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REVIEW

It is 2015: What are the best diagnostic and treatment options for Ménière's disease?

Safeer Shah, Abel Ignatius, Syed Ahsan

Safeer Shah, Abel Ignatius, Wayne State University School of Medicine, Detroit, MI 48201, United States

Syed Ahsan, Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health System, Detroit, MI 48202, United States

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Correspondence to: Syed Ahsan, MD, FACS, Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health System, 2799 W. Grand Blvd. K-8, Detroit, MI 48202, United States. sahsan3@hfhs.org
Telephone: +1-313-9167442

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Abstract

Ménière's disease (MD) is a common cause of recurrent vertigo. Its pathophysiology is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops (EH). However, not all cases of hydrops are associated with MD and it may represent the end point of various etiologies. The diagnostic criteria for MD have undergone changes during the past few decades. A recent collaboration among specialty societies in United States, Europe and Japan has given rise to a new set of guidelines for the diagnosis and classification of MD. The aim is to develop international consensus criteria for MD that would help improve the quality of data collected from patients. The diagnosis of MD can be difficult in some cases as there is no gold standard for testing. Previous use of audiometric data and electrocochleography are poorly sensitive as screening tools. Recently magnetic resonance imaging as a diagnostic tool for identifying EH has gained popularity in Asia and Europe. Vestibular evoked myogenic potentials are also used but lack specificity. Finally, the treatment for MD has improved with the introduction of intratympanic treatments with steroids and gentamicin as well as less invasive treatment with the Meniett device.

Key words: Ménière's disease; Review; Pathophysiology; Diagnosis; Treatment

Core tip: The pathophysiology of Ménière's disease (MD) is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops. This finding is utilized in the newest method of diagnosis

using magnetic resonance imaging with intratympanic or intravenous gadolinium. Changes to the diagnostic criteria have been proposed with collaboration from various international societies. This will help in communication and improve quality of published data. Finally, the use of intratympanic steroids and Meniett pressure treatments offers less invasive and destructive treatments for patients with MD.

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INTRODUCTION

Ménière's disease (MD) is an inner ear disorder that is characterized by episodic vertigo, low-pitched tinnitus and fluctuating hearing loss lasting for a minimum of 20 min. In the United States, 190 people per 100000 are affected, with a 2:1 female to male ratio[1]. MD was named after the French physician Prosper Ménière, who in 1861 first argued that MD was an inner ear disorder and not a neurological one[2]. Much time after his death, the most common finding in postmortem human temporal bone studies of MD patients was endolymphatic hydrops (EH), which is the dilation of the membranous labyrinth of the inner ear[3]. It should be noted however that not all cases of EH are associated with MD[4]. The lack of certainty in understanding the pathophysiology of MD makes it difficult to properly diagnose and treat. Most treatments are aimed at reducing endolymphatic size and pressure after which non-responders go on to ablative treatments.

PATHOPHYSIOLOGY

MD is an idiopathic disorder wherein the mechanism underlying its pathophysiology is still unclear and controversial. Affected individuals differ in terms of etiology and thus many studies propose various explanations for the manifestation of symptoms. However, it is generally agreed upon that EH is a consistent histological hallmark of the disease, a phenomenon seen in numerous temporal bone studies[4-7]. EH can be described as a pathologic finding in which the structures bounding the endolymphatic space are distended by an enlargement of endolymphatic volume[8]. The consequent hydropic state leads to various mechanical and chemical perturbations that ultimately give rise to the classic symptoms of MD.

In the cochlea, distension of the scala media causes the endolymphatic space to impinge on the bordering perilymphatic compartments. According to Wit *et al*[9] the degree of distension is related to the mechanical compliance of the membrane involved. This explains why EH is more prevalent in the cochlea and saccule, which are relatively more compliant than other structures such as the utricle or semicircular canals. Long-term distension may eventually lead to rupture of inner ear membranes. For example, rupture of Reissner's membrane has been reported in patients with MD, although Paparella *et al*[10] note the absence of rupture in two thirds of patients. Nonetheless, it has been theorized that membrane rupture leads to an electrolyte imbalance, causing acute vertigo and hearing loss[4,5,8,10,11]. Chemically, the hydropic state also creates a neurotoxic environment that leads to apoptosis of spiral ganglion cells[5]. Excitotoxicity may therefore contribute to the auditory symptoms of MD.

Previous research has shown that almost all patients diagnosed with MD present with EH in the affected ear. However, this consistent finding does not imply that EH is the direct underlying cause of MD. Several studies involving histopathological examinations of human temporal bones have revealed that not every patient with EH presents with symptoms of MD[4,12,13]. This makes it difficult to infer a simple cause-and-effect relationship. Instead, EH may be the result of various etiologies that disrupt normal endolymphatic fluid homeostasis. Semaan *et al*[5] separate these etiopathogenic factors into intrinsic or extrinsic. Intrinsic factors may include hypoplasia of labyrinthine structures, anteriorly and medially displaced sigmoid sinus, genetic factors, and other causes attributable to the inner ear itself. Extrinsic factors include autoimmune disease, allergy, otosclerosis, viral infection and trauma[5].

Genetics

Genetically, MD follows an autosomal dominant pattern with 60% penetrance[14]. Koyama *et al*[15] (1993) found relatively higher levels of histocompatibility antigens in affected patients, with HLA-DR, DQ, DP, A2 and B44 being particularly noteworthy[16]. Furthermore, a missense mutation of the *COCH* gene in the DFNA9 locus has been shown to produce MD-like symptoms such as progressive sensorineural hearing loss and vestibular dysfunction[17]. However, Morrison and Johnson propose that the *COCH* gene is an unlikely candidate for MD[18]. Lastly, an animal model of postnatal EH in mice suggests that genetics may play a role in posttranscriptional modification of the gene product, which also explains phenotypic differences between patients[5]. Overall, investigations into the genetic basis of MD suggest that multiple genes may be involved, and in combination they render certain individuals more susceptible to developing the disease.

Autoimmunity

It is believed that the immunological basis of the pathogenesis of MD may involve reactions between antibodies and tissue antigens, or IgG- and IgM-mediated circulating immune complexes (CICs)[19]. While larger CICs are cleared from circulation, smaller complexes can

Table 1 1995 American Academy of Otolaryngology-Head and Neck Surgery diagnostic criteria for Ménière's disease

Certain	Definite Ménière's + histological confirmation
Definite	⩾ 2 definitive spontaneous vertigo episodes ⩾ 20 min + all criteria in Probable Ménière's disease
Probable	1 definite episode of vertigo audiometric hearing loss on ⩾ 1 occasion Aural fullness or tinnitus in the affected ear Other causes exclude
Possible	Episodic vertigo of Ménière's type with no documented hearing loss or Fluctuating or fixed SNHL with disequilibrium without definitive vertigo episodes Other causes excluded

SNHL: Sensorineural hearing loss.

continue to circulate and accumulate in inner ear tissues, causing a local inflammatory response[19]. Deposition within the stria vascularis and endolymphatic sac may even lead to increased vascular permeability, and the sudden efflux of fluid induces EH and even rupture of Reissner's membrane[20]. Success with steroid-based treatments, which act as an anti-inflammatory agent, also bolsters the argument for an immunologic mechanism in the development of MD[5]. Furthermore, other studies note the presence of intraluminal eosinophilic material within the endolymphatic duct, and conclude that it is evidence of an immunodefensive system in the inner ear as this material contains the macrophages that trap antigen[21,22].

Endolymphatic duct and sac

The longitudinal flow theory states that the unidirectional flow of endolymph begins in the stria vascularis where it is produced, travels through the endolymphatic duct, and is eventually absorbed by the endolymphatic sac[5]. Thus, it follows that narrowing of the endolymphatic duct could impair endolymph absorption at the sac, and consequently result in a hydropic state. In fact, numerous guinea pig models show the development of hydrops following surgical obstruction of the endolymphatic duct[4]. However, Salt and colleagues found that the hydropic state could not be a result of the blockage of longitudinal flow because the rate of endolymph flow was too small. Instead, they believe that endolymphatic homeostasis is not volume-dependent; rather, it is dominated by ion transport and water equilibration *via* osmotic gradients[23,24]. Shinomori *et al*[25] (2001) further this idea by proposing a cytochemical mechanism for the development of hydrops. After blocking the endolymphatic duct in 22 guinea pigs, changes were noted in the cytochemistry of type Ⅰ and Ⅱ fibrocytes as well as nonsensory epithelial cells before the development of hydrops. Blocking the endolymphatic duct changed the composition of perilymph, thus placing osmotic stress on fibrocytes, which are important in maintaining fluid homeostasis. Merchant *et al*[4] hypothesizes that the dysfunction of fibrocytes interferes with K^+ recycling, leading to osmotic imbalance and expansion of the endolymphatic compartment.

CLASSIFICATION

The criteria for diagnosis of MD have undergone various changes within the past few decades. In 1974, the Japanese Society for Equilibrium Research proposed a set of conditions that classified the disorder into either definite or suspicious/uncertain MD. Lopez-Escamez *et al*[26] briefly outlined those conditions as the following: (1) repeated attack of whirling vertigo; (2) fluctuating cochlear symptoms; and (3) exclusion of central nervous system involvement, CN Ⅷ tumor and other cochleovestibular diseases. A diagnosis of definite MD required fulfillment of all three conditions while suspicious/uncertain MD involved two of the conditions with the third being necessarily included[26].

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) also developed a set of guidelines in 1972, which were revised in 1985 and again in 1995. Nearly all studies since then have been based on the 1995 criteria, which classified MD into possible, probable, definite and certain[27] (Table 1). A recent collaboration among the Equilibrium Committee of the AAO-HNS, the Japan Society for Equilibrium Research, the European Academy of Otology and Neuro-Otology, the Korean Balance Society and the Bárány Society gave rise to a new set of guidelines for the diagnosis and classification of MD (Table 2). The aim was to develop international consensus criteria for MD to improve the quality of data collected from patients. Furthermore, clarification was needed with regards to the nature of auditory symptoms[26].

DIAGNOSIS

Audiogram

Traditionally, the most common audiometric configuration for patients with MD involved a "rising" pattern during the early stages, indicating low frequency hearing loss, followed by a flat audiogram in later stages of the disease[28-30]. However, Opheim and Flottorp began to notice a pattern involving a "peak" audiogram in many of their patients with MD[31]. Further investigations have been conducted in order to assess the usefulness of the peak audiogram as a diagnostic tool. In one study, 363 hearing impaired ears with MD were assessed for evidence of a peak audiogram. Paparella *et al*[28] (1982) noted the presence of a peak audiogram "if the air conduction threshold for one test frequency was at least 10 dB better than both hearing thresholds for the two adjacent octave frequencies". The reported sensitivity of the peak audiogram in detecting MD was 41.7%, while the specificity was 93.4%[28]. Therefore, the audiogram appears to be useful in ruling out the possibility of MD in patients without a peak configuration. However, its low sensitivity makes it a poor diagnostic tool on its own. Perhaps the peak audiogram may best be used as an

Table 2 New proposed diagnostic criteria for Ménière's disease

Definite MD
Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h
Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo
Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis
Probable MD
Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h
Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis

MD: Ménière's disease.

adjunctive test to more advanced imaging techniques.

In a separate study by Lee *et al*[29], other audiometric patterns were considered in addition to the peak configuration. These included flat, rising, falling and dip configurations. The results once again supported a relatively higher proportion of the peak audiogram (50.65%), followed by the falling audiogram (26.26%), the dip audiogram (9.24%), and other types accounting for the remaining portion[29]. Again, the low sensitivity of the peak audiogram makes it an unreliable diagnostic test for MD, and this study along with others show the involvement of a wider variety of configurations.

Paparella *et al*[28] also found that those with severe or profound hearing loss were just as likely to have a 2000 Hz peak audiogram as those with mild or moderate hearing loss. This implies that the prevalence of the peak audiogram is unrelated to the degree of hearing loss. Instead, prevalence of the peak audiogram appears to be affected by bilaterality and duration: Bilateral peak configurations are more likely to result in patients with bilateral diseased ears of longer duration[28].

Magnetic resonance imaging

The use of magnetic resonance imaging (MRI) as a diagnostic tool for identifying EH gained popularity in 2007. Nakashima *et al*[32] (2007) used 3-T MRI following transtympanic (TT) gadolinium injection to visualize the endolymphatic space of patients diagnosed with MD, and since then it has been regarded as a possible gold standard test. It is also worth noting that a modified method involves intravenous (*iv*) administration of gadolinium.

The main outcome measure in using MRI as a diagnostic tool is perilymphatic enhancement in various portions of the labyrinth. Perilymphatic enhancement is an indirect measure of EH with progressively lower enhancement representing growing occupation of the perilymphatic space by the hydrops[33]. For example, in the cochlea, decreased visualization of the scala vestibuli indirectly infers increased displacement of Reissner's membrane brought about by EH[34]. Though perilymphatic enhancement is a reliable tool for inferring the presence of hydrops, the possibility of false positive findings cannot be ruled out. This could be due to impaired filtration of gadolinium into the perilymphatic compartment as a result of degenerative changes in the inner ear[33].

Gadolinium injection followed by MRI appears to be a well-tolerated test with good image quality, and relatively few, if any, complications have been reported[35,36]. Furthermore, numerous studies support a high sensitivity of the test for identifying EH in symptomatic ears, whether the contrast is administered intravenously or using the TT method. Recent studies investigating the use of MRI as a diagnostic test report a relatively consistent sensitivity as high as 90%-100%[33,36,37]. These results are comparable with previous investigations and bolster the usefulness of MRI as a diagnostic tool for the presence of EH in symptomatic ears. It is worth noting a recent study that compared MRI with tone burst electrocochleography (ECoG) in the diagnosis of MD. The sensitivity results with MRI differed significantly from previous studies, reporting 47%, 29%, and 8% for definite, probable and possible MD respectively[35].

While gadolinium-enhanced MRI shows promise as a reliable tool for positively identifying hydrops in patients with MD, its specificity requires further investigation. Few studies have been conducted on this measure and the results are variable. For example, Pyykkö *et al*[37] found that MRI visualized EH in 65% of asymptomatic ears (35% specificity). In contrast, other studies yield better results in terms of correctly not identifying hydrops on MRI in asymptomatic ears. Baráth *et al*[34] used Ⅳ Gadolinium injection followed by MRI to look for hydrops in 53 patients with MD, reporting a specificity of 78%. Fiorino *et al*[33] had even better results with TTGad injection, noting no perilymphatic enhancement defects in all unaffected contralateral ears of patients with MD (100% specificity).

Generally, TTGad injection is preferred over the Ⅳ route because it provides a higher perilymphatic signal and thus a better visualization of the compartment[38]. However, the advantages of Ⅳ injection should not be ignored and perhaps could be used in special cases. Of particular importance is its less invasive nature, the ability to simultaneously examine both ears for comparison and the fact that perilymphatic enhancement is independent of the status of the round window membrane[34,39].

ECoG

ECoG is a technique that measures the electric poten-

tials generated in the cochlea in response to an auditory signal. The usual ECoG response consists of a cochlear microphonic (CM), the summating potential (SP) and the cochlear nerve compound action potential (AP). The CM is mainly generated by the outer hair cells closest to the recording electrode. Due to its proximity, the CM closely resembles the waveform of the stimuli and vibrations of the basilar membrane. If the polarity of the stimulus is reversed, the polarity of the CM will also reverse. The alternate polarity stimuli are used to cancel the amplitude of the CM so that SP and AP can be measured. The SP consists of a shift in the baseline of a CM in response to click stimuli and a deflection before the AP in response to tone-burst stimuli. Finally, the AP is the sum of the individual APs from the auditory nerve fibers[40]. Two methods of obtaining ECoG differ by where the electrode is placed: TT has an electrode on the promontory wall of the middle ear and Extratympanic (ET) has one outside of the tympanic membrane. The ET method has a slightly lower sensitivity and specificity because of low signal amplitude, but is still the preferred method due to it being non-invasive and easy to implement. Using tone burst auditory stimuli is more reliable than the commonly used auditory clicks stimuli[41].

The SP/AP ratio is commonly used to identify EH. The thresholds for the ratio vary with some authors suggesting 0.5 for ET with clicks and alternating polarity while others suggest 0.33 for TT. There is no universally agreed SP/AP ratio that we could find[41]. It is thought that altered SP and AP is the result of mechanical asymmetry in the basilar membrane[42].

Electrovestibulography (EVestG) is similar to ECoG except that it measures saccule function instead of cochlear function. Instead of acoustic stimuli, the patient experiences passive whole body tilts in a hydraulically controlled chair located in an electrically and acoustically shielded chamber. The test has shown encouraging results in other neurological diagnostic applications such as Parkinson's disease, depression, and schizophrenia disorder by other studies. It is possible that with more research, EVestG could be used to identify neural firing patterns that are diagnostic in patients with MD[43].

Sensitivity of ECoG ranges from 57% to 71% and specificity ranges from 94% to 96%[41]. A study found 1 kHz tone-burst stimuli to be the most reliable stimuli with a sensitivity of 86% and specificity of 80.5%[44]. ECoG interpretation is complicated by the fluctuating behavior of MD. Sensitivity can go from 60% to 92% when ECOG is used during a symptomatic period[41]. Additionally, sensitivity is found to increase with duration and severity of the disease. A study found 71% sensitivity in stage 1 MD compared to 90% in stage 4, and 43% in MD for less than 1 year duration compared to 100% in 30 years duration[45]. However, ECoG is not a useful tool in differentiating between definite and probable MD[41].

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMPs) are becoming a popular tool to assess inner ear function. Cervical VEMPs utilize the vestibulocolic reflex by measuring the inhibitory potentials of the ipsilateral sternocleidomastoid muscle in response to loud auditory signals. Signals from the acoustically responsive sensory cells and neurons of the saccule are conducted centrally *via* the inferior vestibular nerve[46]. Studies have shown that altered motion mechanics of the distended saccule can lead to an altered VEMP response in MD patients[46]. A cVEMP curve is made by plotting the dB SPL as a function of frequency for tone bursts at 250, 500, 750 and 1000 Hz. Healthy patients are most sensitive at 500 Hz and patients with MD showed a sensitivity shift to 1000 Hz[47]. Thirty percent of unaffected ears in patients with unilateral MD also show a sensitivity shift, but to a lesser degree. This could be because the unaffected ear has a minor form of MD. It was found that normal adults above the age of 60 show a sensitivity shift. In some cases they showed flattening of the threshold response curve. A high proportion of patients with caloric asymmetry $\geqslant$ 25% did not show any VEMP response[47].

Another version of VEMP called ocular VEMP records excitatory potentials from the superior vestibular nerve going to the inferior oblique and inferior rectus muscles of the opposite side[48,49]. It is thought that utricular afferents and some saccular afferents travel through the superior nerve division and most saccular afferents travel through the inferior division. With more research, VEMPs could be used to differentiate dysfunction in the otolith and saccule[50]. VEMP measurement has been found to be a more reliable test for saccule function compared to a calorics[51]. It has been suggested that a negative VEMP test does not rule out MD, however a positive test result suggests that MD is probable[47].

MIGRAINE AND MÉNIÈRE'S

Since the term MD was first coined, the prevalence of migraine among MD patients and MD among migraine patients has suggested a possible link between these two diseases[52]. What was once called Vestibular Ménière's is no longer recognized by the current guidelines for MD[53]. Others suggest that most likely this variant of MD was actually undiagnosed vestibular migraine (VM)[54,55].

Recently, the Migraine Classification Subcommittee of the International Headache Society has proposed diagnostic criteria for VM which have been included in the International Classification of Headache Disorders (ICHD) 3rd beta edition. It should be noted that the term VM could be used interchangeably in other papers with migraine-associated dizziness/vertigo and migrainous vertigo. According to the ICHD, VM is characterized by vestibular symptoms such as vertigo and head motioned-induced dizziness lasting between 5 min and 72 h. Common symptoms in MD such as tinnitus, aural pressure and fluctuating hearing loss other than profound can occur in VM. Likewise, migraine headaches, photophobia and even migraine auras are

common in MD[56]. A pathophysiological relationship between MD and VM remains uncertain however some theories have been proposed. The prevalence of allergy among MD and migraine patients compared to the general population may suggest an immunological link[57]. There is some evidence of increased IgE levels in MD patients that could lead to EH in MD and meningeal vasculature changes in migraines[57,58]. However, more work needs to be done in this area to support this claim.

Early MD can present with early episodic vertigo only and can be difficult to separate from VM. Differentiating MD from VM can be done through the patient's history or by means of vestibular function tests[56]. In VM the spells of vertigo can be anywhere from few minutes to over 24 h. Migraine is more likely the source of vertigo if there are associated features like photophobia, paresthesia, visual disturbances (scintillating lights, visual hallucinations). Meanwhile, patients with MD will eventually develop a progressive hearing loss. In VM while audiometric and vestibular test findings can be found, they are typically mild and do not fluctuate over time[52]. A recent study using VEMP separated MD from VM with a sensitivity of 90% and specificity of 70%[59]. Shepard suggests that if VM is likely, even though MD has not been ruled out, it is better to treat for migraine. Even in cases where both migraine and MD coexist, it is better to treat migraine first[52].

TREATMENTS

Dietary/salt restrictions

The typical first treatment option for an MD patient is a low salt diet consisting of sodium in the range of 1000 mg to 2000 mg per day[60,61]. Some patients with MD report that a salt binge seems to precede an acute episode of MD[61]. The purpose of the diet is to reduce endolymphatic pressure, due to the idea that a high-salt diet can influence the osmotic gradients in the inner ear to develop hydrops[61]. Some however have challenged the idea that a salt diet could affect the plasma sodium level or fluid dynamics in the inner ear. Sodium levels in endolymph have been found to be normal in animals with induced EH and patients from which endolymph were sampled. Thai-Van *et al*[62] suggests the alternative theory that a low sodium intake influences aldosterone secretion that may affect endolymph regulation.

There have been some reports that a low sodium diet associated with diuretics brings positive result[63,64]. However, the evidence in the literature to support low sodium diet as an effective treatment for MD has been lacking. A low salt diet can limit the patient's lifestyle and quality of life. This can often make it difficult to remain on the diet in the long-term[61].

Diuretics

Diuretics are relatively inexpensive and commonly used to treat MD[60]. The purposes of diuretics are to alter ion concentrations in order to reduce endolymphatic volume and pressure. Some have argued against the use of diuretics suggesting that there are too many active mechanisms and buffer systems in the inner ear for diuretics to be useful[65]. As previously noted, smaller studies have found that the use of diuretics with a low salt diet can be beneficial[63,64]. A recent Cochrane review found no evidence in support for or against the use of diuretics because of the lack of articles that meet accepted review standards[66]. Common side effects are weakness, dizziness and headache. Serious side effects are cardiac arrhythmias, hyperkalemia, renal failure and hypersensitivity[67]. Side effects are much more prevalent in the elderly population[68]. It is important to avoid drugs that increase serum potassium concentration and antiarrhythmic drugs because Dyazide can potentiate toxicity. In addition, Dyazide interacts with methotrexate, lithium, cyclophosphamide, pixantrone, and others[67]. Pirodda *et al*[65] suggests diuretics lower blood pressure, which can exaggerate a vasomotor response inducing local ischemia, which can lead to damage.

Betahistine

Betahistine is one of the most widely used drugs to treat MD, with 94% of surgeons prescribing it in the Europe and United Kingdom[60]. In addition to being an H1 agonist and an H3 antagonist, it is thought to promote blood flow into the cochlea through the stria vascularis by its suspected vasodilatory effects[69]. Several clinical trials have shown that Betahistine may in some way improve vertigo, nausea and vomiting[70-74]. However, long term, longitudinal, uncontrolled trials have failed to show a benefit on hearing loss[75,76]. A Cochrane review looking at 243 patients concluded that there is insufficient evidence for the effectiveness of betahistine[77]. Some suggest that it should not be considered the gold standard therapy for MD[78]. However, others suggest that Betahistine is a cheap drug with limited side effects and that if there is no improvement it should be withdrawn[68]. Common side effects are bronchospasms, asthma, drowsiness, lethargy, nausea, headache, eye and skin irritation, peptic ulcers due to its histamine-like activity, mild stomach discomfort[79-81]. However, systematic reviews still tend to underreport the side effects[82].

TT steroid

Steroids have been used to treat an autoimmune response, ischemia and sudden sensorineural hearing loss, all of which have made it a likely candidate for the treatment of MD[61,67,83]. Studies show that steroids can also have mineralocorticoid effects. Dexamethasone increases the principal epithelial sodium transporter of semicircular canals by threefold, possibly influencing the sodium and fluid dynamics in the inner ear[84].

An older study showed promising results, with 82% of patients having improved vertigo when treated with steroids compared to 57% treated with saline injections[85].

One trial showed that 91% of MD patients had adequate control with intratympanic dexamethasone injections and did not require more ablative treatments[86]. A recent review looking at 5 RCT's found that there is enough evidence to support the effectiveness of intratympanic steroid for treating vertigo[87]. There is a small risk of tympanic membrane perforation and middle ear inflammation[67].

TT gentamicin

Gentamicin is an aminoglycoside antibiotic that is used as an ablative treatment for MD. Although both vestibulotoxic and cochleotoxic, the drug has a high affinity for type 1 vestibular hair cells and therefore results in more vestibular damage than hearing loss[88]. Gentamicin is thought to operate by accumulating in hair cells and also interfering with calcium dependent receptors in the plasma membrane by competitive inhibition[89,90]. Aminoglycosides can also interfere with hair cell secondary cell messengers and the integrity of the cell membrane[91]. The drug is titrated to control vertigo symptoms, although some argue to titrate until there are signs of unilateral vestibular weakness. The main goal is to titrate just enough to get the most reduction of vertigo with the smallest reduction of hearing and balance. Titration of gentamicin until there is complete unilateral vestibular ablation is usually unnecessary and can result in worse hearing and balance outcomes[67].

Gentamicin has been shown to be an effective treatment for vertigo with minimal vestibular loss compared to ablative surgeries[87,92]. One RCT comparing intratympanic gentamicin to saline found a reduction of vertigo with an average reduction in hearing thresholds of only 8 dB[93]. Another RCT comparing intratympanic gentamicin to dexamethasone found greater control of vertigo with gentamicin, with minimal hearing damage[94]. Typically 54% of patients only require one injection and 96% do not need further ablative surgeries[95]. Clinical evidence shows that anatomic factors such as adhesions or bone dust can prevent drug uptake by blocking the round window. Middle ear exploration with exposure of the round window membrane and direct application of gentamicin is effective at controlling vertigo in 75% of gentamicin non-responders[96].

Resultant unilateral vestibular hypofunction can cause symptoms of imbalance with rapid ipsilateral head turns[97]. Hearing loss can occur in 17% to 25% of patients[98,99].

Meniett therapy

The Meniett device operates by adding positive pressure to the middle ear, which has shown to influence pressure in the inner ear[100]. This is a noninvasive procedure that involves a short-term ventilation tube and consists of a repeated 0.6-sec. pulse at a range of 0 to 20 cm H_2O at 6 Hz applied to the middle ear. The treatment consists of three to four cycles per day with each cycle lasting for 5 min[101]. It is thought that the pulses vibrate the round window aiding in endolymphatic turnover[67].

A 2014 meta-analysis looking at 12 studies including 2 RCTs found that the device improved short-term vertigo and some hearing[101]. A recent Cochrane review from 2015 looked at 5 RCTs and found that only one showed an improvement in vertigo with positive pressure therapy[102].

The Cochrane review found moderate quality evidence in two studies that hearing is worsened after use of the device[102]. The Meniett device is minimally invasive other than the associated risks of inserting a ventilation tube.

Endolymphatic sac surgery

The endolymphatic sac is an outpouching of the endolymphatic membrane in contact with the dura of the temporal bone[67]. It was originally thought to be involved in the resorption of endolymph but more recently was found to also have an immune function[103]. Endolymphatic sac surgery is aimed at shunting, draining or decompressing the sac, which is thought to prevent hydrops by facilitating outflow of endolymph[67]. Similar results have been noted in decompressing the sac *vs* shunting[104]. The most common shunting technique is the endolymphatic mastoid shunt which involves draining endolymph from the sac into the mastoid cavity[105]. A histological study looked at temporal bones after sac surgery and found that correct placement of the shunt had no relation to vertigo improvement[106]. Ghossaini *et al*[107] noted that in situations when the endolymphatic sac cannot be found, decompressing the surrounding dura gives positive results. Additionally, it is possible that removing the bone surrounding the endolymphatic sac could also lead to decompression[107].

Endolymphatic sac surgery, although invasive, is considered a conservative approach because it leaves the vestibular neuroepithelium and innervation intact. Unilateral MD patients with intractable vertigo and especially bilateral MD patients that do not respond to medical treatments are considered for endolymphatic surgery in order to avoid possible hearing loss with ablative treatments[107]. Some trials have found high rates of long-term improvement in vertigo with low risk of hearing loss[108,109]. Some studies report 55% to 85% hearing stabilization or improvement[110-112]. However, a Cochrane review in 2013 noted that 2 RCTs found no difference between treatment and placebo groups[113]. It should be noted that the low number of patients considered for surgery out of the already low number of patients unresponsive to medical treatment makes it difficult to obtain high-level evidence. Patients who had good primary results from endolymphatic surgery but experience recurrence of symptoms after a period of time can be considered for revision sac surgery. The idea is that iatrogenic osteogenesis and perisaccular fibrosis reestablishes the pathogenic

state by compromising endolymphatic drainage[114-116]. Huang[117] found that perisaccular fibrosis is linked with recurrence of symptoms after surgery. It has been shown that correctional surgery will provide symptom relief[114]. Some reports show that use of intraoperative mitomycin C to the endolymphatic sac area may prevent perisaccular fibrosis[117]. Endolymphatic sac surgery has a small risk to residual hearing, up to 2%[118]. Bleeding from the lateral sigmoid sinus and cerebrospinal fluid leak are other potential complications in endolymphatic sac surgery. Conductive hearing loss after endolymphatic sac surgery has been reported and is thought to be secondary to bone dust making its way to the middle ear[118].

Vestibular nerve section

The purpose of vestibular nerve section (VNS) is to treat vertigo by selectively cutting the vestibular portion of CN Ⅷ while preserving the cochlear portion. This surgery is usually the last option for clinicians when dealing with unilateral MD patients with hearing function that have exhausted all other medical and surgical treatments. Patients without hearing function would be considered for a labyrinthectomy. Patients with bilateral vestibular disease are not considered for a VNS because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss[107]. VNS can be accomplished through either retrosigmoid or retrolabyrinthine approach. The retrosigmoid approach requires a suboccipital craniotomy and the retrolabryinthine approach requires mastoidectomy. Both usually involve decompression of the internal auditory canal in order to identify and section the vestibular nerve. Care must be taken in order to avoid injuring the facial and cochlear nerve[67]. VNS is the most effective treatment for vertigo in MD[107]. Vertigo control rates between 78% and over 90% have been reported in the literature[119-124]. Possible reasons for failure are incomplete sectioning of the vestibular nerve in order to avoid injury to the cochlear nerve and inability to identify the vestibulocochlear cleavage plane[125]. Remaining or recurrent vertigo after surgery can be further treated by intratympanic gentamicin[107]. About 4% of patients experience significant hearing loss[124]. Other complications are facial nerve paralysis, cerebrospinal fluid leak, and headache[107].

Labyrinthectomy

Labyrinthectomy is a destructive treatment involving the removal of the neuroepithelium from the five vestibular organs. The treatment is typically the last resort for unilateral MD patients with severe hearing loss that do not respond to medical and surgical treatments. As was the case for VNS, bilateral MD is a contraindication because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss[107]. Several studies have shown excellent control of vertigo in up to 97% of patients[16,126,127]. There is a 2% risk of facial nerve injury and a 3% risk of CSF leak[128].

CONCLUSION

The pathophysiology of MD is still unclear and controversial, however EH represents the hallmark histological finding in postmortem temporal bone studies of patients. More than likely, it represents the end point of various causes. As we become more experienced with evaluating these patients it is necessary to fine tune the diagnostic criteria for improved communication and improve the reporting of research data across specialties. The new international consensus on diagnostic criteria is an important step towards this.

The diagnosis of MD can be difficult and many commonly used tests are poor screening tools. More specific diagnostic methods are needed to fine-tune the diagnosis and to help differentiate MD from Migraine associated vertigo. Recently MRI for identifying EH has gained popularity.

Finally, new and less invasive and destructive treatments of MD are available with the introduction of intratympanic treatments with steroids and gentamicin as well as the Meniett device.

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