Correlation of the VEMP score, ambulation and upper extremity function in clinically isolated syndrome

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Abstract

Objective: To investigate the correlation of the vestibular evoked myogenic potential (VEMP) score with Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), Paced Auditory Serial Addition Test (PASAT) and EDSS in patients with multiple sclerosis (MS).

Methods: This prospective, cross sectional study included 52 patients with clinically isolated syndrome (CIS). Cervical VEMP (cVEMP) and ocular VEMP (oVEMP), analyzed in the form of the cVEMP, oVEMP and VEMP scores, T25FW, 9HPT, PASAT and Expanded Disability Status Scale (EDSS) were performed.

Results: The only predictor of walking impairment in this study was general disability as measured by the EDSS, after controlling for age, gender, PASAT and EDSS the effect of VEMP score was non-significant (p=0.419). 9HPT of the dominant hand did not correlate with the oVEMP score (r_s=0.258, p=0.065), however after controlling for age, gender, PASAT and EDSS, the effect of the oVEMP score on 9HPT of the dominant hand was statistically significant (p=0.017). After controlling for age, gender and oVEMP score, the effect of the PASAT on 9HPT variable for the non-dominant hand was statistically significant (p=0.001).

Conclusion: We found possible effects of brainstem dysfunction on walking impairment, however they were not seen after correction for EDSS and cognitive dysfunction. On the other hand, dominant hand function seems to be influenced by upper brainstem dysfunction measured with oVEMP, while cognitive dysfunction is related to non-dominant hand function.

Key words: Vestibular evoked myogenic potentials, clinically isolated syndrome

Timed 25-Foot Walk, 9-Hole Peg Test, Paced Auditory Serial Addition Test

Highligts

- The only predictor of walking impairment was general disability measured by the EDSS.
- We found positive correlation of the oVEMP score and 9HPT of the dominant hand.
- In brainstem/cerebellar type of CIS, MSFC strongly correlated with cVEMP.

1. Introduction

Predicting disease progression is critical for patients with multiple sclerosis (MS), especially in the initial phase of the disease. This initial phase is in about 85% of patients a relapse, which is known as a clinically isolated syndrome (CIS). Several clinical, MRI and neurophysiological parameters have been used to assess disability and try to predict development of future disability in MS patients. The Expanded Disability Status Scale (EDSS) has long been considered the gold standard for measurement of disability and disease progression in MS. (1) However, the EDSS has several limitations, including the need for a neurologist to examine the patient and derive the score; at the lower end of the scale the EDSS becomes imprecise because of the subjectivity in determining the scores; in the middle and upper regions of the scale, the EDSS is weighted heavily toward ambulatory disability and is less sensitive to other dimensions of MS such as arm and cognitive function; and nonlinearity of the scale (2). In the last two decades, the Multiple Sclerosis Functional Composite (MSFC), a 3-part quantitative instrument that measures arm, leg, and cognitive function with the 9-Hole Peg Test (9HPT), the Timed 25-Foot Walk (T25FW), and the Paced Auditory Serial Addition Test (PASAT), respectively, was introduced to supplement the EDSS. (3) The MSFC has excellent test-retest reliability, has the power to differentiate patients with primary or secondary progressive MS compared with relapsing-remitting MS (RRMS), and significantly correlates with the EDSS, the Sickness Impact Profile, and the Short Form-36 (patient-reported survey of patient health) and MRI changes. (2) More importantly, it has been shown that baseline MSFC scores in patients with RRMS were predictive of brain atrophy 2 and 8 years later. (4,5)

On the other hand, several evoked potentials (EP) have been successfully used in the determination of functional impairment in MS patients: somatosensory EP (SSEP), motor EP (MEP), visual EP (VEP) and brainstem EP (BAEP). More importantly, several studies have shown that the total number of pathological EPs better correlates with EDSS compared to MRI and can predict future disability of MS patients.(6,7) The main problem with the EP score is that the brainstem is underrepresented in the overal score, since none of these EPs demonstrate good correlation with brainstem involvement. On the other hand, the p14 component of medial nerve SSEP correlates with the brainstem involvement (8), however there are no direct comparisons between VEMPs and SSEPs. Furthermore, p14 component of the SSEP was not analyzed in the original EP score calculation (7).

Our group has recently developed the vestibular evoked myogenic potentials (VEMP) score with the aim to explore its potential to replace the BAEP in the EP score. The VEMP score is the sum of four 4-graded scores derived from the evaluation of 2 ocular VEMPs (oVEMP) and 2 cervical VEMPs (cVEMP). oVEMP evaluates the upper part of the brainstem (midbrain and upper pons), while cVEMP evaluates the lower part of the brainstem (lower pons and medulla oblongata), as well as upper parts of the cervical spinal cord. We found that the VEMP score correlates well with disability and disease duration and enables better evaluation of brainstem dysfunction than the MRI in patients with RRMS. (9)

Therefore, the aim of this study was to investigate the correlation of the VEMP score with walking in the form of T25FW, hand function in the form of 9HPT, and overall disability in the form of EDSS and MSFC.

2. Methods

2.1. Design

This was a prospective, cross sectional study which included consecutive patients who were diagnosed with a first clinical symptom of multiple sclerosis (CIS) from the 1st of August 2014 until 1st of May 2015 at the Department of Neurology, University Hospital Center Zagreb - a tertiary medical center and a referral center for multiple sclerosis. Diagnosis of CIS was made with the following criteria: 1) acute or subacute development of neurological symptoms and/or signs lasting longer than 48 hours in the absence of fever or infection, 2) brain and spinal cord MRI showing at least 2 demyelinating lesions larger than 3 mm or 1 lesion larger than 3 mm that corresponded to the symptom and/or sign. Based on the clinical presentation, patients were classified into 5 CIS subtypes: optic neuritis (ON), incomplete transverse myelitis (TM), brainstem/cerebellar (BC), hemispheral (H) and multifocal (M).

The Ethical committees of the University Hospital Center Zagreb and University of Zagreb, School of Medicine approved the study. All participants gave written informed consent.

2.2. Vestibular evoked myogenic potentials

Methods of recordings and analysis of recorded data were designed according to previously described details. (10,11)

The stimuli were delivered via a pair of headphones in series of 50 trials to one ear at a time and repeated two times for each ear in order to provide

reproducibility. The stimuli used were acoustic clicks of 1ms duration at an intensity of 130dB (pSPL) and a stimulation frequency of 1Hz. The recordings were performed using a Brain Products Brain Vision Recorder (Brain Products GmbH Munich, Germany) and the analysis of the recorded data was performed using a Brain Products Brain Vision Analyzer (Brain Products GmbH Munich, Germany). Signals were filtered with a bandpass filter from 0.5 Hz to 1000 Hz. For the purpose of the analysis, signals were divided in segments of 120 ms duration (20 ms before the stimulus appearance and 100 ms after the stimulus appearance) and averaged for each set of 50 trials. A grand average was computed and used for further analysis from the averaged responses of the two sets.

The following VEMP components were analyzed: peak-to-peak n10-p13 amplitude, n10 and p13 latencies for oVEMP, and normalized p13-n23 amplitude, p13 and n23 latencies for cVEMP. We used baseline normalized values of the SCM amplitude data instead of the absolute value of the amplitude, because absolute amplitude of the evoked response depends on the amplitude of the muscle activity (muscle contraction) and is not a reliable measure. The baseline normalized value of amplitude is calculated by dividing the absolute peak to peak amplitude (p13-n23) with mean value of rectified activity of muscle in the period prior the stimulus. For the ocular muscles (OM) amplitudes we used absolute values. Due to the variability of evoked potentials, SCM amplitudes were considered abnormal if the amplitude was decreased for > 1.0 standard deviation compared to the mean value of the laboratory or when it was decreased for > 50% compared to the contralateral response. OM amplitudes were considered abnormal if the amplitude was < 50% of the mean value of the

laboratory or when it was decreased for > 50% compared to the contralateral response. These amplitude criteria are more lenient than those typically used to detect vestibular abnormalities in other laboratories. They provide increased sensitivity to subtle VEMP abnormalities, but may include false positives. Similarly, latencies were considered prolonged when there was an increase in > 2.5 standard deviations to the mean value of the laboratory. Absent responses (presumed conduction blocks) were also considered as abnormal findings.
All VEMP results were interpreted according to the VEMP score. (9) The VEMP score is the sum of four 4-graded scores derived from the evaluation of each VEMP. The 4 grades are: 0 = normal, 1 = increased latency with normal amplitude and morphology of major potentials, 2 = decrease in amplitude or altered morphology of major potentials, 3 = absence of a major potential. Minimal and maximal values of the oVEMP score and cVEMP score are 0 and 6, and the VEMP score 0 and 12, respectively.

2.3. Clinical assessment

Participants completed all testing in a single session, which included the following: Expanded Disability Status Scale (EDSS), followed by the MSFC, which was administered to patients using a standardized protocol. (3) The order of testing in a session was as follows: (1) T25FW (trial 1 and trial 2), (2) 9HPT (dominant hand: trial 1 and trial 2; and nondominant hand: trial 1 and trial 2), and (3) PASAT (3-second interstimulus interval). T25FW and 9HPT results were analyzed as absolute values when they were used separately, and in the form of the z score for MSFC analysis.

2.4. Outcomes

Outcomes of the study were to determine whether the VEMP score correlates with walking impairment measured with T25FW and with upper limb function measured with 9HPT in patients with CIS. Furthermore we wanted to determine the impact of cognitive function measured with PASAT on T25FW and 9HPT; whether the VEMP score correlates with the EDSS, brainstem functional score of the EDSS (BSFS) and MSFC; and if there is a difference in T25FW, 9HPT and MSFC between the three major CIS subtypes: ON, BC and TM.

2.5. Statistical analysis

Statistical analysis was performed using the IBM SPSS software, version 20. The Kolmogorov-Smirnov test was applied to test whether the data had a normal distribution. Differences in quantitative variables were determined with the use of the Mann Whitney U test. Correlations for parametric variables were performed by Pearson, and for nonparametric variables by Spearman correlation. We used a linear regression method in order to examine the influence of predictors of interest on specific outcome. P values less than 0.05 were considered significant.
When interpreting the strength of correlation, we used the following categorization: 0.1-0.3 modest, 0.3-0.5 moderate, 0.5-0.8 strong, 0.8-0.9 very strong and 1 perfect.

3. Results

3.1. Patients

We included 52 patients with CIS (40 were female), mean age of 32.79 ± 10.15 years, with the median EDSS of 1.0 (0-3.5) and median BSFS of 0 (0-3). There were 17 patients with ON, 18 with BC, 12 with TM, 4 hemispheral and 1 multifocal type of CIS. Table 1 summarizes the mean values of EDSS, BSFS, and VEMP scores results with respect to the specific types of CIS.

Regarding the cVEMP, 26 patients had normal cVEMP amplitudes, 20 had small cVEMP amplitudes and 6 patients had absent cVEMP response. Regarding the oVEMP, 16 patients had normal oVEMP amplitudes, 25 had small oVEMP amplitudes and 11 patients had absent oVEMP response.

3.2. Ambulation/walking

In the whole group, oVEMP score correlated with the T25FW (r_s=0.280, p=0.045). The VEMP score did not correlate with T25FW (r_s=0.248, p=0.076). There was no correlation between VEMPs and T25FW for each individual CIS subtypes (Table 2). As well, there was no difference in the oVEMP, cVEMP and VEMP scores between patients with BC type of CIS and all other patients (p=0.223, p=0.417, p=0.846, respectively).

In order to evaluate the relationship between cognitive dysfunction and walking impairment, we correlated PASAT with T25FW, and found a significant

correlation (Pearson correlation=-0.281, p=0.043), indicating that a lower performance on the PASAT test is related to worse performance on the T25FW. Results of linear regression analysis with T25FW as an outcome are presented in supplementary table 1. After controlling for age and gender, the effect of the PASAT on T25FW was reduced and non-significant. There was also a non-significant effect of VEMP score on T25FW. Also, after controlling for age and gender, the effect of the oVEMP score on T25FW was reduced and non-significant, as presented in supplementary table 2. The only significant predictor for T25FW was EDSS, when controlling for age and gender.

3.3. Upper extremity function

There was no correlation of the 9HPT of the dominant hand and the oVEMP score, cVEMP score or VEMP score (Table 3). However, when we analyzed correlations for each subtype of CIS (ON, BC and TM) we found a positive correlation between 9HPT of the dominant hand and oVEMP score for BC subtype (r_s=0.581, p=0,011). Regarding the 9HPT of the non-dominant hand, we found no correlations with the oVEMP, cVEMP and VEMP scores (Table 3).
In order to evaluate the relationship between cognitive dysfunction and upper extremity function, we correlated PASAT with 9HPT and found a significant correlation (Pearson correlation=-0.490, p<0.0001) with 9HPT of the non-dominant hand, indicating that a lower performance on the PASAT score is related to worse performance on the 9HPT. There was no correlation between PASAT and 9HPT of the dominant hand (Pearson correlation=-0.204, p=0.146).

Results of linear regression analysis with 9HPT for the dominant hand as an outcome are presented in supplementary table 3. After controlling for age and gender, the effect of the PASAT on 9HPT was not statistically significant. After controlling for age, gender and PASAT, the effect of the oVEMP score on 9HPT was statistically significant, as was the effect of the EDSS. Results of linear regression analysis with 9HPT for the non-dominant hand as an outcome are presented in supplementary table 3. After controlling for age and gender, the effect of the PASAT on 9HPT was statistically significant. After controlling for age, gender and oVEMP score, the effect of the PASAT on 9HPT for the non-dominant hand was statistically significant. The effect of the EDSS was also statistically significant. The effect of the oVEMP score was not statistically significant for the non-dominant hand.

3.4. Multiple sclerosis functional composite

For the whole group, MSFC did not correlate with any of the VEMP score variables (Table 4). However, in the BC subgroup, MSFC significantly correlated with the cVEMP score (r_s=0.547, p=0,019).

Finally, the VEMP score did not correlate with the EDSS or BSFS (r_s=0.023, p=0,869 and r_s=0.219, p=0,118, respectively); however, the oVEMP score correlated with the BSFS (r_s=0.308, p=0,026). EDSS did not correlate with the MSFC (r_s=0.051, p=0,722); however, it did correlate with T25FW and 9HPT of the dominant hand (r_s=0.353, p=0,010 and r_s=0.364, p=0,008, respectively).

4. Discussion

The first finding of this study is that any significant relationship between VEMPs and T25FW was mediated by age and/or gender. The only measure that was independently correlated with T25FW after controlling for all other factors was the EDSS.

Several studies have tried to address the pathophysiological aspects of walking impairment in MS, mainly focusing on impaired motor control and/or sensation in lower extremities. (12, 13,14) Furthermore, several MRI studies tried to correlate MRI burden of the disease with walking impairment. (15,16) However, as the information provided by evoked potentials is more related to function unlike the information provided by MRI, which is more related to anatomy, evoked potentials may prove to be more useful in monitoring disease evolution in MS (17). For some neurophysiological methods, like the blink reflex, it has even been shown a good correlation between the pathological response and brainstem disease burden. (18) Despite of this, only one study investigated the correlation between T25FW and different evoked potentials (motor and somatosensory evoked potentials) (19). That study has shown that both motor and somatosensory evoked potentials and their combination correlate well with T25FW, indicating that evoked potentials might be useful in the clinical follow up of MS patients. Our study showed that the same is not true for VEMPs, which did not independently predict walking impairment.

Although most of the attention has been focused on lower limb impairments, cognition is another factor that should be taken into account when evaluating walking impairment in MS. It has been shown that processing speed and

executive function tests were significant predictors of lower and upper motor function in MS; where cognitive tests predicted variability in motor function after controlling for disease duration and physical disability. (20) We found a modest correlation between PASAT and T25FW, however, this effect was reduced to non-significant after controlling for age and EDSS.

The possible explanation for non-significant correlation of both VEMP and PASAT on T25FW after adjusting for age and EDSS, could be partly explained by the fact that only patients with early MS and thus very mild disability were included. Further research should focus on combining MRI and evoked potentials in the evaluation of the brainstem and its influence on walking, to further explore this possible association.

The second finding of this study was the strong positive correlation between 9HPT of the dominant hand and oVEMP score for CIS patients with brainstem/cerebellar symptomatology. Furthermore, linear regression analysis on the whole group showed that after controlling for age, gender and PASAT score, the effect of the oVEMP score on 9HPT of the dominant hand was statistically significant. Unlike the walking impairment, only few studies evaluated upper extremity impairment in MS. (21) It has been shown that a significantly longer time to complete the 9-HPT is needed in patients with abnormal somatosensory evoked potentials of the median nerve. (22) More precisely, patients with undetectable P14 responses (which represent a brainstem response) performed the 9-HPT in a significantly longer time than patients with detectable P14 responses, indicating that the brainstem is responsible for upper extremity dysfunction. These findings are in line with the

present study as well, showing the correlation between oVEMPs and 9HPT of the dominant hand. In contrast, there was no correlation between non-dominant hand function and brainstem function measured with VEMPs. However, we found a strong correlation between cognitive function measured with PASAT and non-dominant hand function measured with 9HPT. This discrepancy between dominant and non-dominant hand function in MS has been described previously with functional MRI studies. Firstly, it has been shown that movement-associated cortical activation in patients with progressive MS is widely distributed and also involves multimodal "nonmotor" cortical networks. (23) Secondly, it has been shown that increased cognitive effort is required for performing non-dominant hand movements. (24) Moreover, a recent fMRI study by Rico et al. examined bilateral movements in CIS patients with low disability and devoid of corticospinal dysfunction found activation of different brain areas when patients performed non-dominant hand movements compared to dominant hand movements. (25) These findings suggest that non-dominant hand movements result in recruitment of brain networks involved in cognitive control in MS patients with minimal or no disability. Taking all of this into account and with the results of the present study it seems that there is a difference between dominant and non-dominant hand function in MS.

The third finding of this study is significant correlation of the MSFC with the cVEMP score in the BC subgroup of CIS patients. This finding is interesting given the fact that spinal cord cross-sectional area correlates significantly with the MSFC score, and cVEMP measures vestibulospinal pathways up to the C4 level. (26)

The limitations of this study are the relatively small number of participants and the fact that only CIS patients with very mild disability were included. This could explain the negative results of the linear regression analysis on the VEMP influence on T25FW.

In conclusion, the only predictor of walking impairment in this study was general disability as measured by the EDSS. On the other hand, dominant hand function seems to be influenced by upper brainstem dysfunction, while cognitive dysfunction is related to non-dominant hand function. Further studies including a combination of different MRI measures and combination of different evoked potentials are warranted.

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Tables

Table 1. Mean values (range) of EDSS, BSFS, and all the VEMP scores with regards to type of CIS. ON - optic neuritis, TM - incomplete transverse myelitis, BC – brainstem or cerebellar type of CIS.

	ON	TM	BC
N	17	12	18
EDSS	1.0 (0-2.5/10)	1.0 (0-3.0/10)	2.0 (0-3.5/10)
BSFS	0 (0-2/5)	0 (0-2/5)	1.5 (0-3/5)
VEMP score	4 (0-12/12)	5.5 (0-10/12)	4 (0-9/12)
oVEMP score	3 (0-6/6)	3 (0-6/6)	4 (0-6/6)
cVEMP score	1 (0-6/6)	2.5 (0-5/6)	1 (0-4/6)

Table 2. Correlations of the VEMP scores and T25FW in the whole cohort and different CIS subtypes. ON - optic neuritis, TM - incomplete transverse myelitis, BC – brainstem or cerebellar type of CIS, /XX indicates the maximum score possible.

		oVEMP score	**cVEMP score**	**VEMP score**
CIS				
T25FW	r_s	0.280	0.159	0.248
	p value	0.045*	0.262	0.076
ON				
T25FW	r_s	0.285	0.202	0.255
	p value	0.267	0.437	0.323
TM				
T25FW	r_s	0.348	-0.096	0.118
	p value	0.267	0.766	0.715
BC				
T25FW	r_s	0.324	0.256	0.434
	p value	0.190	0.305	0.072

Table 3. Correlations of the VEMP scores and 9HPT for dominant and non-dominant hand in the whole cohort and different CIS subtypes. ON - optic neuritis, TM - incomplete transverse myelitis, BC – brainstem or cerebellar type of CIS.

		oVEMP score	**cVEMP score**	**VEMP score**	**oVEMP score**	**cVEMP score**	**VEMP score**
		dominant hand			*non-dominant hand*		
CIS							
9HPT	r_s	0.258	-0.081	0.154	-0.018	0.027	0.024
	p	0.065	0.568	0.277	0.901	0.849	0.864
ON							
9HPT	r_s	0.429	-0.021	0.278	-0.095	-0.248	-0.121
	p	0.086	0.937	0.279	0.716	0.338	0.643
TM							
9HPT	r_s	-0.181	-0.210	-0.324	0.131	-0.149	-0.075
	p	0.574	0.512	0.303	0.685	0.645	0.817
BC							
9HPT	r_s	0.581	-0.391	0.295	-0.067	0.273	0.170
	p	0.011*	0.109	0.235	0.792	0.273	0.501

Table 4. Correlations of the VEMP scores and MSFC in the whole cohort and different CIS subtypes. ON - optic neuritis, TM - incomplete transverse myelitis, BC – brainstem or cerebellar type of CIS.

		oVEMP score	**cVEMP score**	**VEMP score**
CIS				
MSFC	r_s	0.008	0.143	0.083
	p value	0.957	0.113	0.559
ON				
MSFC	r_s	-0.060	0.287	0.067
	p value	0.820	0.265	0.799
TM				
MSFC	r_s	0.014	-0.040	-0.011
	p value	0.965	0.902	0.974
BC				
MSFC	r_s	-0.010	0.547	0.346
	p value	0.970	0.019*	0.159