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OAEs and Meniere Disease

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Abstract

Otoacoustic emissions (OAEs) are responses originating from the inner ear. Clinically they are evoked by different families of acoustic stimuli, such as transient acoustic clicks, tone pips, and pure tones. Upon stimulation, the acoustic energy is transformed in the middle ear at acoustic pressure acting upon the stapes footplate. The pressure wave inside the cochlea stimulates the OAE generators and a reverse acoustic energy (the OAE response) propagates from the inner ear, through the stapes and the middle ear structures, to the tympanic membrane. Considering that the acoustic energy has to cross the middle ear structures twice, the functional status of the middle ear can influence or attenuate considerably the OAE response. In this context, any vestibular alteration can influence the middle ear mechanics (mainly the middle ear impedance) and consequently the OAE response characteristics. The data in the literature indicate that OAEs are very sensitive to changes in the intracranial pressure. These pressure alterations during the Meniere's hydrops phase are expressed as changes in the intralabyrinthine pressure. Other studies have presented data supporting the assumption that OAEs can adequately monitor middle ear changes induced by the presentation of the glycerol test. The data in the literature suggest that OAEs can monitor the progress of Meniere's disease using reliable indices.

Keywords: Ménière, hearing threshold, glycerol test, vestibule, otoacoustic emissions, distortion product otoacoustic emissions, transient otoacoustic emissions, middle ear mechanics

1. Introduction

Otoacoustic emissions (OAEs) are responses originating from the inner ear and they were first described by David Kemp [1, 2]. They are evoked by different families of acoustic stimuli, such as transient acoustic clicks and chirps, tone pips, and pure tones. Upon stimulation, the

acoustic energy is transformed by the middle ear in acoustic pressure applied to the stapes footplate. The pressure wave inside the cochlea stimulates the OAE generators and a reverse acoustic energy (the OAE response) propagates from the inner ear, through the stapes and the middle ear structures, to the tympanic membrane. There it can be recorded by a sensitive probe (microphone), inserted in the acoustic meatus.

The classical classification scheme categorizes OAEs according to their evoking stimulus [3]. In this context, the OAE responses can be elicited by transient clicks (TEOAEs), transient tone bursts (TBOAEs), or by pure tones (distortion product OAEs – DPOAEs). Responses evoked by random thermal noise in the cochlea are called Spontaneous OAEs (SOAEs), which have limited clinical applications. The newest and most accepted taxonomy classifies the responses according to their generation mechanisms [4]. According to Shera and Guinnan [4], the OAE responses are evoked by a linear reflection (of the travelling wave energy) on the basilar membrane, or by nonlinear processes "orchestrated" by nonlinear characteristics of the outer hair cells (OHCs) and the cochlear amplifier per se. The clinically used responses (TEOAEs or DPOAEs) are a mixture of these two mechanisms.

The OAE values, express a measure/metric of the cochlear amplifier functionality, which has found numerous applications in Audiology and Hearing Science. The most known application is in the area of hearing screening. TEOAEs can detect sensorineural deficits up to 35 dB HL; DPOAEs are more sensitive and can detect deficits up to 40 dB HL [3]. The great advantage of OAEs, in comparison to traditional audiometry tests, is that they can detect a deficit before it registers as a hearing deficit (i.e., it is in a subclinical phase) [3]. When an external or internal stressor causes severe mechanical alterations on the functionality of the OHCs, intrinsic and extrinsic apoptotic processes are initiated [5]. Within the next time-frames (days/months), the corresponding OAEs are severely altered and gradually, the OHC damage induces an intrinsic neural apoptosis and a subsequent hearing deficit.

Therefore, the OAE response characteristics are altered by inner ear disorders, such as Meniere's disease (MD), a condition in which the whole inner ear can be damaged, including all the structures of the cochlea (outer and inner hair cells) and the vestibular system.

This chapter is an excursus of the current scientific findings relating vestibular and middle ear alterations, as observed in various stages of the Ménière's disease, with measurements of otoacoustic emissions. The latter are considered the test of choice to identify preclinical effects on the human hearing threshold and alterations in the inner ear.

2. A short introduction of Ménière's disease (MD)

MD is an idiopathic disorder of the inner ear. It is characterized by paroxysmal unpredictable crisis, with a typical symptomatological triad: tinnitus, hearing loss associated to fullness and objective vertigo with neurovegetative symptoms [6]. The crises have a variable duration (from few minutes to 24 h) and the intercritical periods are characterized by residual dizziness or wellness, configuring, anyway, a particularly invalidating disease, particularly considering the unpredictability of the crisis.

MD occurs typically between the fourth and sixth decades of life, with a mild prevalence in women. It is frequently unilateral, but both ears may be affected with the progression of the

disease. Although most cases of MD are sporadic, a 5-15% has a familiar configuration and seems to have a hereditary transmission.

To date, the etiology of MD is unknown, but anatomopathological and histopathological studies on Menieric patients temporal bones, have revealed an enlargement of the membranous labyrinth due to an endolymphatic hydrops [7, 8]. Therefore, the most accredited theory about MD pathogenetic mechanism is the increase of the endolymphatic volume, due to a disorder of either production or reabsorption mechanisms of endolymph, with an expansion and a possible rupture of the membranous labyrinth [9–11]. The damage to the hair cells may be due to both the pressure, during the hydrops phase, and the mixture of endolymph and perilymph, if the membrane rupture occurs. In this case particularly, it has been stated that the crisis may be produced by a potassium intoxication of the labyrinth sensorial epithelium, after the Reissner's membrane rupture [12, 13].

Even though infrequent, endolymphatic hydrops can be congenital and it may be consequent to inner ear malformations, such as Mondini dysplasia [14]. More frequently, the acquired hydrops can be a consequence of viral or bacterial labyrinth infections, or traumas [15].

It has been reported that endolymphatic hydrops has been observed also in asymptomatic patients; this suggests that there should be many 'triggering factors' that may rouse a MD crisis, such as hydric retention, viral infections, stress, cranial traumas, vitamin deficiency, and endocrine disorders [16].

The diagnosis of MD is difficult and it can be defined only after some vestibular crisis with the typical triad. In 1995, the American Academy of Otolaryngology-Head and Neck Surgery published the diagnostic criteria for MD, then updated in 2015, defining a "possible", "probable", and "definite" MD, depending on the frequency of the typical symptoms, until the "confirmed" diagnosis of MD, achievable only with a histopathological examination [17, 18]. A careful history taking and the audiovestibular instrumental examination are recommended. Otoscopy is usually negative.

In the initial phases of MD, the tonal audiometry finds a unilateral cochlear sensorineural hearing loss, affecting the low frequencies. At the beginning, the MD hearing loss is typically fluctuating, reflecting the inner ear hydrops phase: only during this phase, it is possible to perform an osmotic test (Glycerol test) and to observe the improvement of 10 dB in the hearing threshold, at least on two frequencies between 500 Hz and 2000 Hz, within 3 hours, after the administration of 1.5 ml/Kg of body weight of oral glycerol (a potent osmotic agent) with the same volume of isotonic saline solution [19, 20]. The glycerol test is not a diagnostic evaluation, but it allows in determining the reversibility of the early phase of MD and, therefore, it has a prognostic and therapeutic significance. The verbal discrimination is initially preserved at the vocal audiometry. In an advanced MD, hearing loss becomes permanent, pantonal, and often bilateral [21, 22]. The evaluation of the acoustic reflex threshold also demonstrates the recruitment phenomenon, typical of cochlear lesions. Auditory brainstem responses (ABR) can exclude a retrocochlear disease. The vestibular instrumental examinations could be normal at the beginning; during the progress of MD, it reveals a unilateral vestibular hyporeflectivity. Electrocochleography can determine, during the hydropic phase, an increased summating potential, due to the distension of basilar membrane into the scala tympani and then an increased action potential/summating potential ratio [23].

Neuroimaging, such as laboratory exams, are recommended during the differential diagnosis in order to exclude other diseases causing Ménière's-like symptoms or congenital malformation/anatomic variations of the inner ear or metabolic, electrolytic, endocrine, vitaminic, immunologic disorders potentially implicated in MD [24].

3. OAEs and MD

It has been suggested that OAEs and, in particular, distortion product otoacoustic emissions (DPOAEs), may determine the important information about which cochlear regions have been involved in the first phase of MD characterized by recurrent hydropic crisis [25, 26]. Considering that the acoustic energy has to cross the middle ear structures twice, OAE response may be reduced or even suppressed due to imperfections of the middle ear transmission mechanism. In this context, inner ear disorders can influence the OAE response characteristics [27]. The endolymphatic hydrops (confined primarily in the cochlear duct and in the saccule [15]), increase the impedance at the level of the stapes, attenuating any forward or backward acoustic energy transmissions [28].

4. DPOAEs and MD

De Kleine et al. [29] found that, in patients affected by MD, DPOAEs have smaller amplitude than the unaffected ears in relation to the mechanical alterations which were hydrops-induced. An early report on MD by Eggermont and Schmidt [30] stated that in the early phase of MD, a minimal variation on the outer hairy cells function, caused by hydrops, can determine the typical auditory threshold fluctuation; this phenomenon can be indirectly observed as a reduction in the DPOAE amplitude particularly in the low DPOAE frequencies. In cases of advanced MD, the severe damage or the loss of inner ear, outer hair cells, is responsible for DPOAEs absence. Unfortunately, these claims have not been verified in subsequent reports and one of the criticisms Eggermont received [31] was that DPOAEs have very low signal-to-noise ratios (S/N) at the lower frequencies (i.e., 0.5 kHz and 0.75 kHz).

DPOAEs have also been considered as an objective monitor system, for any middle ear functional changes induced by the administration of the glycerol test [32], during the hydrops phase of MD. The osmotic effect and its influence on the intracranial pressure determine a reduction of the labyrinth hypertension, because of the movements of fluids outside the inner ear. This effect can be monitored through: (i) a tonal/vocal audiometry. Effects include a hearing threshold improvement of 10 dB HL in least two frequencies between 500 Hz and 2000 Hz, or an improvement of the verbal intelligibility score of at least 10%; (ii) through electrocochleography (EchoG). Effects include a decrease of the summating potential amplitude [33]; (iii) through OAEs, in particular with an improvement of the DPOAEs amplitude [19]. Overall, the data in the literature [19, 20, 29, 32] suggest that DPOAEs can monitor successfully how glycerol recovers the hearing threshold, compromised by the presence of hydrops.

DPOAEs are very sensitive to changes in the intracranial pressure [34]. Although Rotter et al. [35] found that DPOAEs are not as accurate as the transtympanic electrocochleography, other authors [27, 29, 30] support the role of DPOAEs as a reliable method allowing the detection of endolymphatic hydrops and the cochlear damage in MD [19, 33].

Theoretically, an MD case presenting multiple lesions in the inner ear should condition the OAE responses. In this context, one expects that the OAE responses should be attenuated at low or at high frequencies. There are a few reports in the literature showing the exact opposite [36]. In a study by van Huffelen et al. [36], MD cases were classified into 4 groups. When hearing thresholds were above 60 dB HL, no detectable OAEs were recorded. For those cases, presenting hearing thresholds within 30–60 dB HL, abnormally high DPOAE responses were observed. The authors suggested that these emissions are generated by cochlear sites, sustaining the residual hearing of the patient. Some MD case studies have also been reported presenting anomalous DPOAEs. Hall [37] describes a case diagnosed with a unilateral MD, where the left ear DPOAE responses were shown to be quite robust, despite the fact that the audiogram showed a low-frequency sensorineural hearing impairment. The same author shows that data analyses from groups of MD patients follow the patterns reported widely in the literature (i.e., attenuation of OAEs caused by OHC dysfunction).

5. TEOAEs and MD

One of the first publications relating MD with TEOAEs was a German study by Nubel et al [38]. Their data supported the hypothesis that a combination of TEOAEs and a masker tone at 30 Hz (in an adjustable relation to one another) could discriminate well cases of endolymphatic hydrops. Their protocol examines TEOAE suppression at 0° and 270°. For the latter, normal subjects showed a complete suppression, whereas MD cases showed partial or no suppression. The same protocol was reevaluated in a subsequent study by Hof-Duin and Wit [39], who reported that the Nubel et al. model was correct but their interpretation of the data was erroneous. According to Hof-Duin and Wit, the observed changes were not directly caused by the endolymphatic hydrops but by other alterations in inner ear structures, for example, in the gain of the cochlear amplifier (i.e., induced hearing loss).

The search for a particular TEOAE pattern in MD patients has not been very successful. TEOAEs detect alterations in the middle ear stimulus transmission or in the stimulus decodification and amplification (cochlea). From a TEOAE point of view, MD cases presenting hearing losses are identical to cases presenting a sensorineural deficit. **Figures 1** and **2** present TEOAE data obtained from the two subjects presenting an initial phase MD. The characteristics of these cases were similar: no use of drugs and prolonged exposure to noise, a low frequency humming feeling (tinnitus), and dizziness. Pure tone audiometry revealed a moderate hearing loss in the low frequencies up to 1.0 kHz. Acoustic Immitance and stapedial reflexes were found normal. Subject 1 was a female of 46 years old. Subject 2 was a male of 37 years old. The TEOAE responses indicate a sensorineural deficit and are **indistinguishable** from other responses originating from patients with sensorineural deficits.
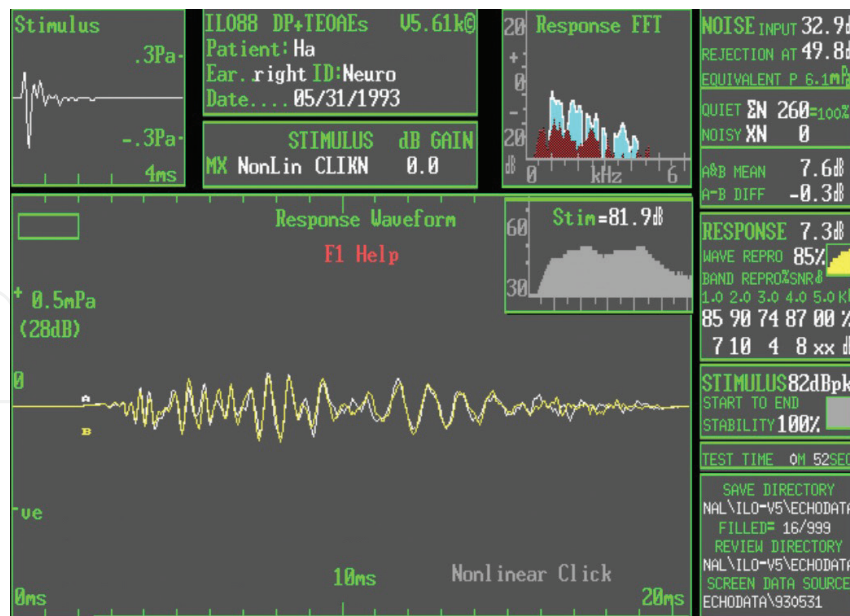
Figure 1. Subject 1: female 46 years, with a typical MD hearing loss profile. Pure tone audiometry revealed a moderate hearing loss, in low frequencies. The TEOAE S/N ratios indicate responses up to 4 kHz, an indication of a normally functioning (although partially compromised) cochlea.

Hatzopoulos et al. [40] used advanced time-frequency (TF) spectral methods to examine the frequency content of TEOAE responses from patients presenting sensorineural deficits. Forty subjects presenting moderate hearing losses (in the range of 1.0 kHz to 8.0 kHz) were enrolled in the study. Five of these subjects were MD cases (two of them are presented in **Figures 1** and **2**). The TF patterns from these subjects followed the TF profiles of the other sensorineural cases and no particular TF-markers were observed for the MD subgroup.

TEOAEs have been employed in the detection of the hearing impairment component of MD. A French group, coordinated by Paul Avan, has made considerable contributions to the influence of intralabyrinthine pressure and endolymphatic hydrops on evoked emissions [25, 28, 41–43]. One way to understand this influence is to assess the alterations of the TEOAE phase shift (the latter is a component provided by the FFT decomposition of the TEOAE response). According to Mom et al. [41], "Acoustic phase shift highlights a variation in intra-cochlear functioning that is worth understanding. By analogy to what is observed in intracranial pressure variation as described by Büki et al. [42], it is logical to expect a marked disturbance in intralabyrinthine pressure. There may be a change in the rigidity of the annular ligament of the footplate under pressure from the perilymphatic compartment that is pushed back by the endolymphatic compartment containing the hydrops; or there may be some more subtle endocochlear modification. The endocochlear pressure resulting from change of posture would be the equivalent for the "hydropic" cochlea of a considerable rise in intracranial pressure. In Büki et al.'s experiment, the functioning of a normal cochlea reflected change in intracranial pressure [42]. In MD, however, cochlear functioning is not normal, by definition. As the model does not distinguish which part of the inner ear is being measured but considers it as a single whole, it can reasonably be considered applicable even in a pathological ear. TEOAE phase change in a test performed in an ear affected by MD during the acute phase may be attributed to the hair bundle of the outer hair cells (OHCs). OHC hair bundle inclination,
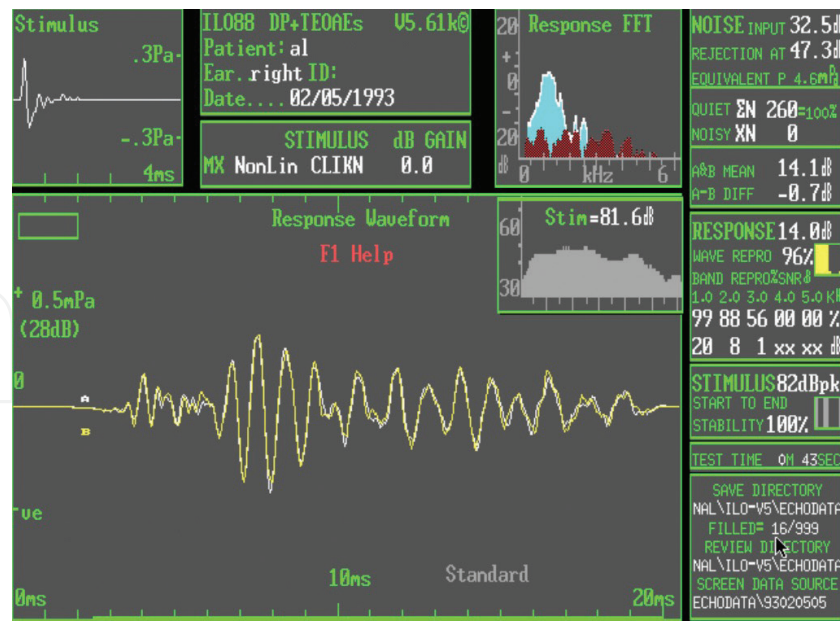
Figure 2. Subject 2: male 37 years, with a typical MD hearing loss profile. Pure tone audiometry revealed a mild to moderate hearing loss, in the low frequencies. The majority of the TEOAE energy is concentrated around 1–1.5 kHz. The TEOAE S/N ratios above 3.0 kHz indicate lack of responses. How this response can be possible, when the pure tone audiometry shows a low frequency deficit? Most probably the strong TEOAE response (from the first 6–10 ms in the TEOAE trace) is generated by cochlear regions above 1.0 kHz, where the subject presents better hearing thresholds.

inducing opening of specific ion channels, compared to gating springs, determines OHC excitation level, which in turn defines the OHC resting point which may shift along the characteristic OHC input-output (I-O) curve, as faithfully reflected in the amplitudes of some types of OAE (quadratic distortion-product OAEs) or in the phase of others. The data from Büki et al showed that phase shift was significantly elevated beyond the normal interval in 18 of the MD patients with range, –80° to +145° and sensitivity, 90%. Overall, in patients, in whom the transient evoked OAEs (TEOAEs) were present, positive predictive value was 100% and negative predictive value was 92.3%.

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. [44] two groups were assessed: one classified as Meniere (22 ears) and one as Meniere 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 Sakashita paper [45] are different. The glycerol effect on TEOAEs was decomposed on the effects on four 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 independently 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, 2.0 kHz) was more sensitive to the glycerol test. They concluded that the DPOAE values at 1.0 and 1.5 kHz are useful for a clinical practice.

6. Conclusions

The data in the literature suggest that OAEs represent a valid noninvasive instrument, which can monitor the cochlear damage entity in patients affected by MD, and could also monitor its progress. OAEs are not just reliable tools, but they are a low-cost methodology in comparison to standardized MD monitoring methods, such as electrocochleography.

The data in the literature shows that alterations in the inner ear caused by the presence of a hydrops can be monitored accurately with OAEs. Glycerol results can also be monitored successfully. Some reports suggest that a DPOAE protocol can be more suitable for MD monitoring tasks, but considering the mechanisms of OAE generation this might not be true. TEOAEs and DPOAEs can similarly detect inner ear alterations as long as these affect the basilar membrane mobility and the functioning of outer hair cells.

Although promising, this field of research still needs to be expanded, where experimental studies are lacking. It is likely that in the future, either implementing our knowledge among MD, or implementing the OAE technology, the application of the OAE for patients affected by MD could be further expanded and offered with more information to the clinical practice.

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