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Assessment Tools for Use in Patients with Ménière Disease: An Update

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A number of electrophysiological tests have been proposed for the initial diagnostic assessment or for the follow-up phase of patients affected by Ménière disease. The most common are: (i) vestibular evoked myogenic potentials (VEMPs); (ii) electrocochleography (ECoChG); and (iii) otoacoustic emissions (OAEs). This paper presents the latest clinical developments with these 3 testing modalities.

The PubMed, Embase, and Cinahl databases were searched from 2006 to December 2016. Full-text articles were obtained in cases where the title, abstract, or key words suggested that the study may be eligible for this review. The medical subject heading (MeSH) terms included the following: Ménière, hearing threshold, vestibule, otoacoustic emissions, inner ear, ECoChG, VEMPs. There were 368 identified papers, out of which 87 were eligible for inclusion.

Overall the data in the literature are still limited and the recommended procedures have not reached an international consensus. From the available data, one can conclude that none of the electrophysiological tests could be considered as pathognomonic, for the diagnosis of Ménière disease: presently, the tests could be mostly used in a supportive role to the clinical diagnosis. Hopefully, in the future, improved technology in electrophysiological testing could contribute to the development of better strategies for the diagnosis of Ménière disease.

MeSH Keywords: **Hearing Loss • Ménière Disease • Otoacoustic Emissions, Spontaneous • Vestibular Evoked Myogenic Potentials • Vestibule, Labyrinth**

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Background

Ménière disease (MD) can affect both cochlear and vestibular end organs. The early stage of MD is characterized by a recurring hydropic crisis. The hydrops phase is caused by an increase in endolymphatic contents, mainly limited to the cochlear duct and the saccule [1], due to an alteration of the endolymphatic volume regulation (production and or reabsorption mechanisms) [2,3]. This condition determines an increased impedance at the staples footplate, causing a reduction in acoustic energy transmission and anomalies in middle and inner ear function [4].

Several electrophysiological tests have been proposed for the evaluation of MD patients. These include: vestibular evoked myogenic potentials (VEMPs), electrocochleography (ECoChG), and Otoacoustic Emissions (OAEs). The fluctuating course of the disease often complicates the interpretation of electrophysiological tests and proper hearing assessment of affected subjects.

The aim of this paper is to present an update on the main electrophysiological and acoustical procedures clinically available for MD assessment.

Ménière Disease: A Brief Overview

MD is an idiopathic disorder of the inner ear, characterized by unpredictable crisis with a typical symptomatological triad: tinnitus, hearing loss, and vertigo. In addition, ear fullness with neurovegetative symptoms can be associated. This triad was first reported by Prosepero Ménière in 1861 [5–7]. The duration of the vertigo crisis can vary from a few minutes to 24 hours, and the inter-critical periods can also be totally asymptomatic, while the pattern of sensorineural hearing loss in MD can be fluctuating in the early stages and become permanent and severe in the advanced stages [5,6]. Typically, MD occurs between the fourth and sixth decades of life, with a mild predominance in women; it is frequently unilateral, but both ears may be affected with the progression of the disease [5,6]. Although most cases are sporadic, familial forms have been described in the literature [5,6].

Diagnosis of MD can be difficult and even anecdotal. Therefore, in an attempt to reach a consensus regarding MD diagnosis, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1995 first defined 4 levels of certainty for MD: certain, definite, probable, and possible. Ten years later, the Barany Society (2015) reduced the levels to 2: definite and probable [5,6,8,9]. These criteria are defined by the presence of vertigo crisis and by audiometric findings, because there is currently no pathognomonic test that can characterize the presence of MD. Electrophysiological and acoustical procedures could contribute to the assessment of patients with MD.

Table 1. Paper selection according to PRISMA criteria (<http://www.prisma-statement.org/>).

Total number of articles obtained by PubMed, Embase, and Cinahl search	358
Other papers from references in the published literature	10
Total number of papers identified	368
Papers excluded ¹	201
Articles assessed for eligibility	167
Papers excluded ²	80
Total number of papers finally identified	87

¹ Inclusion criteria were: clinical series, review papers. The exclusion criteria were: unavailability of a full text; manuscripts not in the English language; case reports. ² Inclusion criteria were: for clinical series, papers with an adequate group of patients studied ($n>20$); for reviews, papers published on relevant journals and papers showing a rigorous methods and rigorous reporting.

Methods

The PubMed, Embase, and Cinahl databases were searched from 2006 to December 2016. Full-text articles were obtained in cases where the title, abstract, or key words suggested that the study may be eligible for this review. The medical subject heading (MeSH) terms included the following: Ménière, hearing threshold, vestibule, otoacoustic emissions, inner ear, ECoChG, VEMPs.

The search was also conducted according to PRISMA guidelines (<http://www.prisma-statement.org/>); it was carried out independently and restricted to papers in English. The initial number of total identified papers was 358. Additional papers were also identified from references in the published literature ($n=10$). Inclusion criteria were: clinical series, and review papers. Exclusion criteria were: unavailability of a full text, manuscripts not in the English language, and case reports. The authors, subsequently, met to critically discuss disagreements on citation inclusions, and subsequently performed a critical evaluation of 167 selected papers by reading abstracts and/or texts to decide whether the identified papers were relevant to this search. In this case, inclusion criteria were: for clinical series, papers with an adequate group of patients studied ($n>20$); for reviews, papers published in relevant journals and papers showing a rigorous methods and rigorous reporting. Therefore, after a critical evaluation, a total of 87 articles were finally identified as appropriate for this study by all authors and were therefore reviewed (Table 1).

Vestibular Evoked Myogenic Potentials (VEMPs)

The sacculle, after the cochlea, is among the inner ear structures most affected by hydrops [10]. In a study by de Waele et al. [11], the cervical VEMPs were absent from the pathological side in 54% of patients affected by MD. The same study also documented a highly significant correlation between presence of hearing loss and alteration or absence of cervical VEMPs [10,11]. The absence of the ipsilateral cervical VEMPs can be interpreted as alteration of the vestibulocollic ipsilateral reflex at any level in its course [10].

Also, a low amplitude of cervical VEMPs may be found in the side of the affected ear, as reported by de Waele and Kim [11,12]. Cervical VEMPs have also been reported to show a different tuning among those affected, particularly when hearing loss is also present. This has been related with the use of 500 Hz cervical VEMPs even if doubts have been reported since the sacculle and the cochlea have different stimulation mechanisms [13].

The recording of cervical VEMPs is a non-invasive test, which can easily be implemented in clinical practice. Nevertheless, some categories of subjects can present difficulties with the VEMP recording, including: generally non-collaborating subjects; young children who do not understand directions; and subjects who underwent cervical surgery or who present some form of cervical spinal damage [10].

Ocular VEMPs, evaluating the utriculo-ocular reflex, have been reported to be useful in the diagnosis of MD, but the findings are not yet conclusive. Data from Winters et al. showed higher air conduction amplitudes and lower thresholds in ocular VEMPs of those affected by MD compared to normal subjects [14]. However, Murofushi et al. [15] reported regular ocular VEMP values in terms of amplitude and thresholds in MD patients when confronted to normal subjects, and concluded that hydrops does not significantly affect this test.

In conclusion, there is some evidence in the literature suggesting that VEMPs could be useful for the evaluation of patients with MD, but the available data do not support the hypothesis that VEMPs can be used in MD diagnosis.

Electrocochleography (ECoChG)

It has been reported that electrocochleograms of patients with MD often display abnormally enlarged amplitudes of the summing potential (SP) [16]. This observation could be related to an increase in the endolymphatic volume, which creates a mechanical distortion along the organ of Corti and alters the

characteristics of the SP [16]. However, the incidence of an enlarged summing potential in MD patients is reported to range widely, from 20% to 65% [16–18]. It has been reported that ECoChG can be more sensitive to MD (i.e., can identify the disease better) if patients are tested when they are symptomatic [16]. On the other hand, testing a patient during an MD crisis is not clinically feasible [16]. An enlarged magnitude ratio of the action potential/summing potential has been related to MD; however, the incidence of this ratio is reported to vary widely among those affected [16]. Enlarged summing potential magnitudes have also been reported in cases of perilymphatic fistulae; therefore, the proposed “ratio index” cannot be considered highly specific [16].

Abnormal ECoChG findings have not been correlated to the stages of the disease, the duration of the symptoms (i.e., duration of vertigo crisis), the degree of hearing loss, or to the audiometric configuration [17,19,20]. Therefore, the clinical utility of ECoChG for the diagnostic evaluation of those affected by MD remains rather very limited.

Recently, instead of the traditional transtympanic needle electrodes for a direct promontorial recording, a peri-tympanic ECoChG electrode has been proposed, inserted in the proximity of the tympanic membrane surface. This approach alleviates the need for anesthesia, making the application of ECoChG easier. The main drawback of this technique could be a very high electrode impedance and therefore a poor quality of the assessed data. Our literature search did not yield any studies conducted on a relatively large group of MD patients, using the transtympanic approach.

Otoacoustic Emissions (OAEs)

It is well known that inner ear disorders alter otoacoustic emissions [21] and Ménière disease, being an idiopathic endolymphatic hydropic disorder [22,23], can induce alterations in the properties of OAE signals. In this context, an OAE-based evaluation may be used to monitor the entity of the cochlear damage and the evolution of MD.

OAEs were discovered by David Kemp in 1978 [24,25] and initially were defined as “cochlear echoes” generated by the inner ear as a response to external acoustic stimulus. Traditionally, evoked OAEs are classified according to the eliciting stimulus to: TEOAEs (transient evoked OAEs), induced by transient acoustic clicks; TBOAEs (transient tone burst evoked OAEs) induced by transient tone bursts; and DPOAEs (distortion product OAEs) induced by 2 pure tones having a minimal frequency ratio of 1.21 [26].

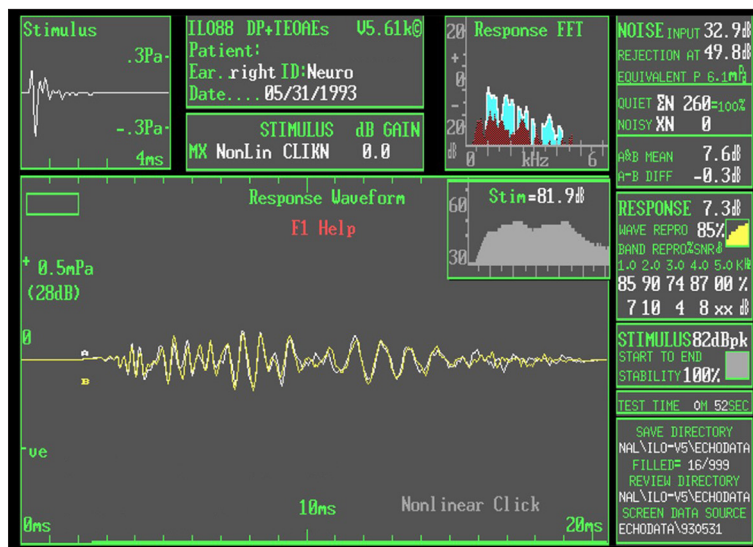


Figure 1. Subject 1: Female 46 y.o. with a typical MD hearing loss profile. Pure tone Audiometry revealed a moderate hearing loss in the low frequencies (≤ 500 Hz). The TEOAE screen information was captured from a ILO -292 device (Otodynamics, UK) running software 5.61. The main panel shows the TEOAE response with dominant peaks at 5.0, 8.0, and 12 ms. After 16 ms, no response is evident. The TEOAE S/N ratios (panel to right under the label RESPONSE) indicate responses up to 4 kHz, an indication of a normally functioning (although partially compromised) cochlea. The TEOAE pattern shown is extremely similar* to other TEOAE responses from subjects with no MD symptoms and in the same age group. * For the similarity assessment, it is necessary to confirm that the tested subjects were not exposed (extensively) to loud noise.

Data in the literature suggest that OAEs and, in particular, DPOAEs may monitor the initial phase of MD and may be able to identify the precise cochlear site involved in an MD crisis [27,28]. In 1985, Eggermont and Schmidt [29] suggested that in the first stage of MD, a variation of the outer hair cell (OHC) function, caused by hydrops, may determine the typical hearing threshold fluctuation of the disease and may be indirectly registered as a decreased DPOAE amplitude at the low DPOAEs frequencies. They also suggested that in advanced MD, the significant injury or the loss of OHCs, due to both chronic mechanical pressure during the hydropic phase and the potassium intoxication of the inner ear cells after the disruption of Reissner's membrane [30,31], may explain the absence of DPOAE responses. In more recent years, de Kleine et al. [32] suggested that the smaller DPOAE amplitude in the ears affected by MD are probably caused by inner ear mechanical alterations related to hydrops. Eggermont and Schmidt were also criticized for the fact that at low DPOAE frequencies the signal-to-noise ratio (S/N) is very small, thus their hypotheses could be erroneous [33]. Furthermore, data from other studies have shown that in patients in the MD hydrops phase, the DPOAEs are amplified rather than reduced [34,35].

Another clinical application of DPOAEs during the hydrops phase in MD is the possibility of monitoring objectively and non-invasively middle ear functional changes induced by glycerol testing [36]. DPOAEs are very sensitive to intracranial pressure variations [37]. The glycerol osmotic effect, acting also on the intracranial pressure, determines a reduction of the pressure in the membranous labyrinth due to hydrops, causing movement of fluids outside the inner ear. This phenomenon can be assessed by 4 different methods: (1) by tonal audiometry: Seeking a hearing threshold improvement of 10 dB HL in at least 2 frequencies between 500 and 2000 Hz [38,39]; (2) By vocal audiometry: seeking a minimum ($>10\%$) improvement of the verbal intelligibility performance; (3) By the decreased

summating potential's amplitude in the ECochG [40]; and (4) By an increased amplitude of DPOAEs [38]. DPOAEs are shown to adequately monitor the glycerol effects on recovering the hearing threshold impaired by labyrinthine hydrops [32,36,38,39].

In comparison to a transtympanic EChG, DPOAEs are not as accurate measures of MD hydrops according to the data of Rotter et al. [41]. Nevertheless, other studies support that DPOAEs is a reliable technique for detecting endolymphatic hydrops and cochlear damage in MD cases [38,40].

TEOAEs may identify variations in the acoustic stimulus transmission through the middle ear or in the decodification and amplification of the stimulus in the cochlea by the OHCs. The investigation of a specific TEOAE response pattern from MD patients has not been very successful, and the TEOAEs responses in MD patients presenting a hearing deficit are indistinguishable from those revealed in unaffected patients presenting sensorineural hearing loss. A typical example is presented in Figure 1.

Nubel et al. [42] published one of the first reports on the application of TEOAEs in MD patients. They suggested that a combined stimulation of TEOAEs and a masker tone of 30 Hz, adequately adjusted in phase, could identify endolymphatic hydrops. Later, this finding was challenged by Hof-Duin and Wit [43], who suggested that the TEOAE alterations observed by Nubel et al. were caused not by endolymphatic hydrops, but by other alterations in the inner ear structures; for example, in the gain of the cochlear amplifier. At present, it is not possible to extract data from *in vivo* studies supporting the

modifications suggested by Hof-Duin and Wit or the endolymphatic hydrops modifications suggested by Nubel et al., so this issue of TEOAE applicability remains to be resolved.

TEOAEs can be useful for detecting a hearing impairment in MD patients. The French group of Avan et al., has published many papers on the influence of intra-labyrinthine pressure and endolymphatic hydrops on TEOAEs [21,27,44–46]. The data from these papers report on the cochlear pressure alteration after postural changes, which result in an increased stiffness of the staples footplate, as an equivalent of an increased intracranial pressure during a hydrops phase in MD patients. In the hydroptic phase of MD, the alterations of the TEOAEs might be attributed to the hair bundle of OHCs.

Two different groups in Japan have assessed the effects of the glycerol test on the TEOAE variables, and have reported different success rates. In the study by Inoue et al. [47], 2 groups were assessed: 1 classified as Ménière (22 ears) and 1 as Ménière with cochlear losses (20 ears). Three hours after a 1.5 g/kg glycerol administration, patients from both groups were assessed with TEOAEs and pure tone audiometry. The authors report that the TEOAE evocation rate (i.e., identification of a robust TEOAE response) improved in both groups: in the MD group from 50% to 63.6% and in the cochlear MD group from 66.7% to 83.3%. The findings from the Sakashita paper [48] are different. The glycerol effects on TEOAEs was decomposed on the effects on 4 aspects of the TEOAE waveform, including the “Total TEOAE Response Power”, or the “Filtered TEOAE response power” in the 1–2.0 kHz range. They reported positive results in 11/22 ears and added that positive TEOAE results were present independent of the threshold improvement in the 1.0 and 2.0 kHz octaves. Interestingly, they reported that a DPOAE protocol (a DPOAE growth function at 1.0, 1.5, and 2.0 kHz) was more sensitive to the glycerol test. They suggested that the DPOAE values at 1.0 and 1.5 kHz might be useful in clinical practice.

Conclusions

The objective of this paper was to present the latest findings on the assessment tools available for MD. The data were extracted from the available literature spanning the years 2006–2016. The focus of the paper was mainly on electrophysiological and acoustical methods.

Data from the literature suggest that the diagnostic criteria for MD are defined by the American Academy of Otolaryngology – Head and Neck surgery (AAO-HNS) and therefore from the Barany Society, and they are based on the audiometric findings [8,9]. Electrophysiological and acoustical testing (i.e., OAEs) is used to confirm and support diagnosis of the disease. In this context, the role of electrophysiological and acoustical testing

is rather limited because data in the literature are sporadic and not inconclusive. Unfortunately, we have not reached an international consensus on the protocols for the electrophysiological and acoustical assessment of the MD patients.

The information obtained from the application of VEMPs and ECoChG is still limited; these tests could be helpful in the clinical monitoring of the MD patients, but they are not specific for the diagnosis. Moreover, the ECoChG (the transtympanic approach) is a costly and invasive test.

At present, there is no pathognomonic test available for the diagnosis of MD. However, some more specific information about the function of the inner ear can be acquired while performing the electrophysiological studies. The presence of specific electrophysiological patterns could help to evaluate those affected by MD, particularly assessing their acoustic or vestibular function (i.e., DPOAEs and OHC function). These features could be useful for the differential diagnosis. In particular, this includes acute vestibular neuritis, even if vertigo episodes are usually longer and not associated to auditory dysfunction, and otosclerosis, especially the cochlear variant [5].

OAEs may be a reliable, non-invasive and, above all, low-cost method for monitoring the entity of cochlear damage in MD patients, particularly for monitoring disease progression. It has been suggested that TEOAEs and DPOAEs can equally identify inner ear damage, as in the hydrops phase of MD, because of the pressure effects on the basilar membrane and, as a consequence, on OHC functionality. Data in the literature suggest that DPOAEs might be more accurate than TEOAEs for monitoring inner ear alterations hydrops-induced and for following the effects of glycerol testing. This needs support from further studies to elucidate why DPOAEs perform better in MD cases.

For now, we believe that it is necessary to accurately evaluate all patients presenting MD clinical features, and also to test them, possibly, by using the electrophysiological tests available, once they have been selected according to AAO-HNS and Barany Society clinical diagnostic criteria. This could allow definition of the electrophysiological ‘picture’ of the cochlear and vestibular function, including hair cell function of each MD patient and, possibly, the evolution of the clinical picture.

Although promising, this field of research still needs to be expanded. Hopefully, in the future, additional information about MD and an improved technology in electrophysiological testing can contribute to the strategies available for MD diagnosis, monitoring, and treatment.

Conflict of interest

None.

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