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ORIGINAL ARTICLE

Systematic Evaluation of Diagnostic Tests Including Vestibular Evoked Myogenic Potentials and Multi-Frequency Tympanometry in the Differential Diagnosis of Episodic Vertigo

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Objective: To evaluate the additional role of multi-frequency tympanometry (MFT) and vestibular evoked myogenic potentials (VEMP) in the differential diagnosis of episodic vertigo.

Study Design: Controlled cross-sectional.

Setting: Tertiary referral center.

Patients: 60 samples (15 healthy controls(HC), 15 Meniere's disease(MD), 15 recurrent vestibulopathy(RV), 15 migrainous vertigo(MV)) were included.

Interventions: Pure tone audiometry, VEMP and MFT were performed to all patients and healthy controls, caloric test was performed only to the patients.

Main Outcome Measure: "Audio-vestibular diagnosis score" was described and calculated which was based on the evaluation of the results of four diagnostic tests.

Results: Ear resonance frequency (RF) was 921.6 Hz and 1092.3 Hz in healthy subjects and Meniere patients respectively ($p<0.01$). VEMP thresholds were 84 and 97.3 dB on 250 Hz, 89 and 104 dB on 500 Hz, 97.6 and 110.7 Hz on 1000 Hz in HC and MD respectively ($p<0.01$). "Audio-vestibular diagnosis score" was effective in differentiating MD from other etiologies ($p<0.01$).

Conclusions: RF was significantly higher in MD and this might indicate pressure of the hydropic saccule on stapes footplate. VEMP thresholds were significantly higher in MD. "Audio-vestibular diagnosis score" was helpful in the differential diagnosis of episodic vertigo with the additional role of MFT and VEMP especially in patients with RV or patients with ovelapping diseases such as MD+Migraine or MV+hearing loss. Relatively normal inner ear function in MV patients may enlighten the controversial pathophysiology of this disease in the favor of central hypotheses.

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Introduction

Episodic vertigo is a common symptom which has Meniere's disease (MD), migrainous vertigo (MV) and recurrent vestibulopathy (RV) in the differential diagnosis. Patient's history still stands to be the most important diagnostic tool. Definite MD and definite MV may be relatively easier to diagnose, however RV which comprises heteregenous group of patients and doesn't comply with the criteria of both diseases, yields a diagnostic dilemma in clinical practice.

Pure tone audiometry (PTA), caloric test (CT) are two of the most common tools used in patients with episodic vertigo. Vestibular evoked myogenic potentials (VEMP) and multi-frequency

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tympanometry (MFT) are two evolving methods which may help to differentiate these diseases. VEMP suggested to have altered tuning properties in MD [1]. Ear resonance frequency (RF) which is assessed with MFT, may reflect inner ear status in MD patients [2]. However there is no defined systematical approach in evaluating these diagnostic tests.

The main and most important component in the pathogenesis of MD is endolymphatic hydrops [3]. Hydrops was most prominent and early seen in saccule and cochlea in the labyrinth [3,4]. VEMP as an indicator of the functional status and RF as an indicator of the mechanical status of saccule, both may have benefits in the diagnosis of early endolymphatic hydrops. Therefore, this hypothesis warrants more studies to identify exact value of the tests. Previously suggested hypotheses to explain the controversial pathophysiology of MV include both central (aura, ischemia and trigeminovascular system) and peripheral (endolymphatic hydrops and labyrinthine sensitivity) etiologies [5-10]. Audio-vestibular tests may enlighten the pathophysiology of MV.

Recurrent vestibulopathy is suggested to be a distinct clinical entity, which comprises early onset MD and MV patients along with some other diagnoses [11]. We hypothesize that, with the help of a systematical approach to evaluate the dagnostic tests, one can better differentiate the diagnosis, predict the prognosis and manage the patients.

The aim of this study is to assess the additional role of MFT and VEMP in the differential diagnosis of episodic vertigo and to constitute and estimate the value of a systematical approach in evaluating the results of the diagnostic tests. The pathophysiology of the diseases are also discussed in the light of the results.

Materials and Methods

This study was conducted at Ege University Otolaryngology Department. Forty-five patients and 15 healthy controls (HC) were recruited in the study between november 2008 and september 2009. Informed consent was taken from all individuals. All patients were evaluated by a special referral council that comprises specialists from otolaryngology, neurology and physical medicine departments. Each patient has been referred due to episodic objective spontaneous vertigo as an illusion of spinning or rotation sensation.

Patient selection

Sixty individuals (16M,44F)were included in the study within four groups: 15 MD, 15 MV, 15 RV and 15 HC. Patients underwent routine systemic and detailed neurological and otolaryngological examinations.

MD inclusion criteria;

- Episodic objective spontaneous vertigo as an illusion of spinning or rotation sensation
- Normal otoscopy
- None additional systemic disease
- At least definite MD diagnosis according to the guidelines from AAO-HNS Committee of Hearing and Equilibrium [12]
- Clinically unilateral MD
- None conductive-type hearing loss
- None headache which met the migraine criteria of IHS [13]

MV inclusion criteria;

- Episodic objective spontaneous vertigo as an illusion of spinning or rotation sensation
- Normal otoscopy
- None additional systemic disease
- Met the criteria of possible or definite MV according to Neuhauser et al [14]
- None met the criteria for MD according to the guidelines from AAO-HNS Committee of Hearing and Equilibrium [12]

RV inclusion criteria;

- Episodic objective spontaneous vertigo as an illusion of spinning or rotation sensation
- Normal otoscopy
- None additional systemic disease
- Normal PTA
- None otologic symptoms such as tinnitus or aural fullness
- None met the criteria for MD according to the guidelines from AAO-HNS Committee of Hearing and Equilibrium [12]

- None headache which met the migraine criteria of IHS [13]

HC inclusion criteria;

- None dizziness or vertigo symptoms
- Normal otoscopy
- None additional systemic disease
- Normal PTA
- None otologic symptoms such as tinnitus or aural fullness

Instrumentation and procedure

VEMP, MFT, PTA and CT was performed as a routine audio-vestibular battery to all patients who were referred to vertigo council. MFT, PTA and VEMP was performed to HC.

CT was performed with Nystar software (Nicolet Instrument Inc. Madison, USA) by applying +4°C, 10 ml water to both ears.

VEMP was recorded with Synergy device (Medelec, Oxford Instruments Medical Inc. UK). In order to record the surface electromyographic (EMG) activity, an active electrode was placed on the upper half of the sternocleidomastoid (SCM) muscle ipsilateral to the stimulation, with the reference electrode placed on the upper third of sternum and the ground electrode on the middle of the forehead. Patients were seated on an arm-chair and were asked to turn their head contralaterally to the ear being tested to achieve maximal activation of the SCM. The acoustic stimuli were short tone-bursts at frequencies 250, 500 and 1000 Hz with 0.1 ms rise-fall and 2 ms plateu time, delivered at a frequency of 5 Hz (consecutive 100 stimuli) through a headphone unilaterally to each ear. The EMG signal was band-pass filtered from 10 to 1000 Hz and averaged over a 100-msec interval. The initial positive/negative polarity of the waveform with peaks was termed p13 and n23 on the basis of respective latencies. The latencies of peaks p13 and n23 and peak-to-peak amplitude of p13-n23 were measured. Stimuli was first applied at 100 dB, decreased 10 dB in response-positive and increased 10 dB in response-negative to determine the thresholds. A VEMP record of a RV patient is seen in Figure 1.

RF was taken as the quick estimate of resonance given by the GSI Tympstar v.2 device between 250 and 2000 Hz frequencies. GSI tympstar was calibrated before examinations. Tympanograms were obtained at resonant frequencies that were determined by tympstar. In this algorithm, susceptance is measured in a frequency sweep at one extreme pressure and at tympanometric peak pressure and the frequency at which total susceptance is equal to zero is taken as resonant frequency. We payed special attention on the patterns of tympanograms obtained at resonant frequencies if the estimation correlates with tympanograms.

Main outcome measures

Five study groups were constituted from 120 ears of 60 individuals. Study groups are seen in Table 1.

Average pure tone audiometric thresholds at 0.5, 1, 2 and 4 kHz were calculated. Stage of MD was determined according to average pure tone thresholds[15]. Caloric testing was evaluated for side difference (a 25% difference being considered significant) and bilateral hypofunction (maximal SPV of nystagmus for cold plus warm caloric stimulus should not exceed 12°/s). VEMPs were evaluated according to VEMP configuration [16]. First, average normal VEMP thresholds (nHL) at three distinct frequencies were assessed in HC. Any VEMP threshold out of 95 percentile of normal thresholds was regarded as abnormal. Patients with at least two normal VEMP thresholds among three frequencies regarded to have "normal VEMP configuration", patients with at least two abnormal VEMP thresholds regarded to have "abnormal VEMP configuration". Similarly, average normal RF value was first determined in HC. Any RF value higher than 95 percentile was regarded as abnormal RF.

"Audio-vestibular diagnosis score (AVDS)" was described according to the diagnostic tests and calculated in all patients. AVDS was calculated as follows:

Table 1. Distribution of 120 ears according to study groups

Study groups	Number of ears
Healty control	30
Meniere's disease (affected ear)	15
Meniere's disease (opposite ear)	15
Migrenöz Vertigo	30
Rekürren Vestibülopati	30

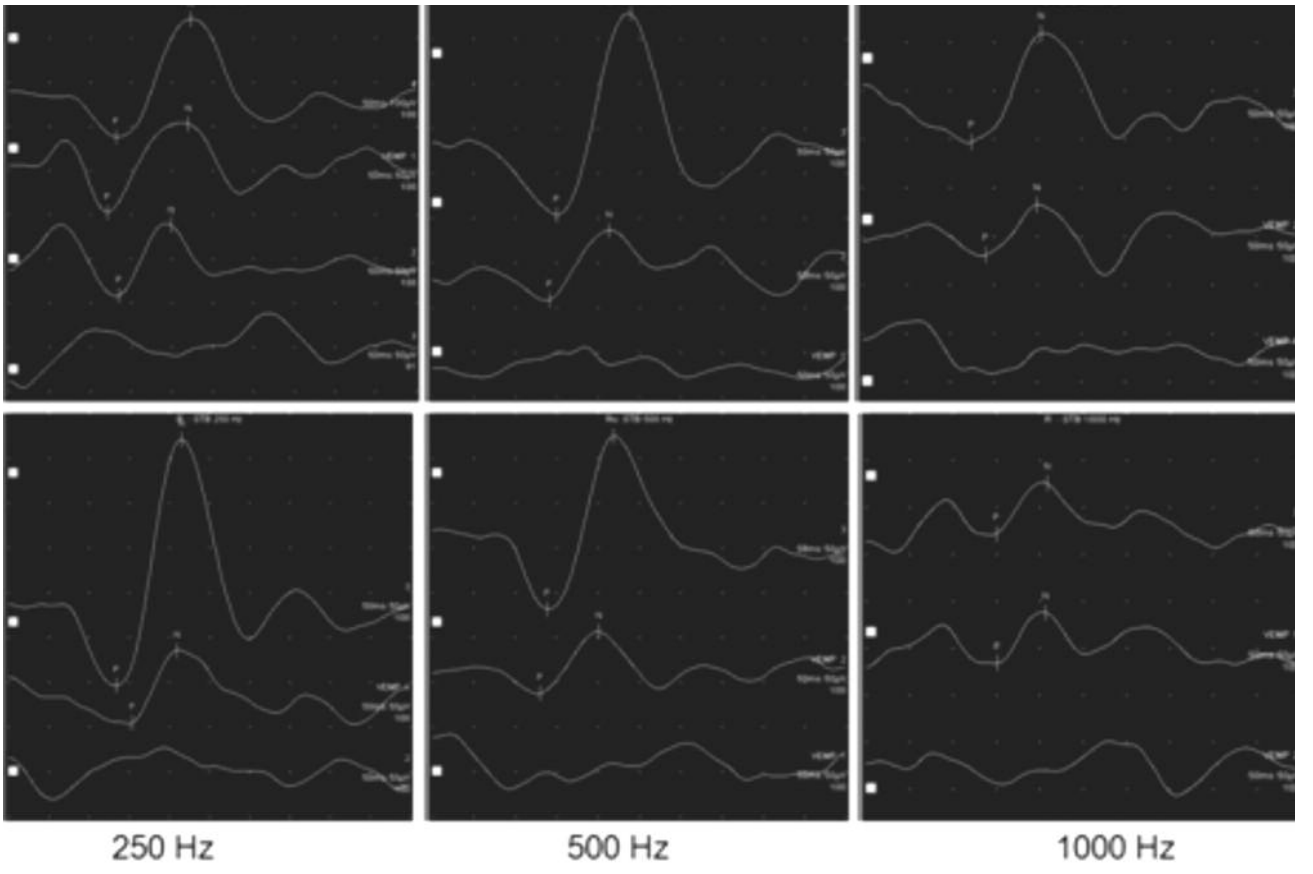

Figure 1. Vestibular evoked myogenic potential record of a patient with recurrent vestibulopathy.

PTA: "1" if normal in both ears, "2" if abnormal in at least one ear

CT: "1" if symmetric, "2" if asymmetric

RF: "1" if within normal range in both ears, "2" if increased or asymmetric in at least one ear.

VEMP: "1" if within norml range in both ears, "2" if abnormal or asymmetric in at least one ear.

"AVDS=PTA+CT+RF+VEMP"

AVDS was described between 4 and 8. Smaller results represent better audio-vestibular status.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS v17.0) software. Mann Whitney U, Kruskal Wallis, Chi-square, Pearson's correlation and reciever operating characteristic (ROC) analyses were performed. Firstly, data of HC was analysed. Abnormal values were described as if the results were out of mean ± 2SD (standard deviation) or 5-95 percentile.

Results

Average PTA thresholds were 6.0, 38.0, 10.7, 8.3, 8.2 dB in HC, MD, MD (opposite ear), RV and MV respectively ($p<0.01$) (Figure 2). This significance was due to the data of MD and others on post-hoc tests (Bonferroni, Tukey). Average RF values were 921±115 (650-1100), 1092.3, 853.3, 845.0, 851.7 Hz in HC, MD, MD (opposite ear), RV and MV respectively ($p<0.01$) (Figure 2). This significance was between the data of MD and others on post-hoc tests.

CT 19.5, 31.6, 34.5, 47.8 degree/sec in MD, MD (opposite ear), RV and MV respectively ($p<0.01$). This significance was between the results of MD and MV patients on post-hoc tests. VEMP thresholds were 84 and 97.3 dB on 250 Hz, 89 and 104 dB on 500 Hz, 97.6 and 110.7 Hz on 1000 Hz in HC and MD respectively

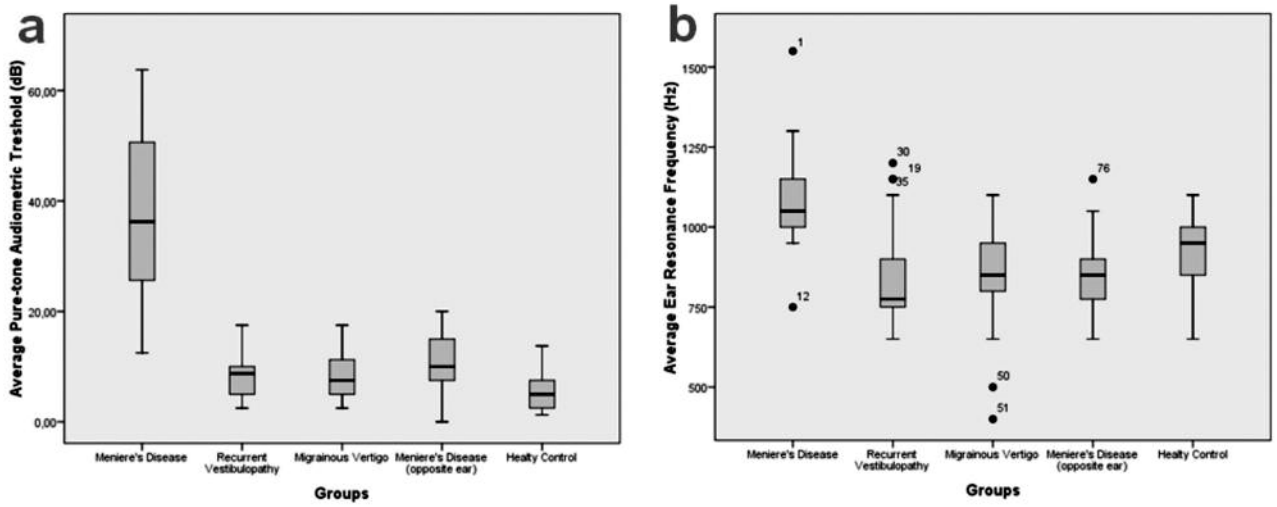

Figure 2. a) Average pure-tone audiometric thresholds, **b)** average ear resonance frequency values according to the study groups are shown.

($p<0.01$) (Figure 3). VEMP thresholds were significantly higher in MD in all three frequencies.

CT, RF and VEMP abnormalities are shown in Figure 4. AVDS was found to be superior in differentiating MD from other etiologies of episodic vertigo (Figure 4), however the difference did not reach a statistically significant level (ROC analysis, area under curve: 0.97, $p>0.01$). AVDS of 6 or higher successfully differentiates MD. Abnormality in two out of 4 diagnostic tests (AVDS≥6) may aware the clinician in the favor of a degenerative process in inner ear. Correlation of MD stage and and AVDS was statistically significant (correlation coefficient: 0.75, $p<0.01$). Higher AVDS correlated with higher MD stage (Table 2).

Discussion

Patient's history and PTA are two most important clinical tools in the differential diagnosis of episodic vertigo. MD and MV may be easily differentiated according to the diagnostic criteria [12,14] in a particular group of patients. However, patients with episodic vertigo have not always been presented with classical clinical picture. There are many overlaps such as migraine plus MD and hearing loss plus MV. MD was found to be more frequent among migraine patients[9]. Some patients describe the clinical picture which was named RV with only episodic vertigo without any aural symptoms or headache. Differential diagnosis of these particular clinical pictures are many times a

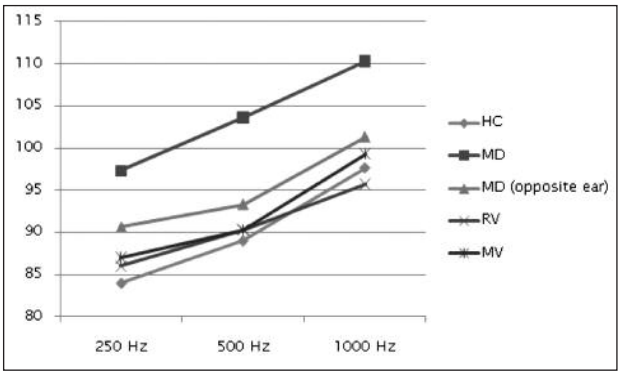

Figure 2. a) Average pure-tone audiometric thresholds, **b)** average ear resonance frequency values according to the study groups are shown.

Table 2. Disease stage and audio-vestibular diagnosis scores (AVDS) of 15 Meniere patients.

AVDS	Stage
8	3
6	3
7	3
8	3
8	3
7	3
8	2
7	2
7	2
7	2
7	2
8	1
6	1
6	1
6	1

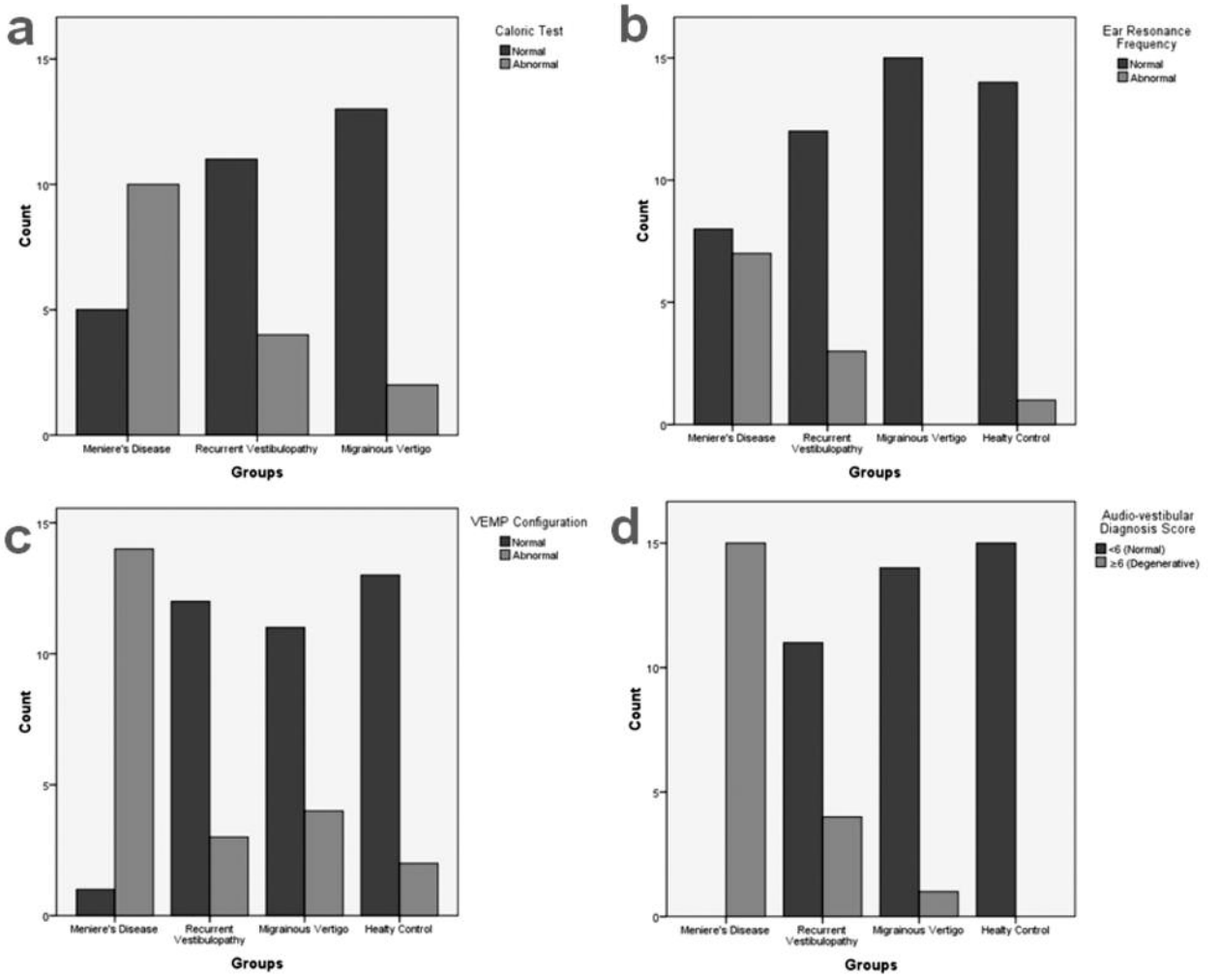

Figure 4: a) Caloric test, **b)** ear resonance frequency, **c)** vestibular evoked myogenic potential, **d)** audio-vestibular diagnosis score, normal and abnormal counts in the study groups are given.

challenging situation for the clinican and diagnostic tools should be put into use in these patients. VEMP and MFT with more frequently used PTA and CT are relatively non-invasive tests which may be helpful in the differential diagnosis of episodic vertigo, however there is lack of a systematic approach in their evaluation. Although no test is perfect, there are problems with the application and the assesments of these tests individually, especially in relatively newer MFT and VEMP.

Saccule was shown to be one of the first places that hydrops develops [3,4]. The importance of VEMP in episodic vertigo is due to its capability of reflecting saccular function as a part of vestibulocollic reflex. Similarly, the role of MFT is due to the mechanical properties of saccular hydrops reflecting into the midddle ear through stapes footplate. The interaction of stapes footplate and saccular membrane in moderate and severe hydrops was shown in a previous study[16].

There are very few studies about the role of MFT in MD. In a previous study, increased RF values before Meniere attack and decreased values after the attack was reported. Authors connected these changes to the decreased inner ear pressure after the attack [2]. Our findings are apart from this study. We found that increased RF may be seen without an attack in MD and it is not stricly related to the attacks. Also we know that there is an entity called "asymptomatic hydrops" without attacks [16]. MFT may not be a single diagnostic test to show early saccular hydrops due its very wide

range of false positive or false negativity, however it may have better clinical value when evaluated with other diagnostic tests. Additionally, there are some other diseases such as otosclerosis that may be presented with dizziness, tinnitus, hearing loss and increased RF [17]. Although there are some mild changes on other audio-vestibular tests, we could not show significant RF change in opposite ears of MD patients. This may be explained with our patient selection criteria and relatively small number of cases. We included only and strickly the clinically unilateral MD patients to the study.

VEMP has advantages such as potential of detecting saccular hydrops, however has disadvantages mainly due to lack of consensus on how it will be evaluated and which parameters are of more importance. Clinical value of VEMP is the interest of this study, not the theories about its application or evaluation. We preferred using VEMP configuration, which is described in methods section, according to the results of our preliminary study about VEMP application and evaluation. As MD is a degenerative disease, functional deterioration in the saccule reflecting VEMP results is expected. Increment in VEMP thresholds have been reported in MD [1,18]. In our study, VEMP thresholds were similarly increased in the affected ear as well as in some clinically non-diseased ears. This may be explained by asymtomatic bilaterality of the disease. Since VEMP is a relatively indirect diagnostic test to reveal saccular changes, it has limitations to be solely used in differential diagnosis of episodic vertigo.

An interesting finding of our study reveals with the evaluation of the correlation of VEMP thresholds with RF values. In our study, VEMP thresholds increase in 250 Hz and decrease in 500 and 1000 Hz with the correlated increment in RF values, in HC. This means that, a change in saccular or ear resonance may affect VEMP thresholds directly. However, we could not show this change in MD patients. Thresholds in all three frequencies had been increased in MD. Histologic and functional deterioration in definite MD may be so high that, minor resonance changes may not be detected as in HC. This may not be true for early MD or asymptomatic hydrops patients which generally are categorized in RV group. In contrary to our results, best VEMP threshold was suggested to change from 500 Hz to 1000Hz in some previous studies [1, 18-21]. This frequency shift was suggested to be caused by the resonance change in saccule [1,18]. We advocate that, frequency shift of VEMP thresholds is not detectable due to loss of function of hair cells in saccule [22], however it must be assesed in RV patients to differentiate early hydrops. Further studies are needed to clarify these changes.

Different hypotheses were suggested to clarify the pathophysiology of MV. Some advocate central, whereas others suggest peripheral etiologies [5-10]. We found abnormal VEMP configurations in some MV patients. However, when all diagnostic tests evaluated together, MV seems to have different pathophysiology other than MD. A degenerative inner ear pathology doesn't explain the findings in our study. Frequency shift in favor of 1000 Hz has been proposed in MV in a previous report [23]. We could not demonstrate such changes in our study group. Another finding of our study that may enlighten the pathophysiological pathways of MV, was the higher values of SPVmax responses in CT. Similar with our findings, CT asymmetry was reported to be 20% and 16.6% in MV patients in two different studies [24,25]. In a different report, authors described that, MV patients had more nausea and vomiting during CT [26]. Results of our study are similar with their findings. This data supports the "sensorial sensitivity increase" hypothesis in the pathophysiology of MV. We advocate that, currently no single hypothesis can explain the pathophysiology of MV.

RV is a clinical entity which includes some MV and MD patients, has relatively better prognosis and shorter duration of symptoms. RV is not a widely accepted distinct clinical disease. In a previous study, the diagnosis remained same in 70% of patients who were diagnosed as RV, whereas 30% has been corrected to MD or benign postural vertigo [27]. In another study, 2/3 of patients had spontaneous improvement in their symptoms, wheras 30% were diagnosed MD or MV [11]. Our findings are similar with their studies. We found 26.6% of RV patients who has degenerative type higher AVDS. These may be early MD patients, however we did not followed the patients up in this study, so can't give the precise diagnosis. AVDS may give important data in the differential diagnosis of RV patients. Studies with long follow-up period are warranted.

As a conclusion, systematic evaluation of the diagnostic tests in the differential diagnosis of episodic vertigo, will end up with more accurate diagnosis especially in suspicious cases. We suggest the application of four relatively non-invasive tests in episodic vertigo patients. VEMP as an indicator of the functional status and MFT as an indicator of the mechanical status of the saccule, these tests should be a part of the diagnostic work-up in vertigo patients. Systematic evaluation of these tests, which was AVDS in our study, is strongly recommended for contoversial cases. AVDS was superior to all single tests in differentiating MD from others. RV patients with higher AVDS may be followed-up for a possible future MD diagnosis. RV patients with high SPVmax on CT, should be questioned for MV. MV patients with higher AVDS should be evaluated for overlapping diseases such as MV and MD. Similarly, vertigo patients with hearing loss who has lower AVDS, should aware the clinician for another possible etiology other than MD. Further studies with long follow-up periods are warranted to clarify the role of the diagnostic work-up in the differential diagnosis of episodic vertigo.

Conflict of interest: None

No Financial disclosure

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