but in just 6% of controls ($P > 0.05$). Serologic testing revealed borderline IgM elevation for reactivation of HSV-1 in 75% of patients compared with 13% of controls ($P = 0.01$).[44]

Suzuki studied 31 vestibular ganglia from autopsied adults using a sensitive PCR to detect HSV-1 viral genomes, and reverse transcription-PCR (RT-PCR). He also used ISH methods to demonstrate latency-associated transcripts (LAT) of HSV-1. He found HSV-1 DNA in 6 of 10 (60%) vestibular ganglia using the PCR method. HSV-1 LAT was detected in 5 of 8 (63%) vestibular ganglia using the RT-PCR method. However, using ISH, he found HSV in only 1 of 13 (7.7%) vestibular ganglia was HSV-1 LAT positive. As well, only 1 of 3,830 (0.03%) neurons from 13 vestibular ganglia was found to be positive. He opined "with certainty that HSV-1 does produce latent infections in human vestibular ganglia." Of significance, he found that the percentage of HSV-1 infected neurons was less than that of trigeminal ganglia. From his studies, he wrote that the presence of HSV-1 LAT in the ganglia may correspond to occurrence of vestibular neuronitis resulting from reactivation of HSV-1.[45] In the latter 2 studies, focused not on MD but on the general population, the notion that HSV can be present and can cause vestibular neuritis seems well established. Using the ISH method, Yazawa evaluated 10 MD endolymphatic sacs for herpes family virus DNA (HSV-1 and 2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and human cytomegalovirus. He also did serum antibody titers against these viruses just before the endolymphatic sac surgery in these patients. Of the 10 specimens, 7 were positive for VZV, 4 for EBV, 1 for cytomegalovirus, but none for HSV-1 and 2. None of the patients, however, had elevated serum antibody titers against these viruses. He felt that the profile indicated that the viral DNA in the endolymphatic sac was inactive, thus in a latent form. He postulated that VZV infection in early childhood may reach the endolymphatic sac and play a role in the pathogenesis of MD reporting a $P = 0.02$. Unlike others, he wondered if having both VZV and EBV was important for the pathogenesis of MD, but for that, he reported a $P = 0.06$. In contrast, Gartner in 2008 studied the vestibular ganglia of 7 patients with MD, finding no evidence of HSV or VZV in any while finding one or the other in 34% of controls.[39]

What becomes apparent is that where general population studies find HSV or VZV commonly in the vestibular ganglia or in the endolymphatic sac, some investigators did not find even a general population rate of virus in their MD specimens, raising a question about the validity of the analytic methods in use. The notion would be that this may

be related in part to a lower rate of viral colonization in the vestibular ganglion as found by Wakisaka et al.[46] That implies that relatively low-sensitivity measures would falsely miss the presence of latent virus.

Vestibular neuritis immune modulation

If HSV plays a role in acute vestibular neuritis, presuming that it precedes MD, another question is what immunocompetent cells known to be associated with HSV infection might also be present in the vestibular ganglia. Rinaldo reviewed the subject finding that CD4+ and CD8+ white blood cells are pertinent to latent viral control.[47] Arbusow and colleagues in 2010 found CD8+ effector cells related to HSV type-1 latency in the trigeminal, geniculate, and vestibular ganglia from 7 postmortem specimens. HSV-1 LAT was found by ISH and quantitative RT-PCR. Infiltration of the ganglia by CD8+ T cells was detected by immunohistochemistry and quantitative RT-PCR. HSV-1 latency and CD8+ T-cell infiltration were found in the trigeminal ganglia and in other cranial ganglia. Remarkably, perhaps important for detection methodology sensitivity, the HSV-1 latency transcripts in the geniculate and vestibular ganglia were expressed at a very low level. Arbusow opined that colocalization of latent HSV-1 and CD8+ T cells in geniculate and vestibular ganglia indicates that HSV-1 reactivation is possible in these ganglia.[48] CD8+ T cells are uniquely programmed for a specific virus and seem to park in the colonized nerves. Type I interferon[49] produced by CD4+ white blood cells seems to be critical to clearing herpes simplex so that the presence of these cells near neurons seems highly pertinent to the notion that viral control is critical in nerves.

Animal studies

Esaki studied mice to see if herpes simplex could affect the eighth nerve.[50] Hearing loss and vestibular dysfunction were observed in all mice after inoculating the middle ear with HSV type-1 or 2. In the cochlear duct, columnar epithelial cells in the stria vascularis were infected with HSV, but not all infected cells underwent apoptosis. Many uninfected cells in the organ of Corti were apoptotic implying that apoptosis had been triggered, perhaps by the responses of and to viral infected cells. Vestibular ganglion cells were also infected implying that the virus can migrate from the middle ear, through the inner ear to the vestibular nerves. When the vestibular ganglion cells were infected, vestibular dysfunction was observed even if vestibular end-organ cells were not apoptotic.[50] Hirata and colleagues looked at the development of vestibular neuritis symptoms in mice after inoculating the auricle. Four of 30 mice 6 days after inoculation deviated while walking. Examining the vestibular nerve by histopathology and immunohistochemistry, HSV-1 antigens were found in Scarpa ganglion in 2 of 4 mice in which signs of vestibular involvement were manifested.[51] Further studies in 275 mice, postural deviation was observed in 14 mice (5.1%) 6-10 days after the inoculation. HSV antigens were found in the vestibular ganglia in 6 of the 14 mice (43%) that evidenced postural deviation. No antigens were found in the vestibular ganglia of animals which did not display altered postural stability.[52]

Summary

It is apparent that HSV can involve the vestibular nerve in the general population, and studies suggest an increased rate of infection in patients with MD. Animal studies demonstrate both vestibular symptoms and hearing loss in the setting HSV infection of the eighth cranial nerve. This suggests a likely involvement of HSV in MD, and directs treatment to suppression of HSV.

Office treatment of MD

Introduction

Both empiric- and pathology-based approaches to treatment of disease are commonly employed in the treatment of MD. Attempts to understand the pathology of MD have grown a substantial knowledge base but, as yet, relatively few randomized controlled trials (RCTs) establish efficacy in the treatment of MD. No study has established a definitive etiology for MD, leaving empiric management choices in place. In a review of nonoperative options in MD management,[53] Paparella's group reported that 85% of patients with MD are controlled with conservative approaches including intratympanic steroid therapy, intratympanic gentamicin therapy, and endolymphatic sac surgery.[54]

Low sodium diet

Boles in 1975 found that in 500 patients managed with the Furstenburg 1,000 mg low-salt diet method, control of MD had high efficacy.[55] Chui et al, however, found just a 33% control rate with a low-salt diet and a diuretic achieving AAO-HNS class A or B control (Table 5); 33% of their patients with MD were controlled with endolymphatic sac surgery, and 15% of their population with MD went on to successful middle fossa selective vestibular nerve section. With a combination of medical or surgical management, 81% of their patients achieved class A or B results (Table 5).[56] (1985 AAO-HNS Guidelines for Reporting Results in MD: the formula expressing the effect of treatment on the vertiginous spells is as follows: average number definitive spells/month in the 24-monthperiod after therapy divided by the average number of definitive spells/month in the 6-month period before therapy where numeric values are characterized as: 0 = complete control of definitive spells; 1-40 = substantial control of definitive spells; 41-80 = limited control of definitive spells; 81-120 = insignificant control of definitive spells; and >120 = worse (poorer) control of definitive spells. If the duration of

pretreatment observation is less than 6 months, the divisor is the average number of definitive spells per month for the period of observation, which should be specified. This fraction multiplied by 100 would give a figure representing the effects of treatment on the vertiginous spells. It is important that this numeric value be reported). A study of the hormonal effects of a low-salt diet found an increase in the plasma aldosterone concentration that was speculated to increase sodium absorption from endolymph in the endolymphatic sac.[57]

Diuretics

(http://www.uptodate.com/contents/diuretic-induced-hyponatremia). The thiazides act in the cortex in the distal renal tubule; as a result, they do not interfere with medullary function or with ADH-induced water retention. In addition, in vitro data indicate that thiazides increase water permeability and water reabsorption in the inner medullary collecting duct, an effect that is independent of ADH. In addition to water retention, the combination of increased sodium and potassium excretion (owing to the diuretic) and enhanced water reabsorption (owing to ADH) can result in the excretion of urine with a sodium plus potassium concentration higher than that of the plasma. Loss of this fluid can directly promote the development of hyponatremia independent of the degree of water intake. Diuretic management of MD is a long tradition, but articles looking at the relationship are sparse. The use of hydrochlorothiazide (HCTZ) was described in MD in 1961.[58] In an older study, acetazolamide was found to be helpful to MD.[59] A published Cochrane review of 19 articles on diuretic management of MD found 12 retrospective case series, 4 RCTs, 2 case-control trials, and 1 prospective case series. The studies evaluated isosorbide, HCTZ, acetazolamide, chlorthalidone, and nimodipine. All, but one were thought to be low-evidence-level studies suggesting that diuretic therapy may be beneficial for MD management, primarily with improvement in vertigo episode frequency.[60] A single RCT of diuretics compared with placebo management was found in an extensive literature review. In 33 patients with MD (42 ears), triamterene (50 mg)-HCTZ (25 mg) was compared with a double-blind, cross-over, placebo-controlled study. Triamterene-HCTZ had no significant effect on hearing or tinnitus, but was more effective than placebo for controlling vertigo.[61] In another retrospective study of the efficacy of diuretics and low-salt diet in 54 patients with MD, vertigo control at 24 months was approximately 80%.[62] In a study of acetazolamide, hearing improvement at 2 hours' postadministration was most at 250 Hz, with a small threshold shift at 2000 Hz. Improvement in symptoms was found in 44% of patients.[59] In 1982, Peterman compared betahistine HCl with HCTZ and found that the diuretic benefit was notable for months, whereas when combined 3 times a daily with betahistine of 8 mg, three times a day, the combination was more efficacious, but no statistical significance was calculated.[63] Dietary management of MD has relatively high compliance rates for "low sodium" for at least a year; if followed for at least 6 months, it was more helpful. For other food choices, compliance was low.[64] Klockoff did an analytical approach for diuretics finding benefit.[65]

Nonintervention (patient choice)

When low-salt diet and diuretics had failed, nonintervention at patient choice found that after 7 years, vertigo was completely controlled at 2 years in just 8%, slowly increasing to 25% at 7 years after failure of medical management.[66] Silverstein, in a similar manner followed patients who his group felt had been candidates for surgical intervention. Two years after choosing observational management, 57% had complete control of vertigo; after 8 years, 71% had complete vertigo control. By contrast, 2 years after endolymphatic sac surgery, just 40% of patients had complete control of vertigo, and after 8 years, 70% had complete vertigo control (the numbers were surprising). Notably, after a vestibular neurectomy, 93% had complete control of Meniere type vertigo, at an average follow-up of 4.4 years.[67]

Betahistine

Betahistine has been studied in RCTs. In a meta-analysis, Nauta[68] found that the likelihood of a benefit from use of betahistine was almost 2 times higher for treated patients than for placebo-treated patients. However, a randomized, controlled study of placebo vs low and high-dose betahistine demonstrated no statistically significant difference in the rates of vertigo control among the 3 groups.[69]

Our practice does accommodate patients who desire to use betahistine, but it is not US Food and Drug Administration approved for sale in the United States. Our patients send their prescriptions to Canada to be filled, generally recommending 8-16 mg up to 3 times per day.

Meniette device

For the Meniett device, Odkvist did the first RCT and found significant benefit, but it was only a 2-week trial with the device.[70] Early results with relatively short-term use of the Meniett device were encouraging.[71-73] With a 2-year follow-up of 44 patients, the results were less encouraging but Gates suggested, "Use of the Meniett device was associated with a significant reduction in vertigo frequency in approximately two-thirds of the participants, and this improvement was maintained long-term."[74] In contrast, Silverstein and colleagues[67] found a 57% spontaneous remission rate in patients who had elected not to have surgery for troublesome MD. Ahsan evaluated a number of randomized controlled studies finding that the rate of control with the device was improved.[75] The follow-up period was relatively short, the number of subjects was relatively small, and the number of studies available was quite small. Syed in analyzing the RCTs for the Meniett device found a

statistically significant overall "61% reduction in the frequency of vertigo in both treated and placebo groups that was not significantly different between the 2 groups in any study." Nor did Syed's meta-analysis find any statistically significant difference in vertigo-free days between the Meniett device and a placebo device. Neither did he find support for a greater reduction in the severity of the vertigo or hearing loss with the Meniett device compared with a placebo device.[75,76]

Our practice gives patients printed information that includes the Meniett device and we occasionally place a tympanostomy tube to accommodate patients who request a trial with this device. In the patients who have failed low-salt diet, diuretic, and increased water intake, we have not been impressed that the Meniett device is often helpful. Our review of the literature leaves us unclear that the Meniett device is helpful in patients who fail with diet and diuretic management.

Transtympanic steroids

When low-salt diet and diuretics fail, transtympanic steroids can be helpful. Among patients with MD who had failed diet and diuretic management, one study evaluated 30 who had undergone intratympanic dexamethasone perfusion. Using assessment with the Glasgow Benefit Inventory, short-term (4 weeks postperfusion) in 6/30 patients demonstrated a more than than 10 dB improvement in pure tone average. Overall, 6/30 had an increase in speech discrimination scores of at least 15%. At 12 months postperfusion, 5/30 maintained an audiometric pure tone average gain and only 2/30 maintained their speech discrimination score gain. Among those who were followed for a year, 9/18 who had a Glasgow Benefit Inventory gain for vertigo control, 6/18 reported no benefit, and 3/18 reported being worse. Some, therefore, who might have been candidates for transtympanic gentamicin therapy were able to escape that more-morbid in-office treatment option.[77] At 2 years after treatment, Sennarouglu et al[78] found that intratympanic perfusion of dexamethasone had suppressed vertigo completely in 42% of patients and improved hearing significantly in 16%. For transtympanic steroids, a single RCT suggests benefit with 5 consecutive days of transtympanic steroids.[79] In a non-RCT trial, Herraiz found substantial improvement in symptoms in patients with MD with transtympanic steroids, with a low referral rate of patients for more invasive management.[80] Ren et al[81] also found more than 45% sufficient control rates with transtympanic dexamethasone. Miller et al found that a polymer that migrates out of the middle ear more slowly improved control rates with transtympanic steroids.[82] Doyle, however, felt that current evidence is inadequate to assess efficacy of transtympanic steroids in MD.[83]

Transtympanic gentamicin

The first use of an aminoglycoside for MD may have been by Reudi in 1951 who reported on use of streptomycin. Schuknecht reported on use of streptomycin for MD in 1975 with excellent vertigo control, but major worsening of hearing.[84] Lange, in 1968, reported on use of middle ear application of streptomycin, apparently close to the time he began using gentamicin, instead.[85] Lange's first report on use of transtympanic gentamicin appears to have been in 1997, by which time, by inference, he had been using it approximately 9 years. He administered the 0.1 mL of drug, concentration unknown, using a catheter inserted subannular, given every 5 hours until nystagmus or vertigo appeared. Vertigo was completely controlled in 90% and hearing was preserved in 76%. Tinnitus and aural pressure also improved.[86]

The most recent (2001) Mayo Clinic report for transtympanic gentamicin presented a different concept[87] as the change was from complete chemical ablation of vestibular function in the effected ear to sufficient, gentamicin-induced chemical vestibular function alteration. Ablation, although effective in vertigo control, has an associated significant incidence of worse hearing. The goal with chemical alteration was to reduce vestibular function with lesser effects on cochlear function. A single injection of gentamicin was administered and the patient was seen 1 month later. If still symptomatic, another injection was administered and repeat evaluation occurred yet another month later. Follow-up for 2 years or more was achieved in 56 patients. The 4-year results by the AAO-HNS guidelines (Tables 2-5) achieved vertigo control classes A and B in 82% of patients. The patients followed 2-4 years had 86% vertigo class A and B results, better than those followed 4 years who had 76% class A or B vertigo control (Table 5). The goal of minimal cochlear loss was achieved.[88]

Clinical evidence for benefit from antivirals

In 2009, Gacek reported that antiviral treatment controlled vertigo in 32 of 35 patients with MD (91%).[9] In 2013, he reported from a series of 211 patients that the control of MD had been achieved with long-term antiviral usage in 90% of patients with a follow-up of 3-8 years.[89] Gacek noted that this control rate was in patients who had largely failed a combination of diuretics and low-salt diet. When compared with spontaneous resolution rates reported by Silverstein et al,[67] this 90% control rate is noteworthy. More recently, Gacek[90] reported that some patients recover significant hearing acuity with long-term antivirals. During 2012, new 31 patients with a diagnosis of MD were treated with either 800 mg (acyclovir) or 1 g (valacyclovir) 3 times a day for 3 weeks; thereafter, the dose was decreased to twice daily for 3 weeks, and then, all were maintained on once daily medication for a year or longer. Hearing was improved in 12/31 and not improved in 19/31 and all of those with hearing gain had complete control of vertigo. Among those patients with MD with no improvement in hearing were 2 groups. Of 9 with hearing equal to or better than a PTA of 50 dB and SD of 50%, 6 of 7 had vertigo control but 2 were lost to follow-up. Of 10 patients with a pure tone average of 60 dB or more

and speech discrimination scores below 50%, 3 exhibited poor control of vertigo with antivirals. That is, 4 of 31 patients with MD had poor control of vertigo and no improvement of hearing with antivirals. The duration of MD in the group with hearing improvement was shorter, less than 2.5 year, whereas those with no hearing improvement had hearing loss more than 5 years. Thus, it appears that patients with longstanding, active MD and hearing worse than 50%/50 dB have a poorer prognosis with employment of antivirals. In a double-blind trial with famciclovir, Derebery found a trend for hearing improvement in short-term, 6 weeks, use of antivirals.[91]

Suggested protocol based on literature review

For patients with probable or definite MD (Tables 1-5), we start patients with normal renal function on 800 mg of acyclovir 3 times a day for 2 months and then fall back to twice per day. If patients have trouble tolerating acyclovir, we switch to valacyclovir 500 mg three times a day (TID), dropping to twice a day (BID) at 2 months or famciclovir 500 mg TID for 2 months, either then dropping to BID. Some of our patients arbitrarily drop to once daily dosing. Some of our patients have break through on BID dosing, but are well controlled on TID dosing. Some use TID dosing when stressed. Transtympanic steroids or transtympanic gentamicin are elected in less than 15% of our patients and that is in spite of the fact that a majority of our patients have failed a low-salt diet and diuretics before seeing us. The incidence of moving on to endolymphatic sac surgery or labyrinthectomy or vestibular nerve section in our practice is quite rare whereas before the options of antivirals and transtympanic therapies, the incidence of needing surgery was approximately 15%. As reported by Gacek,[89,90] patients with stage 1-2 MD often experience and maintain hearing gains with antivirals. If those with hearing gain stop the antivirals, many lose the hearing again. Many stage 1-2 patients report markedly less hearing fluctuation so long as they continue their antivirals. Approximately 5%-10% of patients fail to tolerate antivirals and getting insurance authorizations for long-term antivirals is occasionally a problem.

Summary

MD remains a multifaceted phenotypic disorder with evidence of roles for heredity, virus, sodium-water regulatory dysfunction, migraine, allergy, and psychiatric cofactors. Tumor is rarely a cause. Bilateral disease develops eventually in as many as 45% of patients so that nonablative management is preferred. Low-salt diet, increased water intake, and diuretics often get patients through early MD. Questioning, and when pertinent, co-managing for allergies and migraine is an essential part of both initial and continuing assessment, especially for those patients whose lives are disrupted. In the past 50 years, the 3 things that seem to have made the largest improvements in vertigo control are transtympanic gentamicin, transtympanic steroids, and antivirals. With that combination, operative intervention has become markedly less common. The group of patients most likely to need transtympanic gentamicin are those with hearing worse than 60 dB with poor word recognition in the affected ear (s). For those with hearing better than that, buying time with transtympanic dexamethasone, in our experience, allows the earlier mentioned conservative measures an interval for remission to take control. Budding avenues of research imply that genetic susceptibility to MD may exist both in response to herpes family viruses[92] and in the research that implies response to thirst challenge may be different in patients MD patients.[20]

Disclosure

The author has no pertinent financial conflicts of interest with respect to any aspect of this article.

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