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Abstract

Background: The aim of this study was to investigate the correlation between autonomic dysfunction in multiple sclerosis (MS) and brainstem dysfunction evaluated with the vestibular evoked myogenic potentials (VEMP) score and conventional MRI.

Methods: Forty-five patients with the diagnosis of clinically isolated syndrome (CIS) suggestive of MS were enrolled. VEMP, heart rate and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing and pain provoked head-up tilt table test, as well as brain and spinal cord MRI were performed.

Results: There was no difference in the VEMP score between patients with and without signs of sympathetic or parasympathetic dysfunction. However, patients with syncope had significantly lower VEMP score compared to patients without syncope ($p<0,01$). Patients with orthostatic hypotension (OH) showed a trend of higher VEMP score compared to patients without OH ($p=0,06$). There was no difference in the presence of lesions in the brainstem or cervical spinal cord between patients with or without any of the studied autonomic parameters. The model consisting of a VEMP score of ≤5 and normal MRI of the midbrain and cervical spinal cord has sensitivity and specificity of 83% for the possibility that the patient with MS can develop syncope.

Conclusions: Pathophysiological mechanisms underlying functional and structural disorders of autonomic nervous system in MS differ significantly. While preserved brainstem function is needed for development of syncope, structural disorders like OH could be associated with brainstem dysfunction.

Key words: Syncope, orthostatic hypotension, brainstem, autonomic nervous system, multiple sclerosis, clinically isolated syndrome

Highlights

- Pathophysiological differences exist between different autonomic disorders in MS.
- Preserved brainstem function is needed for development of syncope in MS.
- Orthostatic hypotension could be associated with brainstem dysfunction in MS.

1. Introduction

Evidence suggests that brainstem involvement in multiple sclerosis (MS) is related to long-term prognosis for patients with clinically isolated syndrome (CIS). (1) However conventional MRI shows poor correlation with clinical symptoms, especially in the brainstem region. (2) We have recently developed a novel way to interpret vestibular evoked myogenic potentials (VEMP) in MS, which enables better evaluation of brainstem dysfunction than the MRI, the so-called VEMP score. (3) 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) (one on each side for each VEMP type), and it correlates well with disability and disease duration. oVEMPs evaluate the upper part of the brainstem (midbrain and upper pons), while cVEMPs evaluate the lower part of the brainstem (lower pons and medulla oblongata), as well as upper parts of the cervical spinal cord. This neurophysiological method enables complete evaluation of vestibulo-ocular and vestibulo-spinal pathways dysfunction in MS patients.

Several studies have suggested that autonomic dysfunction in MS is a consequence of lesions in key regions of the central nervous system, which are a part of the reflex arc responsible for normal function of the autonomic nervous system; such as nuclei in the periventricular region of the fourth ventricle in the brainstem as well as medullar lesions. (4) Studies point to an increased frequency of autonomic dysfunction in patients who have lesions in the pons, and a correlation has been found between atrophy of the spinal cord and orthostatic dysfunction, indicating that axonal degeneration, and not just

demyelination, influences the appearance of autonomic dysfunction. (5,6) For a better understanding of autonomic dysfunction, autonomic nervous system disorders can be classified as structural and functional. (7) Structural disorders are defined as having demonstrable pathologic abnormalities that directly affect autonomic function, prototype of a structural disorder being orthostatic hypotension (OH). On the other hand, functional disorders currently have no consistently demonstrable pathologic basis, and are primarily defined by symptomology; the prototypes are syncope and postural orthostatic tachycardia syndrome (POTS).

We therefore aimed to investigate the correlation between autonomic dysfunction (structural and functional) in MS and brainstem dysfunction evaluated with the VEMP score and conventional MRI.

2. Methods

2.1. Design

This was a prospective, cross sectional study which included consecutive patients who were diagnosed with CIS from the 1st of August 2014 until 1st of March 2015 at the Department of Neurology, University Hospital Center Zagreb - a tertiary medical center and a referral center for MS. The diagnosis was made if the patient had clinical symptoms and/or signs consistent with demyelinating disease of the central nervous system and if brain and/or spinal cord MRI showed at least one demyelinating lesion. CSF analysis was performed in all patients to exclude MS mimics.

Patients were excluded if there was a history of heart disease, however cardiological work-up was not performed on the subjects prior to the study. Ethical committees of the University Hospital Center Zagreb and University of Zagreb, School of Medicine approved the study. All participants gave informed consent.

2.2.Cardiovascular autonomic system testing

All tests were performed in a quiet and dimly lit room. Patients were instructed not to drink coffee or smoke before the testing. Blood pressure and heart rate values were recorded using a Task Force Monitor (TFM) (CNSystems Medizintechnik AG, Austria). After the patient was placed supine on a testing table, pressure cuff and ECG electrodes were adjusted at appropriate sites. A peripheral vein catheter was installed in the antecubital or radial vein of the right arm, and 15 minutes of settling period was given before recording.
The following tests were performed as described previously (8,9): heart rate and blood pressure responses to Valsalva maneuver, as a measure of parasympathetic and sympathetic function, respectively; heart rate response to deep breathing as a measure of parasympathetic function and blood pressure response to passive tilt in the duration of 10 minutes, as a measure of sympathetic function.
The Valsalva maneuver was performed in the supine position by blowing for 15 s through a mouthpiece connected to a mercury manometer. The height of the mercury column was maintained at 40 mm. There was a small air leak in the system to prevent closing of the glottis. The test was repeated until a

reproducible response was obtained. The Valsalva ratio (VR) was calculated as the ratio of the shortest RR interval during or after phase II of the maneuver to the longest RR interval in phase IV of the maneuver. The following parameters from the blood pressure response to Valsalva maneuver were measured: maximal drop of the mean blood pressure during phase II, the peak of the mean blood pressure at the end of late phase II (recovery), overshoot in the phase IV, maximal pulse pressure drop during phase II and pressure recovery time.
The deep breathing test was performed in the supine position over 9 respiratory cycles; the best six responses were chosen and the respective respiratory sinus arrhythmia (RSA) amplitudes were averaged. RSA amplitude was defined as the difference between the end of expiration and end of inspiration in heart rate.
After these tests, a 10-minute pain provoked head-up tilt table test (PPHUT) was performed. (10) It consisted of 10 min 70° passive tilt and if after the tilted phase there was no positive response, a painful stimulus was applied in the shape of a needle prick with 0.7 mm diameter needle on the dorsum of the hand. Responses to passive tilt were defined as follows:

1. Vasovagal Syncope was defined according to the modified Vasovagal Syncope International Study (VASIS) classification (11)
2. OH was defined as a sustained reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of 10 mm Hg within 3 min of head-up tilt to 70° on a tilt table. (12)
3. POTS was defined as an increment of heart rate (HR) ≥30 bpm for adults, and ≥40 bpm for patients younger than 19 years on passive tilt and in the absence of orthostatic hypotension. (12)

All results were interpreted according to the cardiovagal index (parasympathetic function) and adrenergic index (sympathetic function) of the Composite Autonomic Scoring Scale (CASS). (13)

2.3. Vestibular evoked myogenic potentials

Methods of recordings and analysis of recorded data were designed according to previously described details. (14,15)

During the experiment, participants sat in a comfortable chair. Patients were instructed to slightly move their head away from the back of the chair and push it against the elastic band around the forehead in order to activate the sternocleidomastoid muscle. The contraction of muscle was maintained due to the cooperation of patients in maintaining the same position during the test. Participants were also instructed to direct their gaze to the ceiling in order to activate ocular muscles. The evoked response from the sternocleidomastoid muscle (SCM) was recorded from the active surface electrode placed on the middle of the belly of the SCM of the stimulated side and referred to the surface electrode placed on the tendon of the same SCM. The evoked response from the ocular muscle (OM) was recorded from two surface electrodes. The active electrode was situated 2 cm below the contralateral eye, and referred to the reference electrode 1 cm below. The impedance of the electrodes was reduced to < 5 kΩ.

The stimuli were delivered by 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 presented stimuli were acoustic clicks of 1 ms duration at an intensity of 130 dB sound pressure level (SPL) and a stimulation frequency of 1 Hz.

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 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. From the averaged responses from the two sets, the grand average was computed and used for further analysis.

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 the mean value of rectified activity of muscle in the period prior the stimulus. For the 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. 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. (3) 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 VEMP score are 0 and 12, respectively. Examples of normal and pathological VEMP tracings are presented in figures 1 and 2, respectively.

2.3. MRI

All MS patients performed brain MRI on a 1.5T MRI. Cervical spinal cord MRI was analyzed if it was available. MRI sequences included multi-planar dual fast spin-echo PD and T2-WI, FLAIR and T1 postcontrast sequences. A neurologist with at least 5 years of experience in MS reviewed all MRIs for the presence of lesions.

2.4. Outcomes

Primary outcome was to determine whether autonomic dysfunction in MS correlates with the VEMP score. This was assessed by: 1) the correlation of the adrenergic and cardiovagal index of the CASS with the VEMP score; 2) the correlation of different responses to passive tilt (OH, syncope and POTS) with the VEMP score.

Secondary outcomes were: 1) to determine the correlation of the adrenergic and cardiovagal index of the CASS with presence of MRI lesions in the brainstem; 2) to determine the correlation of different responses to passive tilt (OH, syncope and POTS) with presence of MRI lesions in the brainstem; 3) to develop the model that can predict autonomic dysfunction in MS.

2.5. Statistical analysis

Statistical analysis was performed using the IBM SPSS software, version 20. Differences in the distribution of qualitative variables were determined with the $\chi 2$ test, while the differences in quantitative variables were determined with the use of non-parametric Mann-Whitney U test. Receiver Operating Characteristics (ROC) curves were used in order to interpret sensitivity and specificity of proposed methods. P values less than 0.05 were considered as significant.

3. Results

3.1. Patients

During the study period 45 patients, 34 females and 11 males were enrolled. Average age of the patients was 32.2 years (19-56 years). We found no differences in the VEMP score or syncope prevalence between genders ($p>0.05$). In the CIS group there were 15 (33.3%) cases of optic neuritis, 11 (24.5%) of incomplete transverse myelitis, 15 (33.3%) brainstem/cerebellar, 3 (6.7%) cases of hemispheral and 1 (2.2%) multifocal type of CIS. Median EDSS was 1.0 (0-3.0). Median cVEMP score was 1 (0-6), median oVEMP score was 3 (0-6), and median VEMP score was 4 (0-12).

Brain MRI was performed in all patients showing demyelinating lesions consistent with MS. In 42 patients brain MRI and in 33 patients cervical spinal cord MRI was available for detailed analysis (3 patients had a radiologist report without images available for further analysis).

The number of patients with autonomic dysfunction is presented in Table 1.

3.2. Primary outcomes

There was no difference in the VEMP score between patients with and without signs of sympathetic or parasympathetic dysfunction evident on the CASS. However, patients with syncope had a significantly lower VEMP score compared to patients without syncope ($p<0.01$). Patients with OH showed a trend of higher

VEMP scores compared to patients without syncope, albeit with borderline statistical significance (p=0.06). All results are presented in Table 2.

Since patients with a higher VEMP score had a lower chance to develop syncope, we further wanted to determine the cut-off VEMP score value that best differentiates between MS patients with and without syncope. We found that a VEMP score has an area under the ROC curve of 0.804 (Figure 3) and that a VEMP score value of 5 has a sensitivity of 87.5% with a specificity of 40.5%.

When looking at oVEMP and cVEMP scores separately, oVEMP has an area under the ROC curve of 0.755 and an oVEMP score value of 3 has a sensitivity of 87.5%, with a specificity of 54.0% (Figure 3); while a cVEMP score which has an area under the ROC curve of 0.721 and a cVEMP score value of 1 has a sensitivity of 87.5%, and a specificity of 57.0% (Figure 3).

3.3. Secondary outcomes

Results of the MRI analysis are presented in Table 3. There was no difference in the presence of lesions in the midbrain, pons, medulla oblongata or cervical spinal cord between patients with or without any of the studied autonomic parameters.

We subsequently tested which combination of the VEMP score and MRI results had the best sensitivity and specificity indicating that the MS patient can develop syncope. We found that the model consisting of a VEMP score of ≤5 and normal MRI of the midbrain and cervical spinal cord has a sensitivity of 83% and specificity of 83% for the possibility that a patient with MS will develop syncope.

4. Discussion

The principal finding of this study is that MS patients without brainstem involvement have a greater chance to develop syncope. Because we used evoked potentials that evaluate function of the brainstem, this finding leads to the deduction that functional integrity of the brainstem is needed in order to develop syncope. Although this may seem contradictory, several hypotheses and lines of evidence can explain this association.

It has been suggested that vasovagal syncope is a reaction that humans have acquired as a self-preservation response. (16) Most common triggers for syncope are emotions, followed by different situations (e.g. standing) or physical experience (e.g. warmth). (17) As one of the most common triggers for syncope is fear of blood and/or sharp objects, the "paleolithic threat hypothesis" has been proposed as an explanation. (18) Authors of this hypothesis suggest that the vasovagal syncope in these situations represents an atavism of a survival advantage from the evolutionary period for women and children/adolescents (who were non-combatants at that time), who are even nowadays prone to develop syncope. Its very frequent occurrence and genetic propensity suggest that syncope is not selected against over time, so it can be speculated that persistence of this condition has some usefulness. (19,20) In line with this, several advantages of vasovagal syncope have been suggested. One view is that syncope could be considered a transitory means of escape from a momentarily intolerable world. (16) The brain self-preservation theory, on the other hand, argues that loss of postural tonus may be beneficial for brain perfusion. According to this theory, the brain has become so important for humans that it

could be speculated that it has been necessary for it to acquire its own self-preservation autonomy. (16) It is speculated that the initiation of the syncope starts in the brainstem, when midbrain nuclei become aware of the circulatory changes precluding maintenance of sufficient blood supply to the brain leading to a sudden reversal in their operational activity towards a reaction in which salvaging the brain's blood supply becomes the main goal. (16) Therefore, brainstem functionality is crucial for syncope development. Furthermore, the afferent pathways in the vasovagal syncope reflex arch, which are conducted by unmyelinated vagal afferents to the brainstem, have recently been reconsidered. Firstly, there is good evidence to suggest that syncope can occur in patients after cardiac transplantation, when the heart has undergone major efferent and afferent denervation; and second, syncope may occur with the central stimulus in the supine position when the heart is not empty. (21,22,23)

Furthermore, two neurophysiological observations support the brain self-preservation theory: important changes in cerebral hemodynamics occur much earlier than the vasovagal reactions and electroencephalographic slowing which closely follows reduction of systemic pressure corresponds to the onset of transient loss of consciousness. (24,25) Our finding that a VEMP score ≤5 and normal MRI of the midbrain and cervical spinal cord has sensitivity of 83% and specificity of 83% indicating the possibility that the patient with MS can develop syncope, is in line with the previously mentioned hypotheses and indicates that normal function of the brainstem is needed for the development of syncope. One can hypothesize that, according to the brain self-preservation theory, interruption of brainstem pathways responsible for the initiation of syncope by MS lesions prevents the development of the vasovagal syncope. Our findings

indicate that evaluation of the brainstem with neurophysiological methods, which measure the function of these pathways, is more important than morphological detection of the lesions with conventional MRI.

The opposite was seen for the structural disorders of the autonomic nervous system, namely OH. CIS patients exhibiting OH during PP-HUTT showed a higher VEMP score compared to patients without OH, although this did not reach statistical significance ($p=0.06$). This is in line with previous studies, which showed increased frequency of autonomic dysfunction in patients who have lesions in the pons. (5) On the other hand conventional MRI alone did not correlate with any type of autonomic dysfunction, again emphasizing the inability of MRI to depict the whole spectrum of protean MS manifestations. However, newer MRI techniques like magnetization transfer ratio or three-dimensional MRI estimation of volume loss may prove valuable in future studies. (26,27)

This study has several limitations. The first one is that MRIs were not available for detailed analysis in all patients, as mentioned in the methods section. The second one is that patients with very early MS were enrolled and it is known that prevalence of autonomic dysfunction increases with disease duration. (28) It can be presumed that more cases of OH would be present if patients with more advanced disease were included, enabling better estimation of suspected association between brainstem and autonomic dysfunction. On the other hand one can speculate that the relatively high prevalence of syncope (17.8%) in CIS patients compared with previously published studies of prevalence of syncope in the healthy population (around 3%) could indicate possible association between these two conditions. (29) However, more recent studies have shown much

higher prevalence of syncope (17-34%) in young adults (the population at risk of developing MS), and we have recently shown no association between syncope and MS (17,30).

In conclusion, based on the results of previous studies and current results, it seems that pathophysiological mechanisms underlying functional and structural disorders of autonomic nervous system in MS differ significantly. While preserved brainstem function is needed for development of syncope, structural disorders like OH could be associated with brainstem dysfunction. Further studies delineating these differences are warranted.

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Tables

Table 1. The prevalence of different types of autonomic dysfunction in the CIS cohort.

Autonomic dysfunction	**Positive N (%)**	**Negative N(%)**
Adrenergic index ≥1*	19 (43.2%)	25 (56.8%)
Cardiovagal index ≥1	3 (6.7%)	42 (93.3%)
OH	4 (8.9%)	41 (91.1%)
Syncope	8 (17.8%)	37 (82.2%)
POTS	5 (11.1%)	40 (88.9%)

OH Orthostatic hypotension; POTS Postural orthostatic tachycardia syndrome

* One patient was not able to perform Valsalva maneuver, so the adrenergic index could not be calculated.

Table 2. Differences in the VEMP score between different forms of autonomic dysfunction.

Autonomic dysfunction		**oVEMP (ranks / median)**	**p value**	**cVEMP (ranks / median)**	**p value**	**VEMP (ranks / median)**	**p value**
Adrenergic index ≥1*	N	21.00/2.5	0.36	22.06/1	0.78	21.06/4	0.39
	P	24.47/3		23.08/2		24.39/5	
Cardiovagal index ≥1	N	23.65/3	0.22	22.93/1	0.92	23.61/5	0.26
	P	13.83/0		24.00/2		14.50/3	
OH	N	21.91/3	0.08	22.16/1	0.18	21.85/4	0.06
	P	34.13/5		31.63/3.5		34.75/7.5	
Syncope	N	25.04/4	0.02	24.77/2	0.05	25.43/5	<0.01
	P	13.56/1		14.81/0		11.75/1	
POTS	N	23.95/4	0.18	23.44/1.5	0.53	23.73/4.5	0.31
	P	15.40/1		19.50/0		17.20/3	

OH Orthostatic hypotension; POTS Postural orthostatic tachycardia syndrome; N Negative; P Positive

* One patient was not able to perform Valsalva maneuver, so the adrenergic index could not be calculated.

Table 3. Correlation between different forms of autonomic dysfunction and presence of demyelinating lesions in different parts of the brainstem.

Autonomic dysfunction		**Midbrain**		**p**	**Pons**		**p**	**Medulla**		**p**	**C spine**		**p**
		N	P		N	P		N	P		N	P	
Adrenergic index*	0	22	1	0.22	17	6	0.59	20	3	0.73	10	8	0.69
	1	11	3		9	5		11	3		5	5	
	3	3	1		2	2		3	1		3	1	
Cardiovagal index	0	34	5	1.00	25	14	0.54	32	7	1.00	18	14	1.00
	1	3	0		3	0		3	0		1	0	
OH	N	34	4	0.41	26	12	0.59	32	6	0.53	16	13	0.62
	P	3	1		2	2		3	1		3	1	
Syncope	N	30	4	1.00	24	10	0.41	30	4	0.11	14	13	0.21
	P	7	1		4	4		5	3		5	1	
POTS	N	33	4	0.49	24	13	0.65	31	6	1.00	17	12	1.00
	P	4	1		4	1		4	1		2	2	

OH Orthostatic hypotension; POTS Postural orthostatic tachycardia syndrome; N Negative; P Positive

* One patient was not able to perform Valsalva maneuver, so the adrenergic index could not be calculated.

Figures

Figure 1. Tracings from oVEMP and cVEMP responses form a CIS patient with syncope. Two traces in the lower row (SCMR and SCML) present cVEMP, and the traces in the upper row (OL and OR) presents oVEMP. The VEMP score is 0. Timescale is in ms, from -20 ms before the appearance of the stimulus and 100 ms after the appearance of stimulus. 0 ms on the x-axis presents moment in which the stimulus is presented to the participant. Sensitivity is presented in μV (microvolt). cVEMP traces and oVEMP traces have different sensitivity.
SCMR – right sternocleidomastoid response, SCML – left sternocleidomastoid response, OL – left ocular response, OR – right ocular response.

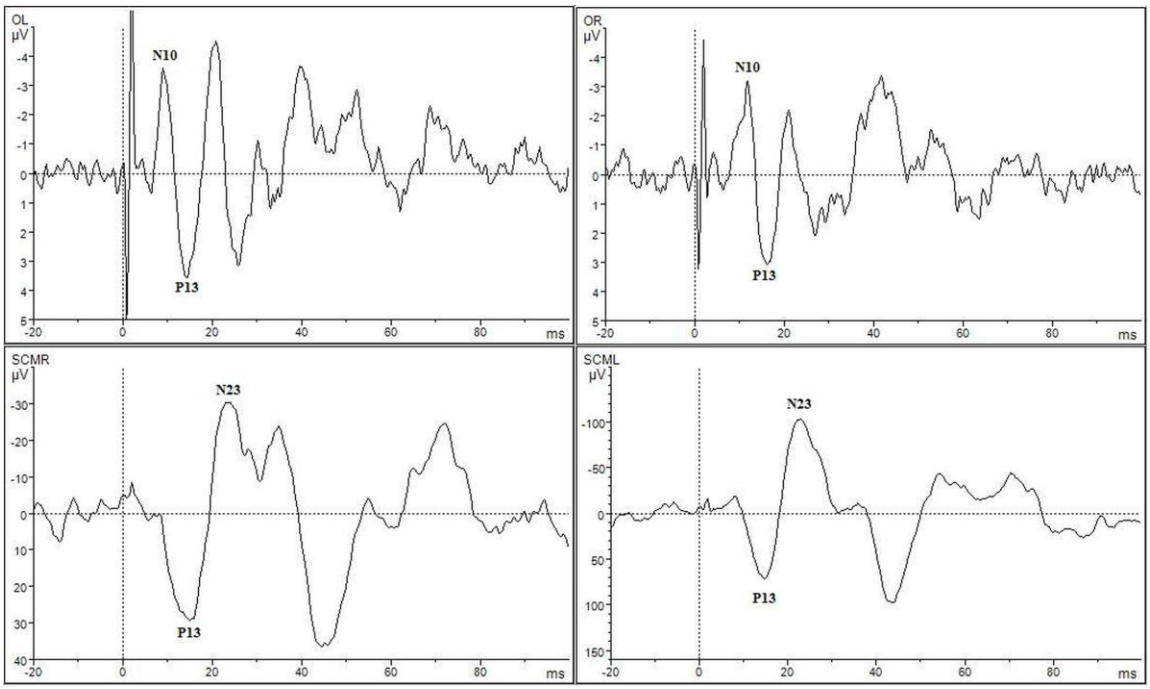

Figure 2. Tracings from oVEMP and cVEMP responses form a CIS patient without syncope. Two traces in the lower row (SCMR and SCML) present cVEMP, and the traces in the upper row (OL and OR) presents oVEMP. The VEMP score is 5

(normal response of both oVEMP responses (OL and OR)=0, conduction block of SCMR=3, reduced amplitude of SCML=2, equals the VEMP score of 5). Timescale is in ms, from -20 ms before the appearance of the stimulus and 100 ms after the appearance of stimulus. 0 ms on the x-axis presents moment in which the stimulus is presented to the participant. Sensitivity is presented in μV (microvolt). cVEMP traces and oVEMP traces have different sensitivity.
SCMR – right sternocleidomastoid response, SCML – left sternocleidomastoid response, OL – left ocular response, OR – right ocular response.

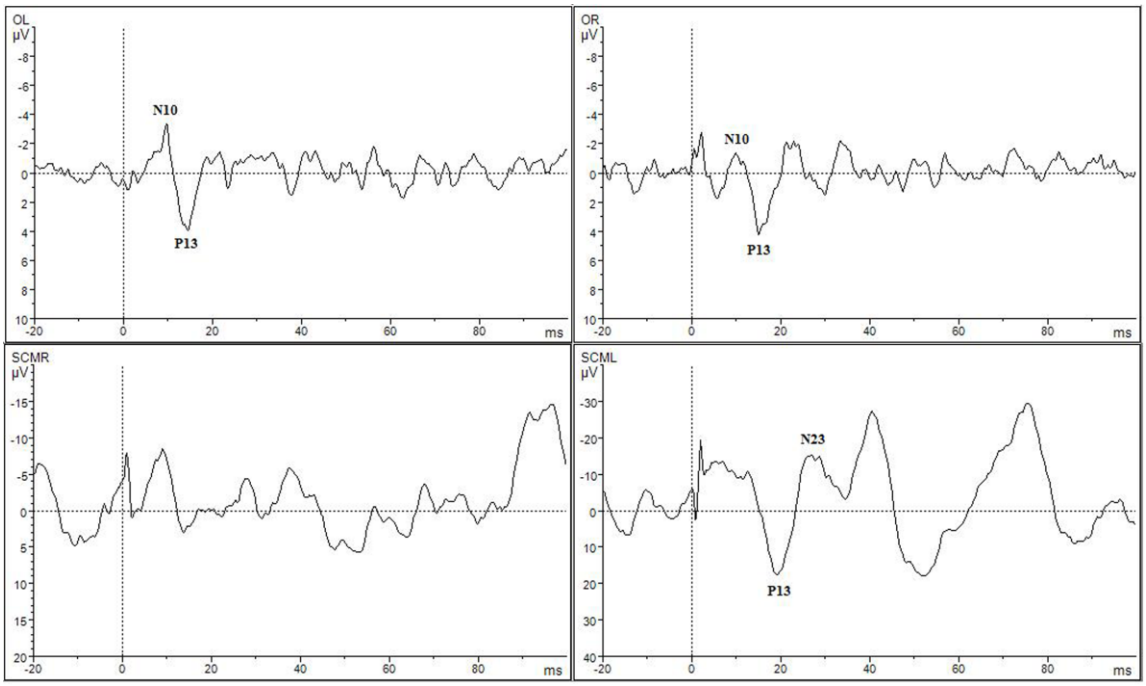

Figure 3. ROC curves for oVEMP (left), cVEMP (middle) and VEMP (right) scores.