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Original Article

Neuro-ophthalmic and Neuro-otologic Evaluation in Individuals with Motion Sickness Susceptibility

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BACKGROUND: Since the physiological background of motion sickness is not entirely clear, it was aimed to examine the physiological differences in groups consisting of individuals susceptible and non-susceptible to motion sickness.

METHODS: Sixty subjects [motion sickness (MS) group: 33 female, 3 male; 28.8 ± 8.1 years; control group: 19 female, 5 male; 24.5 ± 4.3 years] were included in the study. Near visual acuity test on the treadmill in the presence of visual stimulation, pattern visual-evoked potentials, oculomotor tests, and computerized dynamic posturography were applied. Receiver operating characteristic analysis was performed to determine the parameter that provides the excellent discrimination between the groups.

RESULTS: The most effective parameter in differentiating the study groups was determined as dynamic visual acuity with 77.8% sensitivity and 95.8% specificity. Significant differences were found in the vestibular (mean ± standard deviation: 0.63 ± 0.17), visual (0.77 ± 0.18), and composite scores (73.11 ± 11.89) of the patients ($P = .000$) in posturographic evaluation. In the visual-evoked potential examination, a significant decrease was found in the amplitude values between the P100-N145 waves in the binocular (5.0 ± 2.8, $P = .002$), right eye (7.6 ± 3.2, $P = .009$) and left eye (7.9 ± 2.9, $P = .016$) in the symptomatic patients. In binocular oculomotor evaluation, directional asymmetric findings were obtained.

CONCLUSION: It has been shown that the most effective test parameter that distinguishes the MS susceptible and non-susceptible individuals is the dynamic visual acuity value. Based on the results of neuro-physiological tests, it was suggested that a possible visual-vestibular integration disorder in individuals susceptible to motion sickness may affect visual and vestibular performance.

KEYWORDS: Motion sickness, reflex, vestibulo-ocular, visual acuity, evoked potentials, visual

INTRODUCTION

Motion sickness (MS) is a general term for a variety of symptoms that can be elicited by sudden, periodic, or artificial accelerations.[1] Motion sickness is elicited by both linear and angular head acceleration in susceptible individuals.[2] Motion sickness is usually elicited by vestibular stimulation but can also be elicited by visual stimulation.[3] Experimental studies have shown that MS can be elicited by provocative physical movements and impaired vestibulo-ocular reflexes.[4]

A prerequisite for the development of MS symptoms is that the brain receives conflicting information about actual body movements from different sensors.[5] Although the vestibular, visual, and somatosensory systems involved in efficient spatial orientation have optimal frequency ranges that overlap with each other, conflicts between these inputs can cause postural instability.[6] Sensory conflict theory and the neural mismatch model explain why people experience MS when looking at a moving area even when they are stationary.[5]

The visual-evoked potential mechanism is necessary to visually stabilize an object of interest when the body is in motion. In the literature, linear accelerations have been reported to be effective on MS symptoms.[2,7] Motion sickness makes it difficult to integrate angular and linear accelerations for effective reorientation of the head in space.[8] In this study, it was considered that a possible

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dysfunction in the vestibulo-ocular reflex mechanism activated by linear acceleration may have a provoking effect on individuals with MS. In this context, the visual-vestibular integration mechanism was investigated with a near visual acuity test applied to individuals during linear acceleration.

The etiology and neurobiological mechanisms of MS have not yet been definitively established. Individual differences lead to uncertainties in the evaluation and treatment of the disease. In our study, the visual, vestibular, and somatosensory system parameters of individuals with MS were analyzed. In addition, unlike the literature, visual-evoked potentials and videonystagmography were applied to objectively test the visual systems of individuals. In the study, it was aimed to determine the most effective parameters in the clinical diagnosis and evaluation of MS with different test methods applied to individuals.

MATERIALS AND METHODS

The study protocol was approved by the Istanbul University -Cerrahpaşa, "Cerrahpaşa Medical School Ethics Committee Chair" (Approval Number: 59491012-604.01.02, Date: July 3, 2019). The informed consent form was signed by each participant. The study was conducted in accordance with the Declaration of Helsinki.

Participants

Thirty-six individuals (33 female, 3 male) (28.8 ± 8,1 years) in the patient group and 24 individuals (19 female, 5 male) (24.5 ± 4,3 years) in the control group were included in the study. The power obtained for the study with the number of available data in the G*Power program was found to be 95.1%. The susceptibility percentages of the individuals participating in the study were determined using the "Motion Sickness Susceptibility Questionnaire-Short."[9] Individuals with at least 80% rate in the questionnaire constituted the patient group, and those with 0% rate constituted the control group. Hearing loss, abnormal middle ear function, positional nystagmus, migraine, abnormal neurological examination, and metabolic disease were determined as exclusion criteria for all participants. All participants underwent a complete neuro-ophthalmological examination, including visual impairment, visual field defect, inability to fixation, and pupil size. The tests were performed in a randomized order, and a 30-minute break was given between each test. In the absence of nausea or any other condition that prevented the subject from performing the test, the next test was started.

MAIN POINTS

- Vestibular dysfunction and visual input sensitivity may play a role in the development of motion sickness symptoms.
- In individuals with motion sickness susceptibility, the vestibulo-ocular reflex mechanism may not stabilize vision during linear acceleration.
- The current study suggests that the dynamic visual acuity value is the most effective test parameter that distinguishes between motion sickness-sensitive and healty individuals from each other.
- The asymmetry observed in oculomotor recordings in individuals with motion sickness may affect the visual performance of individuals.

Computerized Dynamic Posturography

Sensory organization test (SOT) in computerized dynamic posturography (NeuroCom SMART Balance Master Systems 8.5.0) was applied to all individuals. In this context, vestibular, visual, somatosensory, preference, and composite score parameters were examined.

Near Visual Acuity Test on Treadmill

All subjects underwent dynamic visual acuity (DVA) test and static visual acuity (SVA) test. Static visual acuity was performed in a standing position, with the head stationary and motionless. Dynamic visual acuity was performed in the presence of a moving visual stimulus on a treadmill. The speed of the treadmill was set at 1.67 m/s, which is close to the natural walking speed of an adult and the speed at which angular vertical head rotation fully compensates for linear upward and downward movement without requiring additional eye movement.[10,11] As the sensitivity of translational vestibulo-ocular reflex (°/cm) increases significantly at near visual distances, participants underwent a near visual acuity test.[10] In this context, the revised series Sloan letter ETDRS eye chart calibrated for near distance (40 cm) was used. Since binocular visual cues play a critical role in translational vestibulo-ocular reflex performance, visual acuity test was tested binocularly.[12] Visual acuity test was applied with eye correction factors in individuals wearing glasses or contact lenses. When assessing vestibulo-ocular reflex on a treadmill, a black-and-white moving visual stimulus that could simulate optic flow was projected to the right, left, and front. The following equation was used to calculate SVA, DVA, and visual acuity loss values:[13]

$$SVA\ (logMAR)\ \text{or}\ DVA\ (logMAR) = 1.10 - (A * B)$$

$$\text{Visual acuity loss}\ (logMAR) = \text{SVA}\ (logMAR) - DVA\ (logMAR)$$

A) the sum of the number of correctly read letters, B) the value of each correctly read letter

Pattern Visual-Evoked Potentials

Pattern visual-evoked potential examination was performed with NeuronSpectrum-5 (4/EPM) (Neurosoft, Ivanovo, Russia) in a quiet and controlled dark room. If the subjects had refractive errors, they were corrected with their own glasses or lenses. Standard electroencephalogram Ag/AgCl disk electrodes were placed on cleaned scalp and skin areas. According to the international 10-20 system, the reference electrode (Fz) was placed on the forehead, the ground electrode (Cz) on the vertex, and the active electrode (Oz) 2 cm proximal to the inion. The parameters are as follows: sensitivity 2 μV, rate of presentation/sec 2 Hz, high pass filter 100 Hz, analysis time (sweep duration) 300 ms, mean luminance of the pattern between the center and periphery of the field 50 cd/m^2, background luminance 20-40 cd/m^2, contrast between approximately 50%-80%. An average of 200 was made in each epoch. The impedance was kept below 5 kΩ during the entire examination.[14] Visual-evoked potential examination was performed binocularly and monocularly. The upper limit of P100 response latency was 120 ms for men and 115 ms for women, the minimum amplitude was 2μV, and the upper limit of interocular latency difference was 6 ms. Individuals with symptoms of nausea, drowsiness, increased sleepiness, and dizziness identified during visual-evoked potential examination were used for symptomatic/asymptomatic comparison within the patient group.

Videonystagmography

Binocular oculomotor functions of all participants were recorded using the ICS Chartr 200 VNG (Natus Medical Incorporated, Taastrup, Denmark) device. In this context, saccadic, smooth pursuit, and optokinetic system parameters were evaluated.

Statistical Analysis

All statistics were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). In the research, Kolmogorov–Smirnov test was used to control for normal data distribution. The Mann–Whitney *U*-test was used for intergroup comparisons and the Wilcoxon signed-rank test was used for intragroup comparisons. While the chi-square test was used for categorical data comparisons, Receiver operating characteristic analysis was performed to determine the parameter that provides excellent discrimination between the groups. Within the scope of the research, the level of significance is $\alpha = 0.05$.

RESULTS

Near Visual Acuity Test on Treadmill

In the comparison between the groups, significance was found in SVA, DVA, and visual acuity loss values (Table 1).

Computerized Dynamic Posturography

In the comparison of SOT variables between the groups, no significant difference was found in terms of preference and somatosensory variables, whereas significant differences were found in vestibular, visual, and composite score variables (Table 2).

Pattern Visual-Evoked Potentials

Binocular and monocular visual-evoked potential response forms were within normal limits. While no complaints were observed during the examination in the control group, symptoms such as nausea, drowsiness, increased sleepiness, and dizziness occurred in 14 patients in the patient group.

There was no significant difference between the binocular latency and amplitude values, monocular latency and amplitude values, latency and amplitude difference values in right and left eyes, and latency difference values between N75-P100, P100-N145, and N75-N145 waves for right and left eyes in the patient and control groups ($P > .05$).

Table 1. Comparison of SVA, DVA, and Visual Acuity Loss Values in Patient and Control Groups

Variable	Group	Mean	Median	SD	MWU	*P*
SVA (logMAR)	Patient	.02	.00	.11	221.0	.001*
	Control	−.07	−.10	.06		
DVA (logMAR)	Patient	.38	.34	.12	44.5	.000*
	Control	.16	.14	.07		
VAL (logMAR)	Patient	−.35	−.39	.11	149.0	.000*
	Control	−.22	−.24	.07		

DVA, dynamic visual acuity; MWU, Mann–Whitney *U*-test; SD, standard deviation; SVA, static visual acuity; VAL, visual acuity loss.
*$P < .01$.

Table 2. Comparison of Sensory Organization Test Parameters in Patient and Control Groups

Variable	Group	Mean	Median	SD	MWU	*P*
Vestibular	Patient	.63	.66	.17	139.5	.000*
	Control	.81	.83	.06		
Visual	Patient	.77	.79	.18	186.5	.000*
	Control	.92	.93	.04		
Somatosensory	Patient	.96	.98	.05	422.0	.880
	Control	.98	.97	.03		
Preference	Patient	.99	1.00	.09	365.5	.315
	Control	1.02	1.01	.05		
Composite score	Patient	73.11	76.00	11.89	121.5	.000*
	Control	86.04	86.00	3.44		

MWU, Mann–Whitney *U*-test; SD, standard deviation.
*$P < .01$.

In the control group, no significant difference was found in the latency difference values between the N75-P100, P100-N145, and N75-N145 waves for the right and left eyes. A significant difference in latency difference between N75-N145 waves was detected in the comparison of right (52.97 ± 7.65) and left eyes (54.16 ± 7.42) in the patient group ($P < .05$) (Table 3). Significance was found in the amplitude values between binocular and monocular P100-N145 waves in the patient group in terms of the presence of symptoms ($P < .05$) (Table 4).

Videonystagmography

There was no significance in the right ($P = .207$) and left ($P = .182$) smooth pursuit gain variables between the groups. Statistical significance was determined in the smooth pursuit phase shift parameter between the groups ($P = .001$). In this context, it was observed that the mean value (1.19 ± 1.37) of the patient group in the phase shift parameter was higher than the mean value (−0.15 ± 1.17) of the control group.

Table 3. Comparison of Right and Left Eye Interwave Latency Differences in Patient and Control Groups

Variable and Group	Eye	Mean	Median	SD	*Z*	*P*
N75-P100 (ms) (patient)	Right	22.90	22.95	2.77	−1.835	.066
	Left	23.44	23.35	2.74		
P100-N145 (ms) (patient)	Right	30.07	29.00	5.95	−1.146	.252
	Left	30.72	30.25	5.97		
N75-N145 (ms) (patient)	Right	52.97	53.05	7.65	−2.577	.010*
	Left	54.16	55.35	7.42		
N75-P100 (ms) (control)	Right	23.39	23.65	2.38	−1.615	.106
	Left	24.02	24.15	2.03		
P100-N145 (ms) (control)	Right	31.35	31.75	5.17	−.076	.939
	Left	31.54	31.50	5.45		
N75-N145 (ms) (control)	Right	54.75	55.85	5.06	−1.158	.247
	Left	55.56	56.45	5.67		

SD, standard deviation; Z, Wilcoxon signed-rank test.
*$P < .05$.

Table 4. Comparison of Interwave Amplitude Differences Values of Symptomatic and Asymptomatic Individuals in the Patient Group

Variable and Eye	Group	Mean	Median	SD	MWU	*P*
Binocular P100-N145 (μV)	Symptomatic	5.0	4.9	2.8	59.000	.002**
	Asymptomatic	8.6	8.9	3.1		
Right P100-N145 (μV)	Symptomatic	7.6	7.1	3.2	74.000	.009**
	Asymptomatic	10.6	11.0	3.5		
Left P100-N145 (μV)	Symptomatic	7.9	7.8	2.9	80.000	.016*
	Asymptomatic	10.6	10.7	4.1		

MWU, Mann–Whitney *U*-test; SD, standard deviation.
*$P < .05$.
**$P < .01$.

In the comparison of the right and left saccadic test parameters of the patient group, no statistical significance was found in the accuracy ($P = .365$) and latency ($P = .889$) variables. On the other hand, significance was found in the peak velocity value in the patient group ($P = .000$). In this context, the mean value (417.23 ± 28.92) on the right side of the peak velocity parameter was found to be lower than the mean value (424.91 ± 33.31) on the left side.

In the comparison of the right and left optokinetic gains of the patient group, no significance was found in the gains of both eyes at 20°/s ($P = .490$). However, significance was found in the comparison of right and left gain at 40°/s ($P = .014$). In this context, the mean value (0.64 ± 0.34) in the right gain peak SPV°/s:40°/s parameter is lower than the mean value (0.70 ± 0.30) in the left gain peak SPV°/s:40°/s parameter.

Efficacy Comparison of Parameters Applied to Detect Motion Sickness Susceptible and Healthy Individuals

In the comparison of the differentiating power of the parameters that made a difference in the patient and control groups, the most effective of the values area under the receiver operating characteristic analysis curve was observed in the DVA parameter. Accordingly, the most effective parameter in discriminating individuals was the DVA parameter. The logMAR value of DVA, 0.290, was found to be the cutoff value with 77.8% sensitivity and 95.8% specificity (Table 5) (Figure 1).

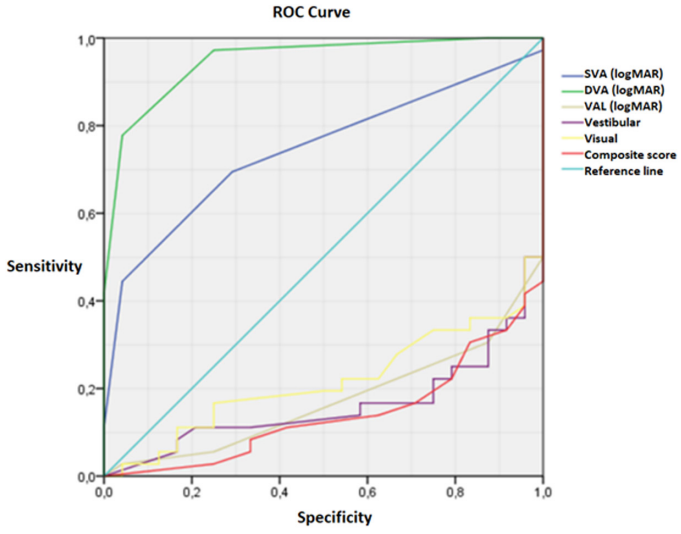

Figure 1. Receiver-operating characteristic curve for the parameters. DVA, dynamic visual acuity; SVA, static visual acuity; VAL, visual acuity loss.

Table 5. Efficacy Comparison of Parameters Applied to Detect Motion Sickness Susceptible and Non-susceptible Individuals

Test Result Variables	Area	SE	*P*	95% CI	
				Lower Bound	Upper Bound
SVA (logMAR)	.744	.063	.001*	.620	.868
DVA (logMAR)	.948	.027	.000*	.896	1.000
VAL (logMAR)	.172	.052	.000*	.070	.275
Vestibular	.161	.052	.000*	.059	.264
Visual	.216	.059	.000*	.100	.331
Composite score	.141	.047	.000*	.049	.232

DVA, dynamic visual acuity; SE, standard error; SVA, static visual acuity; VAL, visual acuity loss.
*$P < .01$.

DISCUSSION

Links between the translational vestibulo-ocular reflex mechanism activated by linear accelerations and the occurrence of motion sickness have been demonstrated.[15] In the literature, patients with vestibular hypofunction have typically shown low DVA scores.[16] It has also been reported that vestibular loss impairs convergence in patients with idiopathic bilateral vestibular dysfunction.[17] In the literature, it is known that translational vestibulo-ocular reflex gain increases at near vision distances, and this increase is mediated by vergence signals.[18] The higher DVA score of the patient group in the present study suggests that the vestibulo-ocular reflex mechanism cannot stabilize vision during linear acceleration in these individuals and that there may be a disorder in the integration of vestibular signals.

In a study on individuals with Mal de Debarquement, it was shown that their symptoms were mainly related to postural instability of vestibular origin. Moreover, the preference value of the patients was not statistically significant when compared with the control group.[19] In this context, our findings support the literature. Our results showed that individuals susceptible to MS tended to rely less on inputs from the vestibular system to maintain their balance, and the composite score was lower than healthy individuals due to hypofunction in the vestibular and visual systems. In addition, a difference of 2 or more between SVA and DVA is considered a sign of vestibular hypofunction.[20] From this point of view, the visual acuity loss value in individuals with MS (–0.35 ± 0.11) supports our dynamic posturography data in favor of vestibular dysfunction.

The oculomotor system is important for the stabilization of the object on the fovea.[21] In the literature, it has been shown that the saccadic peak velocity is higher in the temporal field of the retina and that asymmetries in the visual system affect visual performance and attention.[22] In another study, nasal-temporal asymmetry in saccadic peak velocities was observed in binocular recordings. According to the study, the eyes were not always conjugate, and the saccades of the abducted eye showed a higher saccadic peak velocity than the saccades of the adducted eye.[23] Another study showed nasal-temporal asymmetries in peak velocity during binocular saccadic eye movements in some individuals. Accordingly, saccadic peak velocities of

individuals were found to be higher in the ipsilateral half of the dominant eye.[24] In the present study, the significantly higher left saccadic peak velocity value in the patient group suggests that there may be nasal-temporal asymmetry, and the left eye may play a more dominant role. The results suggest that individuals with MS sensitivity may show asymmetry in binocular saccadic recordings and that the existing asymmetry may affect the visual performance of individuals.

Optokinetic nystagmus constitutes a visual component of the vestibular reflex mechanism that serves to stabilize the retinal image of the environment during head rotation.[25] In a study investigating the effects of space flight on optokinetic nystagmus, a higher gain was recorded on the left side. It was also reported that the cause of the asymmetry is not known exactly and may be a characteristic of the group.[26] In another study, it was shown that the gain of the eye directed towards the nasal area was higher than the gain of the eye directed towards the temporal area.[25] In this context, the statistically significant higher left optokinetic gain in our study supports the literature. A directional asymmetry in left-eye dominance was found in individuals with MS.

In a study examining the changes in oculomotor parameter values of individuals tested at different times of the day, it was reported that the phase shift parameter was affected by attention and fatigue.[27] In our study, although all oculomotor system parameters were within the normative range, the phase shift parameter of the patient group was significantly higher than the control group. Therefore, it is thought that the attention and fatigue status of individuals should be predicted before oculomotor tests.

In the literature, it has been reported that MS symptoms may occur with visual stimulation as well as vestibular stimulation.[3,4] In patients with symptoms during visual-evoked potential testing, P100-N145 amplitude reduction was detected in both binocular and monocular examinations without peak and inter-peak latency pathology. Our findings suggested that these individuals may have difficulty focusing on the target point during their symptoms. It has been shown that visual stimulation without head movement may cause MS symptoms, and this may negatively affect the visual perception of individuals.

Limitations of the Study and Implications for Future Research

In our study, the objective tests we used in the evaluation of MS included the behavioral participation of the patients. Ensuring full focus is known to be one of the main rules in pattern visual-evoked potentials. Therefore, in future studies, we suggest that flash visual-evoked potentials should be preferred in patients who may have difficulty concentrating due to various symptoms. We also suggest that attention and fatigue states of individuals should be taken into consideration in oculomotor tests to be applied to individuals in future studies. Finally, although breaks are given after each test to ensure that MS symptoms induced in individuals do not affect subsequent test results, solutions such as dimenhydrinate can be used prior to assessment to eliminate symptoms.

In our study, as a result of conflicting information processed in the multimodal sensor system of individuals with MS, vestibular and visual system hypofunction was observed in accordance with the neural mismatch model. When vestibular dysfunction in individuals with MS is combined with visual input sensitivity, it is thought that visual-vestibular integration disorder may occur and this integration disorder may play a role in the development of MS. As far as we know, the occurrence of symptoms in patients during visual-evoked potential testing and the resulting decreased visual attention and oculomotor asymmetries have not been previously mentioned in the literature. Considering our findings, it has been shown that sensitivity to visual input in individuals with MS can produce various symptoms that may affect test results. In this context, it should be noted that symptom-triggering visual stimuli such as moving patterns that we used in the visual-evoked potential and DVA tests may negatively affect the performance of individuals during the test. As a result of the analyses, it was shown that the DVA value was the most effective test parameter that distinguished MS-sensitive and healthy individuals from each other. It seems possible that our findings may facilitate the clinical process in this disease, whose diagnosis is still unclear, and provide data that will strengthen our hand in patient management.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Istanbul University-Cerrahpaşa (Approval No:59491012-604.01.02; Date: July 3, 2019).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

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