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Original article

Vestibular Evoked Myogenic Potential in Multiple Sclerosis [MS]

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ABSTRACT

Background: Involvement of the brainstem in multiple sclerosis [MS] has significant implications on the disease course and can be presented with different symptoms. There are many tests able to detect brain-stem involvement in MS with various degrees of success.

Aim of the work: To study the changes in vestibular evoked myogenic potential [VEMP], in patients with MS, and to detect its sensitivity for detection of the brain-stem lesions previously diagnosed with magnetic resonance imaging [MRI] in MS patients.

Patients and Methods: Sixty participants had been enrolled and divided into two groups: 30 healthy subjects [Control group] and 30 MS patients [Study group]. Both groups had been subjected to otological examinations, pure tone audiometry, acoustic impedance, cervical vestibular evoked myogenic potential [cVEMP], ocular vestibular evoked myogenic potential [oVEMP] and MRI.

Results: In MS group, oVEMP mean latencies of n1 and p1 and cVEMP mean p13 and n23 latencies were significantly prolonged. In addition, 14 MS patients [46.7%] had brainstem lesions as confirmed by MRI. Finally, oVEMP test had higher sensitivity than the cVEMP in prediction of brainstem lesions.

Conclusion: oVEMP seems to be useful and more sensitive than cVEMP as an adjunct test in the evaluation of brain-stem dysfunction in MS patients.

Keywords: Multiple Sclerosis [MS]; vestibular evoked myogenic potential [VEMP]; cervical vestibular evoked myogenic potential cVEMP; Vestibular function; ocular vestibular evoked myogenic potential oVEMP

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Multiple sclerosis [MS] is an inflammatory autoimmune disorder affecting the central nervous system. It is a common cause of neurological disability in young adults. Patients with MS can present with different oto-neurological symptoms. The most frequent complaint is dizziness[1]. Brain stem involvement in MS has significant role on the disease course and can be presented with different complaints, among which are those associated with vestibular system. Vestibular system involvement can be subclinical or present with imbalance[2-3]. Imbalance in patients with MS could be due to demyelination of vestibulospinal nerve fibres; VEMPs test represents a meaningful method to spot small brainstem lesions, so it can be used to assess the extent of the vestibular damage and to monitor the disease[4]. Due to weak correlation between radiological findings of the MRI and the extent of the disease clinical presentation[5], it is of great importance to find potential methods for testing brain-stem involvement in MS patients.

AIM OF THE WORK

This study was conducted to study the changes in Vestibular Evoked Myogenic Potentials [VEMPs] in patients with MS and to evaluate the sensitivity of the VEMPs for detection of the Brain-stem lesion that previously diagnosed with MRI in MS patients.

PATIENTS AND METHODS

This case-control study involved 60 subjects, who had been subdivided into two subgroups; the control group included 30 healthy females [aged 20-50 years old] with no history of dizziness or any other systemic diseases; and the study group that included 30 adult females with confirmed diagnosis of MS according to the revised McDonald criteria[6], the MS patients' matched with the control group in age. They had been selected from the Outpatient Neurology Clinic. After the verbal consent both groups had been subject to full history taking, otological examination and basic audiological tests. Vestibular evaluation included vestibular office tests and vestibular evoked myogenic potentials*:*

1-Vestibular office tests [7]:

- **Spontaneous nystagmus.**
- **Posture and Gait tests included**

- Tandem gait testing: is performed by stepping one foot in front of the other

-Romberg's test: The patient stands with feet together, arms folded and with eyes open then closed while the observer watches for swaying or movement of the feet to attain balance

-The tandem Romberg test: The difference in this test is that the patient stands heel to toe rather than with feet together.

-Fukuda test: The test is performed by asking the subject to march in place with the arms extended straight out at the level of the shoulders. The test is done with and without vision. At least 50 steps are required

- **Oculomotor Examination included**

-Range of movement in different positions

-**Smooth pursuit**: the subject had been asked to visually track a slowly moving target, slowly back and forth in a sinusoidal fashion, to a maximum of 20°displacement from the midline while keeping his head stationary.

-**Saccades test:** the subject had been asked to alternatively fixate the examiner's nose and then finger without moving the head. The test had been held at different locations at approximately 15 degrees away from primary position.

-**Gaze-holding test:** the subject had been instructed to gaze at a fixed dot in different positions [central, horizontal and vertical positions], for about 15-20 seconds;

- **Head impulse test HIT [head thrust test]:** the HIT is a quick test that consists of monitoring eye movements as the patient fixates on a stationary target. While the head had been rotated to right or left unexpectedly using passive, small amplitude 10–20 degree, and high-acceleration head movement.

2- **Vestibular Evoked Myogenic Potentials: [cVEMP and oVEMP]**

- **Cervical Evoked Myogenic Potentials [cVEMP].** The recording parameters had been adjusted as described by Murofushi and Kaga[8]. Two reference electrodes [non-inverting] had been placed over the upper half of sternocleido-mastoid [SCM] muscle. The active electrode [inverting electrode] had been

placed at the sternal notch and the ground electrode had been placed on the forehead[9]. Normally, from all recorded traces, the typical response was a bi-phasic waveform with a positive peak after 14ms and the negative peak had been appeared after 24ms. The amplitude measurement of the wave from peak to peak. At least two consecutive traces had been recorded from each side to verify reproducibility. Asymmetry Ratio was calculated using the formula: *100 [[AR-AL]/ [AR+AL]]* [AR was the amplitude of P13-N23 on right side; AL was the amplitude of P13-N23 on left side].

- **Ocular Vestibular Evoked Myogenic Potentials [oVEMP]:** Recording para-meters were the same as cVEMP but the amplifier was different, as the electrical response elicited from an oVEMP was so small; it requires much greater amplification of the signal than cVEMP; 50,000-100,000x amplification had been typically used[10]. The subject had been in the sitting position and had been instructed to raise his/her eyes up approximately 30 degrees[11]. The reference electrode had been placed underneath the eye in the orbital midline, while the active electrode had been placed on the chin, and ground electrode had been placed on the forehead[12].

Analysis of the waves:

oVEMPs had been presented and are marked by a waveform with an initial negative peak [n1] whose latency had been occurred at approximately 10ms and a positive peak[p1] that had been occured approximately 15ms[13]. The interaural difference between the two sides was known as the asymmetry ratio and had been used to determine if either ear was dysfunctional. The formula used for oVEMPs to determine interaural amplitude [AR-AL/AR+AL x 100%]. If the ratios were less than 35%, they were considered normal[14]. The side with the reduced amplitude had been considered the dysfunctional ear[8].

Equipment used were: a sound treated room [locally made], two channel diagnostic audiometer [Piano Plus], Immitancemeter [MAICO model MI44], Vestibular Evoked Myogenic Potential [Intera-coustics Eclipse/EP25].

Statistical Analysis: Data were collected, revised, coded and entered to the Statistical Package for Social Science [IBM® SPSS® Inc., Chicago, USA] version 23. The quantitative data had been presented as mean [measure of central tendency], standard deviations and ranges when parametric and median with inter-quartile range [IQR] when non parametric. Also, qualitative variables were presented as relative frequency numbers and percentages. Comparison between qualitative data had been achieved by using *Chi-square of Fisher exact tests*. In addition, the *Receiver operating characteristic curve [ROC]* had been constructed and used in the quantitative form to determine sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and overall test performance through area under curve [AUC]. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

RESULTS

There was no statistically significant difference between study and control groups in age. All MS patients referred from the Neurology clinic were female so, all subjects of the control group had been selected as females too. The vestibular bedside test had been performed to all subjects except one subject who had marked disability, so posture and gait tests couldn't be done. There was no statistically significant difference between study and controls in bedside vestibular test. However, some tests were abnormal in few patients such as Fukuoka and oculomotor tests. Positive Fukuoka test had been discovered among 2 subjects who had brainstem and cerebellar lesions in MRI. One subject had down-beating spontaneous nystagmus not suppressed by fixation, bidirectional gaze nystagmus, impaired pursuit test and impaired saccade. This female had an attack of MS one month before testing. Also, positive Dix Hallpike test and corrective saccade in HIT had been found in the same subject. This could be explained by presence of active brainstem and cerebellar lesions affecting vestibular function. This subject had long MS duration more than 5 years. In addition, other 3 patients had impaired pursuit test and impaired saccade, their MRI showed associated brainstem and cerebral lesions. In Dix Hallpike test, one subject had up-beating torsional nystagmus denoting right posterior canal BPPV. All MS patients in the study group had MRI scan which confirmed brainstem

involvement in 46.7% and cerebellar involvements in 86.7%. Results of cVEMP revelaed that, cases and controls were significantly different in P13 latency and N23 latency both on right and left sides, where both waves were significantly longer among study when compared to control groups [Table 1].

Receiver operation characteristics curve had been built and the predictive power of cVEMP tests and oVEMP tests of left and right ear had been calculated. The data were presented in table [2] and figures [1 &2].

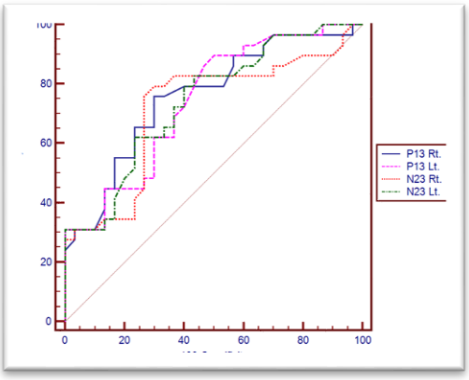

Figure [1]: Receiver operating characteristic [ROC] curve for the cVEMP test P13 and N23 latencies of left and right ear.

In general, oVEMP were more sensitive than cVEMP. In oVEMP study, there was statistical significance difference between the study and control groups in P1 latency, N1 latency and n1-p1 amplitude [Table 3].

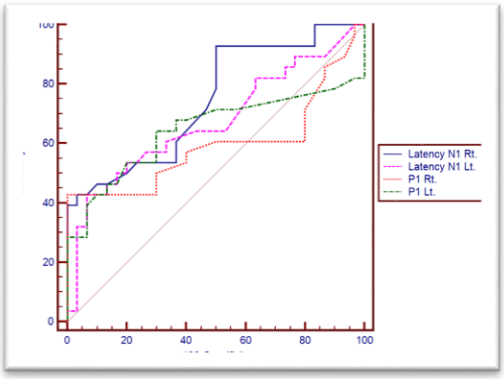

Figure [2]: Receiver operating characteristic [ROC] curve for the oVEMP test N1 and P1 latencies of left and right ear.

Among study group, 57.1% of patients with brain stem lesions had abnormal cVEMP, and only 12.5% of those without stem lesions had abnormal cVEMP.

In addition, 71.4% of patients with brain stem lesions had abnormal oVEMP compared to 18.8% in those without brain stem lesions, with statistically significant difference [Table 4]. oVEMPs were more sensitive than cVEMP in detecting brain stem lesion, while cVEMP was more specific in detecting brain stem involvement [Table 5].

Table [1]: Comparison between control and study groups as regard cVEMP results.

C-VEMP study		Control group [n=30]		Study group [n=30]		t test	P-value
		Mean ±SD	Min. – Max.	Mean ±SD	Min. – Max.		
P13 latency	Right	14.05±0.84	12.02 – 15.59	15.14 ± 1.14	13 – 17.08	***4.213***	***<0.001****
	Left	14.25±0.74	13.03 – 15.96	15.12 ± 1.22	13.5 –17.85	***3.308***	***0.002****
N23 latency	Right	24.23±0.72	23.12 – 25.9	25.05 ± 1.08	23.33 – 26.96	***3.489***	***0.001****
	Left	24.26±0.72	23.01 – 25.61	25.10 ± 0.99	23.63 – 27.01	***3.760***	***<0.001****
Asymmetry Ratio		15.37±4.37	5 – 20	15.45 ± 5.41	6 – 26	0.064	0.949
P13 N23 Amplitude	Right	26.06±7.59	17.6 – 40.54	24.32 ± 5.55	8.81 – 32.84	1.010	0.317
P13 N23 Amplitude	Left	24.71±7.64	15.01 – 40.4	23.01 ± 6.15	8.81 – 34.01	0.934	0.354

*: significant

Table [2]: The predictive power of cVEMP tests and oVEMP tests of left and right ear.

C-VEMP study		**AUC**	**Cut off point**	**Sensitivity**	**Specificity**
P13	Right	0.759	>14.1	76.70%	70.00%
	Left	0.743	>13.98	89.70%	70.00%
N23	Right	0.718	>24.08	80.00%	70.00%
	Left	0.742	>24	82.80%	76.70%
O-VEMP study		**AUC**	**Cut off point**	**Sensitivity**	**Specificity**
Latency N1	Right	0.746	>11.45	70.8	62.1
	Left	0.673	>11.67	72.9	63.3
P1	Right	0.595	>15.67	71.4	60
	Left	0.646	>14.4	64.3	70

Table [3]: Comparison between control and study groups as regard oVEMP study.

O-VEMP study			Control group		Study group		t test	P-value
			Mean ±SD	Min. – Max.	Mean ±SD	Min. – Max.		
N1 Latency	Right	Mean±SD	10.26 ± 0.76	9.33 – 11.8	11.11 ± 1.14	9.53 – 12.89	***3.407***	***0.001****
	Left	Mean±SD	10.28 ± 0.89	9.04 – 11.67	11.03 ± 1.27	9.33 – 13.78	***2.608***	***0.012****
P1 Latency	Right	Mean±SD	14.33 ± 1.08	13.8 – 15.67	15.05 ± 1.35	13 – 17	***2.264***	***0.027****
	Left	Mean±SD	14.41 ± 0.62	13.93 – 15.98	15.02 ± 1.03	13.4 – 16.68	***2.766***	***0.008****
N1P1 Amplitude	Right	Mean±SD	6.74 ± 1.80	2.66 – 9.87	6.42 ± 1.39	2.1 – 8.5	0.770	0.444
	Left	Mean±SD	7.01 ± 1.70	3.48 – 9.18	6.38 ± 1.00	3.41 – 7.9	1.749	0.085
Asymmetry Ratio		Mean±SD	8.87 ± 3.00	2 – 14	7.25 ± 3.72	1 – 20	1.827	0.073

* : significant

Table [4]: Distribution of patients in the study group with brain stem lesions [MRI diagnosis] according to results of the cVEMP, oVEMP tests.

		With brain stem lesions				Fisher exact test	P value
		No		Yes			
		No.	%	No.	%		
Total cVEMP,	Normal	14	87.5%	6	42.9%	6.47	0.011*
	Abnormal	2	12.5%	8	57.1%		
Total oVEMP	Normal	13	81.3%	4	28.6%	8.15	0.009*
	Abnormal	3	18.8%	10	71.4%		

* : significant

Table [5]: Performance of cVEMP & oVEMP, in prediction of brain stem lesions

	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Accuracy
cVEMP	8	14	2	6	57.1%	87.5%	80.0%	70.0%	73.3%
oVEMP	10	13	3	4	71.40%	81.30%	76.90%	76.50%	76.70%

TP: true positive, TN: true negative, FP: false positive, FN: false negative, PPV: positive predictive value, NPV: Negative predictive value.

DISUCSSION

In the current work, there was an overlapping of the presenting complaints, the unsteadiness was the most presenting complaints [70%] among MS patients, followed by fatigue [50%] while headache and blurring of vision were the main complaint in 40% of the MS patients, only 10% had symptoms of true rotatory vertigo**.** This was in agreement with **Peyvandi et al.[15],** who reported that the most common neuro-otologic findings in the MS patients were dizziness [63.3%] and true vertigo had been found in only 6.6% of the patients.

In the present research, there was statistically significant difference between study and control group in p13 and N23 latencies. This data agreed with values reported by **Patko et al.[16].**

To determine the abnormal latencies of the cVEMP, We used the cut off values determined by ROC curve for left and right p13 latency of [>13.98 and >14.1] respectively, and for left and right N23 latency of [>24 and >24.8] respectively**.** This agreed with values in **Zainun et al.[17].** On the other side, there was no statistical significance between study and control group in asymmetry ratio and P13, N23 amplitudes. These results were in agreement with results of **Koura and Hussein[18];** they reported no statistically significant differences between MS patients and controls. Also **Guven et al.[19]** showed that, the mean p1–n1 amplitude was lower in the MS cases than in controls but there were no significant differences between MS and control group in mean p1 n1 amplitudes. This variability in amplitude can be due to the inability of the subject to keep the SCM muscle tonically contracted for a few seconds. Therefore, they suggested that amplitude should not be used as criterion to define the VEMPs as normal or pathological**[20].**

Among the 30 MS patient, there were 10 patients with abnormal cVEMP [33.3%]. The abnormalities were in the form of prolonged latencies of P13 and N23 in 8 patients and total absent cVEMP in 2 patients**.** When we looked at the MRI findings, we found that 80% of the patients with abnormal cVEMP has got confirmed brain-stem lesion in the MRI scan. These results agreed with **Versino et al.[21]** and **Patko et al.[16].** They found 40% and 31.4% abnormal VEMP recording in MS patients. The prolonged latency in MS patients had been explained by low conduction velocity due to demyelination of vestibulospinal tract axons and primary afferent axons in the nerve root entry zone. Absence of

cVEMP response could be due to extensive damage to the myelin sheath or axonal degeneration[22-24].

In the present study, there was statistically significant difference between study and control groups in P1 and N1 latencies. This data agreed with values reported by **Gazioglu and Boz**[25].

In the current study, there was no significant differences in amplitude and asymmetry ratio, this agreed with **Guven et al.**[19].

In the present study 13 out of 30 [43.3%] MS patients had abnormal oVEMP, 10 patients with prolonged latencies and 3 patients had absent response. When we looked at the MRI findings, we found that 10 out of 13 [77%] of the patients with abnormal oVEMP have got confirmed brain-stem lesion in the MRI scan. This agreed with **Gazioglu and Boz**[25] who reported that, 28 0f 62 [45%] oVEMP recording abnormalities in MS patients. The abnormality of the oVEMP are due to the affection of the vestibular nuclei and the oVEMP pathway, which project to the contralateral oculomotor nucleus through the contralateral medial longitudinal fasciculus [MLF], So that MS lesions may impair VEMP responses, affecting the vestibular fascicles, vestibular nuclei and their efferent, and cerebellum all of which are involved in relaying and processing of the vestibular signals [26-27].

In this study, 14 of MS patients [46.7%] had brainstem lesions confirmed with the MRI and the sensitivity of cVEMP and oVEMP in prediction of brainstem lesions were 57.1 and 71.4 respectively. The sensitivity of oVEMP is higher than cVEMP in prediction of brainstem lesion. This agreed with **Gazioglu and Boz**[25] and could be due to higher chance of medial longitudinal fasciculus [MLF] to be affected in MS. Using both oVEMP and cVEMP can allow the assessment of the ascending and descending vestibular pathways in the brainstem. Small demyelinating lesions in the brainstem, which cannot be diagnosed by MRI can cause conduction abnormality, this indicated the value of VEMPs in detecting small silent lesions[28].

CONCLUSIONS

Abnormal VEMP was recorded in MS patients, especially those with brainstem lesions. oVEMP has higher sensitivity than cVEMP in detection of brainstem lesions.

Financial and Non-Financial Relationships and Activities of Interest

Authors declare: None

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