Electrophysiologic Diagnosis of Meniere's Disease

Mark J. van Tilburg · Steven D. Rauch

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Abstract Meniere's disease was first described in 1861 by Prosper Meniere. The exact pathophysiology is still unclear. The history taken by the physician in combination with audiometric testing are still the most important diagnostic tools, however multiple electrophysiological tests have been described to aid in the diagnosis of Meniere's disease. These tests are used because of their presumed sensitivity to structural and/or electrochemical changes brought about by endolymphatic hydrops, although the precise relationship between hydrops and the symptoms of Meniere's disease is still uncertain. Here we discuss the electrophysiologic tests that are currently used clinically in Meniere's disease, namely vestibular evoked myogenic potentials, electrocochleography, and the cochlear hydrops analysis masking procedure. At the current state-of-the-art, results of these tests must be considered corroborative rather than diagnostic.

Keywords Meniere's · VEMP · Electrocochleography

Introduction

Diagnosis of Meniere's disease

Prosper Meniere was the first to describe the syndrome that consisted of continuous or intermittent head noises accompanied by diminution of hearing and intermittent attacks of vertigo, dizziness, uncertain gait, staggering and falling, accompanied by nausea, vomiting and syncope [1]. The syndrome that now carries his name still mostly follows this description: fluctuating hearing loss, aural fullness and episodic vertigo in which the vertigo attacks typically last between 20 min and 24 h [2]. The diagnosis is a clinical one and based on the history taken by the physician and the exclusion of other causes.

While there is no definitive "Meniere test", a number of tests have been developed that can support the diagnosis of Meniere's disease. Here we discuss the most relevant electrophysiological tests currently used clinically. None of these tests can substitute for a careful history, physical exam, and audiogram as the essential tools for diagnosing Meniere's disease.

Meniere's disease affects both cochlear and vestibular endorgans. There are electrophysiologic tests of each that may be informative in the evaluation of Meniere patients; especially vestibular evoked myogenic potentials (VEMP) for vestibular testing, and electrocochleography (ECoG) and modified Auditory Brainstem Response (ABR) for cochlear testing. Since Hallpike and Cairns [3] and Yamakawa [4] first described endolymphatic hydrops as the signature histopathologic finding in Meniere's disease, there has been a presumption that endolymphatic hydrops is also the essential pathophysiologic abnormality, causing all the clinical symptoms of fluctuating and progressive sensorineural hearing loss, episodic vertigo, tinnitus, and

M. J. van Tilburg · S. D. Rauch (✉)
Department of Otolaryngology, Massachusetts Eye and Ear
Infirmary, 243 Charles Street, Boston, MA 02114, USA
e-mail: steven_rauch@meei.harvard.edu

M. J. van Tilburg
e-mail: mark_vantilburg@meei.harvard.edu

S. D. Rauch
Department of Otolaryngology, Harvard Medical
School, Boston, MA, USA

aural fullness. This presumption is now considered to be highly suspect, if not downright incorrect. There are numerous studies confirming endolymphatic hydrops in Meniere's temporal bones post mortem (e.g. [5–7]). However, there are many cases with endolymphatic hydrops that lack clinical symptoms of Meniere's disease [6, 8] and rare cases of Meniere's disease that lack hydrops [9]. More recently magnetic resonant imaging (MRI) has been used to identify endolymphatic hydrops in living patients [10, 11]. Although this method is still in development, studies have shown that not all MD patients have endolymphatic hydrops that could be visualized using specific MRI protocols. Ambiguity about the precise relationship of endolymphatic hydrops to clinical Meniere's disease notwithstanding, the electrophysiologic tests discussed below are used in evaluation of Meniere's disease because of their presumed sensitivity to structural and/or electrochemical changes brought about by hydrops.

Vestibular Evoked Myogenic Potential (VEMP)

Physiology

Acoustic sensitivity of the vestibular system was first investigated by Nobel Prize nominee dr. Pietro Tulio [12]. He made detailed observations of sound-evoked head movement, eye movement and postural changes in animals following surgical fenestration of the bony labyrinth. In 1935 von Békésy [13] was the first to report vestibular responses to sound in healthy human subjects and provided evidence that the responses were not mediated by the cochlea. He confirmed the assumption that the response was of vestibular origin by showing that it was preserved in deaf patients with intact vestibular function.

In 1994 Colebatch et al. [14] re-examined the phenomenon of sound-evoked vestibular responses and showed that responses could be recorded from the ipsilateral sternocleidomastoid muscle (SCM) as well as from the inion as described earlier by others [15]. The characteristics of this VEMP showed a linear relationship between sound intensity and tonic EMG level [16]. Murofushi and Curthoys [17] found more evidence for the saccular origin of the response by retrograde tracing of the click-sensitive afferents showing most neurons to originate in the saccular macula.

Cervical vestibular evoked myogenic potentials (cVEMP) depend on the vestibulocollic reflex which arises from the acoustically responsive sensory cells and neurons in the saccule and utricle with signals conducted centrally via the vestibular nerve [18]. The afferents which are susceptible to noise are known as the otolith irregular afferents [19, 20, 21]. These afferents project to the vestibular nuclei and cause an inhibition of the contracted

ipsilateral SCM when activated by a loud acoustic stimulus [22]. Since saccular endolymphatic hydrops is the most consistent histopathologic change seen in Meniere temporal bones, it has been hypothesized that VEMP behavior, either threshold, amplitude, or frequency tuning will be altered in Meniere ears [23–25].

Air conducted sound (ACS) is the most commonly used stimulus for eliciting cVEMPs. Tone bursts are preferable above clicks because the latter have less reliable results and need higher absolute intensities to evoke a response [20, 24]. Since high intensity sound is required to evoke the VEMP response, the response is easily obliterated by even a small degree of conductive hearing loss. In such cases bone conducted vibration (BCV) can be used as an alternative stimulus to bypass the middle ear problem and provide adequate stimulus to evoke the VEMP [21]. Usually a bilateral response in SCM muscles is produced, where the response in the ear ipsilateral to the bone conduction device occurs earlier and is usually larger [26].

In patients with Meniere's disease cVEMP typically show lower peak-to-peak amplitude and an elevated threshold [24, 27]. Also, VEMP tuning is flattened in Meniere patients. Rauch et al. found that the tuning for cVEMP in different frequencies showed a "V" shape threshold curve, with the optimal response at 500 Hz and higher thresholds at higher and lower stimulus frequencies. In Meniere patients the "V" flattens and the optimal response shifts to higher frequency [24]. In early stage Meniere's an augmented response may be found, attributed to saccular dilatation that abuts the stapes footplate leading to increased saccular sensitivity [28]. Murofushi [27] showed an absent or delayed response in 51 % of MD patients. Young et al. [28] found abnormal cVEMPs in 82 % of Meniere's patients and deWaele et al. [29] found abolished cVEMP responses in 54 % of MD cases. This indicates that the binary assessment of present vs. absent VEMP is not very useful. Rauch et al. [23] showed a statistically significant difference between the thresholds in healthy ears compared to Meniere ears at 500 Hz, indicating that threshold might be a more sensitive way to assess cVEMP results. Other methods to improve sensitivity of the cVEMP include calculation of interaural asymmetry and assessment of VEMP threshold or amplitude slope as a function of stimulus frequency [20, 23, 30].

Interaural Asymmetry Ratio

The interaural asymmetry comparison is usually expressed as a ratio, the interaural asymmetry ratio (IAR). This ratio compares the left and right ear within a subject [20]. Most often cVEMP amplitude is used for this calculation. Normative data suggest that normal subjects have an asymmetry ratio less than 47 % (calculated by the mean + 2

standard deviations) [20, 31, 32]. Young et al. [28] showed that the IAR differed significantly between the various stages of Meniere's disease. It is important to note that Lin et al. [33] showed that 27 % of asymptomatic ears of unilateral Meniere patients manifested a reduced response VEMP (i.e. elevated threshold and/or flattened tuning curve). In the same study they examined pairs of temporal bones from 17 cases of unilateral Meniere's disease and found that 35 % of cases had saccular endolymphatic hydrops in the asymptomatic ear. These findings are highly suggestive that altered VEMP response in the asymptomatic ears of unilateral Meniere patients might be a sign of "preclinical" Meniere's disease, since approximately 25–35 % of Meniere patients eventually develop bilateral disease [34, 35]. This also means that the calculated IAR in unilateral Meniere cases may be less sensitive to detection of an abnormal ear because the contralateral ear has reduced cVEMP as well, resulting in less interaural difference. IAR therefore must be interpreted with caution in cases of unilateral Meniere's disease.

VEMP testing has also been used to distinguish Meniere's disease from some other vestibulopathies. Most notably, superior semicircular canal dehiscence (SSCD) can have overlapping symptoms with Meniere's disease (e.g. Tulio phenomenon). VEMP is very useful to differentiate between the two because cVEMP amplitudes are markedly increased and thresholds are lowered in SSCD and other "third window" conditions, just the opposite of findings in Meniere's disease [36, 37].

Vestibular migraine is a relatively new diagnosis that can present with similar complaints as Meniere's disease [38, 39]. Baier et al. [40] looked at 63 vestibular migraine patients and found significantly reduced cVEMP amplitudes compared to normal controls. Zuniga et al. [41] used cVEMP to attempt to differentiate between vestibular migraine and Meniere's disease. They found decreased cVEMP amplitudes in both groups, with no significant difference, and concluded that VEMP was not useful to separate the two.

Correcting for Muscle Contraction

One major drawback of VEMP is the degree of test variability, especially between subjects [20, 42, 43]. In order to obtain a reliable cVEMP result it is important to reduce the variability of test as much as possible. The VEMP response is a measure of inhibitory modulation of SCM muscle activity, not a "positive" waveform hidden in stochastic noise, as seen in the auditory brainstem response. Therefore, simple signal averaging cannot reduce noise to enhance the signal-to-noise ratio. One method to control this muscle "noise" (i.e. the SCM EMG activity that is not modulated by the sound-evoked cervicocollic reflex) is to

attempt to standardize the magnitude of muscle contraction effort across test subjects by providing visual feedback of muscle effort to the test subject. Different forms of feedback mechanisms (e.g. a blood pressure cuff that had to be held at a certain pressure or visual feedback that showed the EMG level of the contraction) have been shown to decrease test–retest variability [44, 45]. Another method to control for the difference in muscle contraction level between subjects is by using a form of normalization. Normalization is accomplished by dividing the cVEMP waveform by a constant that resembles the individual muscle activity. By correcting for the muscle activation, the cVEMP response is less variable between subjects, which should make it easier to distinguish between a healthy and a pathological response. Previous studies have shown that test–retest variability *within* subjects is so low that it is not significantly reduced by normalization [32, 42]. However, using normalization, the variability between subjects is significantly reduced showing that the normalized cVEMP offers a more accurate indication of saccular and inferior vestibular nerve function and the potential for improved sensitivity to detect abnormal ears [46].

Ocular VEMP (oVEMP)

Ocular VEMPs are similar to cervical VEMPs in that they are both elicited by acoustic stimulation of the vestibular organs and that the response is measured in muscle EMG [47]. The oVEMP is recorded by placing recording electrodes below the eyes and maintaining an upward gaze during recording, forcing the inferior oblique muscle closer to the recording electrode [48]. There are some important differences between cVEMP and oVEMP, which are not all clearly understood yet. A major difference is that the oVEMP is a contralateral response whereas the cVEMP is ipsilateral. This is shown in a study in which the oVEMP was absent on the contralateral side in patients with unilateral vestibular function but present on the ipsilateral side [47]. Secondly the cVEMP is an inhibitory response and the oVEMP is excitatory, as shown in a single motor unit recording study [49]. The more uncertain parts of the test relate to the endorgan responsible for the response. It has been proposed that the oVEMP is mainly mediated by utricular stimulation while the cVEMP is a saccular response [50]. Clinical studies in vestibular neuritis (VN) patients have been used to study the source of oVEMP vs. cVEMP responses. The inferior vestibular nerve contains afferents from the saccule and posterior semicircular canal whereas the superior vestibular nerve carries utricular, lateral and superior semicircular canal afferents. Several studies have shown that patients with superior vestibular neuritis have oVEMP responses that are reduced or absent, while the cVEMP is intact [51, 52]. This evidence is not

conclusive since a small part of the saccular afferents run through the superior vestibular nerve (Voit's nerve), which could provide an alternate mechanism for the observed responses. Others feel this is unlikely based on observations in an animal model; this saccular-ocular connection is shown to be weak in cats [53]. Whether the oVEMP is exclusively a utricular response or a response mediated by both otolith organs (i.e. saccule and utricle) is still heavily debated (e.g. [54]) and further studies will be needed to resolve the issue.

Clinical use of oVEMP is even less standardized than is use of cVEMP. The choice of air- (ACS) vs. bone-conducted stimuli is controversial. Todd et al. [55] showed that using ACS generally causes an upward eye movement and BCV a downward eye movement in humans, which indicates a different endorgan pattern. Curthoys et al. [50] showed in guinea pigs that ACS activates utricular receptors. Iwasaki used recordings of ACS and BCV and different head positions in a guinea pig model to demonstrate that the two different stimuli are activating different populations of otolith afferents [56]. One possibility is that ACS and BCV both can activate irregular otolith neurons, but not all neurons activated by BCV can be activated by ACS. Thus ACS responses most likely are a subset of BCV responses [21].

In Meniere's disease, the oVEMP has been shown to have enhanced amplitudes in the early stages of the disease [51] and decreased amplitudes and increased thresholds in later stages [57, 58]. Others have studied the tuning of the response by looking at the 500 and 1000 Hz stimulus amplitude ratio and found that this ratio was statistically lower in Meniere's patients [59]. This flattening of the tuning curve was previously described for cVEMP [24]. Huang et al. [57] used a variety of vestibular tests to show the location of hydrops formation in 20 patients with Meniere's disease. They used audiometry (cochlea), caloric responses (horizontal semicircular canal), oVEMP (utricle), cVEMP (saccule) as pointers to which part of the inner ear was affected by hydrops. They found the prevalence of abnormal function in decreasing order in the cochlea, saccule, utricle and semicircular canals that would represent the sequence of hydrops formation in Meniere's disease.

Conclusion

The vestibular evoked myogenic potential test depends upon integrity of the otolith organs and vestibular nerves. The cVEMP is primarily a test of saccular and inferior vestibular nerve integrity, while the oVEMP appears to be more dependent on utricular and superior vestibular nerve function. VEMP testing is an emerging and valuable addition to the vestibular function testing "toolbox" since

it enables assessment of each otolith organ in a way not previously available. The details of the underlying physiology and the precise methods of performing, analyzing, and interpreting VEMP responses are still evolving and not yet standardized. Much more research is needed to determine how best to utilize VEMP testing for diagnosis and monitoring of Meniere's disease and other peripheral vestibulopathies.

Electrocochleography (ECoG)

ECoG is an electrophysiological test that records summing potential (SP) and the compound action potential (AP) of the cochlea and auditory nerve elicited by an acoustic stimulus [60]. The SP is a reflection of the out hair cell integrity whereas the AP reflects auditory nerve integrity [61]. The electrode used to measure the electrical potentials can be placed through the tympanic membrane (transtympanic) or against the tympanic membrane. The transtympanic membrane method gives more reliable results but is also more invasive, which is why in most clinics in the US the electrode is placed either against the tympanic membrane or in the external auditory canal [61].

The glycerol test, a modification of the ECoG, was proposed as a way of improving diagnostic accuracy of the audiogram and ECoG by challenging inner ear fluid homeostasis. However, studies show only about a 50 % incidence of glycerol-induced threshold shift (a "positive" test) in Meniere patients [62, 63]. The combination of low sensitivity and significant patient discomfort in performance of the test have led to its abandonment at most centers.

SP/AP Amplitude Ratio

The ratio of the summing potential (SP) and the nerve action potential (AP) in response to auditory stimuli is used as an indicator of endolymphatic hydrops. The exact mechanism of the SP/AP amplitude ratio increase is still uncertain, but it is hypothesized that the excessive fluid volume caused by endolymphatic hydrops deforms the basilar membrane, thereby altering the amplitude and latency of the response [60, 64]. Thus an enhanced SP/AP ratio is considered by many to be a positive indicator for Meniere's disease. Early studies of the SP/AP ratio showed that the measurement was highly variable and deemed its clinical use limited [65, 66]. The sensitivity of the test lies around 60 %, while specificity is reported around 90 % [67, 68], meaning that the test has a strong positive predictive value but low negative predictive value. Only around half of Meniere patients have enhanced SP/AP

ratio. Another limitation of ECoG is that its reliability depends on integrity of outer hair cells so it can only be tested in a patients with hearing threshold ≤ 60 dB [61]. Since Meniere's disease is associated with progressive hearing loss, ECoG is usually of no use in more advanced disease.

SP/AP Area Ratio

Approximately 20 years ago reports were made of an abnormal AP-N1 latency in ECoG when using condensation vs. rarefaction clicks in Meniere patients [69, 70]. The hypothetical explanation for this phenomenon was a change in the velocity of the traveling wave in an hydropic cochlea. The vibration of the cochlear partition may be abnormally restricted or enhanced under such conditions according to the direction of basilar membrane motion. As a result the traveling wave (on which the AP-N1 should be dependent) will differ accounting to whether the initial deflection of the partition is toward the scala vestibuli (as with rarefaction clicks) or the scala tympani (as with condensation clicks). In order to increase the sensitivity of ECoG Ferraro et al. tried to combine the findings of enlarged SP/AP ratio and the increased duration of the AP-N1 latency by calculating the area under the curve and named this the "area ratio". In a study to test this hypothesis, Al-momani et al. looked retrospectively at area ratio and SP/AP ratio and showed that both of the ECoG parameters were statistically significantly different between the Meniere and control group. The calculated sensitivity and specificity were 83.9 and 92 % respectively. However, a subsequent study by Baba et al. [71] could not replicate this finding.

It is possible that using both the SP/AP amplitude ratio and SP/AP area ratio in combination could improve sensitivity and clinical utility of ECoG for evaluation of patients in early stages of Meniere's disease, for example, when the diagnosis is unclear. However, though ECoG specificity is high, the test is sometimes positive in other diseases that can look like Meniere's disease, such as superior semicircular canal dehiscence [72]. Vestibular Migraine is also known to have symptoms similar and sometimes indistinguishable from Meniere's disease [38]. No studies have been conducted to investigate ECoG results in vestibular migraine patients and compare them to results in Meniere's disease.

Conclusion

In conclusion, ECoG is most useful in the early stages of Meniere's disease, however its diagnostic capabilities are limited by a relatively low sensitivity, the inability to distinguish between others diseases and the fact that it can only be used in patients with hearing thresholds better than 60 dB. Furthermore, studies are needed to assess the relation between ECoG

and vestibular migraine, the most common confounding diagnosis.

CHAMP (Cochlear Hydrops Analysis Masking Procedure)

The Cochlear Hydrops Analysis Masking Procedure (CHAMP) uses wave V from the auditory brainstem response (ABR), evoked by clicks, to assess a change in the traveling wave velocity (TWV) by measuring these traveling wave velocities in different portions of the cochlea. This method assumes that cochlear hydrops is the cause of Meniere's disease, and that this could alter the basilar membrane which in turn could affect the electrical potentials [73]. It is hypothesized that the increased endolymphatic volume increases the stiffness of the basilar membrane which would influence the TWV. Previous studies have calculated increased TWV in patients diagnosed with Meniere's disease [74, 75]. The hypothesis that the stiffening of the basilar membrane increases the TWV forms the basis of CHAMP.

The CHAMP methodology was described by Don et al. The cochlea is masked with different frequencies in order to get ABR threshold responses from different areas along the cochlea partition (i.e. basal vs. more apical). In a healthy response, the latency is expected to increase when the masking noise frequency is higher (i.e. more basal), since the sound has to travel farther up the cochlea to evoke a response in an unmasked frequency domain. If the TWV is pathologically increased, there is less latency difference between the different portions of the cochlea [73].

In their first CHAMP study Don et al. tested 38 normal hearing subjects and 23 definite Meniere patients, comparing click-evoked wave V latency with and without a 500 Hz masking noise. They found a 100 % sensitivity and 100 % specificity for differentiating active Meniere patients from controls. This result supports the authors' hypothesis that the TWV is increased in definite MD patients causing the latencies to be similar in different parts of the cochlea. The Meniere subjects in this study represent a subset of the most severe and active cases. Other studies have shown less sensitivity and specificity. Ordonez–Ordonez et al. [76] performed a prospective validation study to evaluate the usefulness of CHAMP. Their study consisted of three groups, definite Meniere's disease ($n = 32$), other vestibulopathic and neuropathic patients ($n = 35$), and normal ($n = 32$). Results showed a 100 % specificity for definite Meniere patients but only 31 % sensitivity. Kingma and Wit [77] analyzed CHAMP results from 22 unilateral definite Meniere patients, defined as sensorineural hearing loss of more than 60 dB, tinnitus and periodic vertigo attacks (at least 2, lasting more than 20 min), and found sensitivity of only 32 %. DeValck et al. [78] looked retrospectively at 45 patients with

oto-vestibular complaints. They wanted to assess the usefulness of the test in a more diverse group, by including not just definite Meniere's patients ($n = 14$) but also probable ($n = 5$), possible ($n = 13$) and non-Meniere ($n = 25$) patients. Disappointingly, 49 % of performed tests were not interpretable, and in those with an interpretable result, sensitivity was 31 % and specificity was 28 %. The high proportion of uninterpretable tests might be due to the more severe hearing loss in the Meniere group. In the definite Meniere group, average threshold were 47.8 dB, SD 18.8. Overall, they found that subjects with a normal CHAMP had an average threshold of 18.4 dB (SD 12.5), those whose CHAMP was deemed "indicative for ELH group" had average threshold of 37 dB (SD 15.2), and the "uninterpretable" group had average threshold of 39.7 dB (SD 22.5). When the uninterpretable data were excluded, the sensitivity was 53 % and specificity 70 %. If only definite Meniere patients were included, 100 % sensitivity and 80 % sensitivity was obtained.

Conclusion

The CHAMP test exhibits very consistent abnormalities in definite Meniere patients compared to normals but has a low sensitivity and specificity in patients with uncertain diagnosis. Therefore it offers little by way of diagnostic power, serving at best as a means of confirming what is already known. Perhaps future research will determine if altering the parameters of the test will help making it a more accurate test but presently it lacks clinical utility.

Conclusion

Diagnosing Meniere's disease is based on criteria set by the AAO-HNS. Besides an audiogram, no other tests are needed for diagnosis. Still there are some tests available that can aid in the physician's confidence to support the diagnosis of Meniere's disease. The VEMP has the ability to test the otoliths, which was not possible before, making it a valuable addition to current tests that has been shown to be useful in Meniere's disease. However there is much more research needed to determine how best to utilize this test. The ECoG seems to have some value in identifying MD in its early stages, however the negative predictive value is low (i.e. low sensitivity). The recently described CHAMP test has shown little diagnostic power. Perhaps future research will determine if altering the parameters of the test will help make it a more accurate test. Presently it lacks clinical utility.

Compliance with Ethics Guidelines

Conflict of Interest Mark J. van Tilburg and Steven D. Rauch declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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