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CLINICAL STUDY

EFFECTS OF COVID-19 ON VESTIBULO-OCULAR SYSTEM

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SUMMARY

Objectives: Dizziness is associated with the involvement of the peripheral and central nervous systems. It is known that dizziness complaints in individuals with Covid-19 may be due to the involvement of the peripheral and/or central nervous system. This study aims to evaluate the effects on vestibular and oculomotor systems after Covid-19.

Material and methods: Twenty-eight individuals with a history of Covid-19 and 20 healthy individuals with no history of Covid-19 were included in this study. Dizziness Handicap Inventory (DHI), videonystagmography (VNG), and video head impulse test (vHIT) were administered to both groups.

Results: In the study group left anterior and right lateral semicircular canal (SCC) vestibuloocular reflex (VOR) gains were lower, the anterior and posterior SCC asymmetry were higher than the control group in vHIT ($p<0.05$). In the study group, the gain values were lower for the right eye at 0.1 Hz, and left eye and right eye at 0.2 Hz, left eye and right eye 0.4 Hz in smooth pursuit test, the accuracy of right moving values were lower in saccade test ($p<0.05$). The gain values were lower in the optokinetic test in individuals with Covid-19 ($p<0.05$).

Conclusion: Covid-19 may not cause a severe dizziness problem. However, the abnormalities we observed in objective test results suggest that this situation may adversely affect the quality of life of individuals in long term.

Keywords: Covid-19; Oculomotor system; Vestibular system; Vestibuloocular reflex

COVID-19'UN VESTİBÜLOOKÜLER SİSTEM ÜZERİNE ETKİLERİ

ÖZET

Amaç: Baş dönmesi, periferik ve santral sinir sistemlerinin tutulumu ile ilişkilidir. Covid-19 geçiren bireylerde baş dönmesi şikayetinin periferik ve/veya santral sinir sisteminin tutulumuna bağlı olabileceği bilinmektedir. Bu çalışma, Covid-19 sonrası vestibüler ve okülomotor sistemler üzerindeki etkileri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya Covid-19 öyküsü olan 28 birey ve Covid-19 öyküsü olmayan 20 sağlıklı birey dahil edilmiştir. Her iki gruba da Baş Dönmesi Engellilik Envanteri, videonistagmografi (VNG) ve video head impulse test (vHIT) uygulanmıştır.

Bulgular: vHIT sonuçlarına göre; çalışma grubunda sağ lateral ve sol anterior semisirküler kanala ait vestibülooküler refleks kazançları (VOR) kontrol grubuna göre düşük elde edilirken, anterior ve posterior semirsirküler kanala ait vestibülooküler refleks asimetrisi daha yüksek olarak elde edilmiştir ($p<0.05$). Çalışma grubunda smooth pursuit test kazanç değerleri 0.1 Hz'te sağ göz, 0.2Hz'te sol ve sağ göz, 0.4 Hz'te sol ve sağ gözde kontrol grubuna göre anlamlı derecede daha düşük elde edilirken, sakkad testte doğruluk değeri sağa bakışta daha düşük elde edilmiştir ($p<0.05$). Optokinetik testte ise Covid-19 öyküsü olan kişilerde kazanç değerleri daha düşük elde edilmiştir ($p<0.05$).

Sonuç: Covid-19 ciddi bir baş dönmesi sorununa neden olmayabilir ancak objektif test sonuçlarında gözlemlediğimiz anormallikler, bu durumun uzun vadede bireylerin yaşam kalitesini olumsuz etkileyebileceğini düşündürmektedir.

Anahtar Sözcükler: Okulomotor sistem; Vestibüler sistem; Vestibulooküler refleks

INTRODUCTION

The cases of pneumonia with unknown causes, which emerged in China in December 2019, were reported to be caused by the novel coronavirus (SARS CoV-2)[1]. On January 30th, 2020, WHO declared a global health emergency due to the spread of the cases worldwide; and it was named SARS CoV-2, Coronavirus Disease 2019 (Covid-19) in February[2]. Common symptoms of Covid-19 are pneumonia, fever, dry cough, fatigue, headache, and myalgia. Guan et al., 2020 reported that these symptoms can be observed in various degrees from moderate to severe[3]. The musculoskeletal system, central and peripheral nervous system are also affected in addition to the respiratory system[4]. The most significant theory of neurological involvement caused by Covid-19 is the mechanism of Angiotensin-converting enzyme 2 (ACE2). ACE2 is defined as a functional receptor for Covid-19, and the virus enters into the cells through this receptor. This enzyme receptor is most commonly found in the Alveolar Type II cells of the lung[5]. On the other hand, its presence in many organ cells such as the heart, lung, kidney, and both peripheral and central nervous systems including glial cells

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and neurons, causes vulnerability against Covid-19 infection[5,6]. The symptoms belonging to the central nervous system constitute the main form of neurological damage. In individuals whose central nervous systems are affected, the most common symptoms are dizziness and headache[4]. Dizziness is associated with the involvement of the peripheral and central nervous system[7]. It is known that dizziness complaints in individuals with Covid-19 may be due to the involvement of the peripheral and/or central nervous system[4].

Alternative entry routes of SARS CoV-2 are via the blood-brain barrier and the leukocytes which results in hypoxia, hypercoagulopathies[6,8]. It is thought that the effect of Covid-19 on neural tissue may be directly caused by the infection in the central nervous system, as well as by a mechanism similar to the vascular damage caused by varicella-zoster virus and human immunodeficiency viruses. Structures in the inner ear are susceptible to ischemia due to their requirement for high energy; therefore, hearing and balance impairments reported in individuals with Covid-19 may result from vascular damage[9].

In the literature, there are many studies that demonstrate the neurological effects in individuals with Covid-19; however, there are a limited number of studies examining the otoneurological effects. Survey studies reported that people with Covid-19 have dizziness and balance problems[9,10]. These problems can induce reducing the independence of daily living activities and reduced quality of life[1-3]. Additionally vestibular disorders are burdensome for society in terms of reduce working performance and social life and health care service cost[11].

Considering the neurological and metabolic effects of Covid-19, it is expected to affect the central and peripheral vestibular systems, and the oculomotor system, which contributes to the balance system. Due to there is not enough study about this issue in the literature we intended to fill the gap. The aim of this study is to evaluate the subjective complaints of dizziness in individuals with a history of Covid-19 using the Dizziness Handicap Inventory, and to investigate the possible effects of Covid-19 on the oculomotor and vestibular systems using objective test methods. By taking into consideration the disease, even if not any complaints about the vestibular system who undergo Covid-19, follow up the patients for a long time can contribute to the quality of life in necessary cases.

MATERIAL and METHODS

This study was conducted in the Bezmialem Vakif University Audiology Clinic. The approval was obtained from Bezmialem Vakif University, Non-Interventional Research Ethics Committee Clinical Research Ethics Committee on December 22nd, 2020 with decision number 21/406, and the study was conducted in accordance with the principles of the Declaration of Helsinki. After the participants were informed about the studies and tests to be carried out, a voluntary consent form was obtained from each participant.

The control group included 4 male and 16 female participants with no history of Covid-19 between 22 and 42 years of age (mean 28.7 ± 7.55). The study group included 9 male and 19 female participants between 21 and 45 years of age (mean 33.60 ± 8.03), who had been diagnosed with Covid-19. The reason of prefer young patients in both groups, is to minimize the risk of age-related changes in the hearing and vestibular system. Due to the lack of information about the effects of the Covid-19 vaccine, all participants were included from non-vaccinated individuals. All participants underwent ENT examination and tympanometric evaluation. Individuals with normal outer and middle ear functions were included in the study. Because of the close location of the hearing and vestibular system any disorders of the hearing system can increase the possibility of vestibular system disorders. Therefore, we chose individuals from among normal hearing individuals in the control group. The control group included individuals with air conduction hearing thresholds of 20 dB and better at frequencies of 250-8000 Hz, who reported no metabolic and neurological disease, dizziness/instability in their anamnesis, and who were able to participate in the tests. The study group included participants, who had been diagnosed with Covid-19 at least 1 month ago with the polymerase chain reaction (PCR) test, received home treatment for Covid-19, who reported no complaints of any metabolic and neurological disease, dizziness/imbalance before

Covid-19, and who reported no hearing impairments. All of the patients' PCR tests returned negative in the study group when we started the study.

The Dizziness Handicap Inventory, which consisted of 25 questions, was administered to all participants in the adopted version in Turkish. The physical, functional, and sensory results of dizziness were evaluated in individuals[12,13].

The oculomotor tests from the videonystagmography test battery (horizontal and vertical eye movement, spontaneous nystagmus, smooth pursuit, saccade and optokinetic) were performed on the participants using the Micromedical VisualEyes™ VNG (Chatham, IL, USA) device and VisualEyes™ EyeSeeCam model glasses. The results were recorded and analyzed using the VisualEyes 4 Channel Spectrum 9.2 software. Calibrations were performed in the horizontal and vertical planes before starting the test, and the patients were asked to look at the target without moving their heads during the test.

Video head impulse test was performed using the SYNAPSYS® vHIT Ulmer II (Marseilles, France) device. During the test, the participants were asked to look hard at the target points located at 0 degree, 20 degree to the right and 20 degree to the left..

The quantitative variables obtained in the study were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Whether the obtained quantitative variables differed significantly between the groups was examined with the independent t-test for the normally distributed data, and the Wilcoxon test for the data that did not have normal distribution. Analyses were performed on the SPSS 20.0 software at 95% confidence level. A $p<0.05$ was accepted as a significant difference.

RESULTS

While all individuals in the control group scored 0 points from the Dizziness Handicap Inventory, 22 individuals from the study group scored 0 points, and 6 individuals scored between 2 and 48 (mean DHI score = 18 ± 10).

In the vHIT evaluation, mean canal gain for each semicircular canal (SCC) and asymmetry values for bilateral SCCs were compared for both groups (Table 1).

While the mean gain values of all SCCs in the study group were lower compared to the control group, this value was significantly lower for the left anterior and right lateral SCC ($p<0.05$). The asymmetry values for all canals were higher in the study group; however, a significant difference was observed in the anterior and posterior SCC asymmetry values ($p<0.05$).

Mean saccade velocity, latency, and accuracy values for the eye movement in the right and left were compared between the groups in the saccade test (Table 2). Saccade velocity and accuracy values were lower, and the saccade latency values were higher for both directions in the study group; only saccade accuracy values for right moving were found to be significantly lower than the control group ($p<0.05$).

In the smooth pursuit test, the pursuit gain and asymmetry values for both eyes in 0.1, 0.2 and 0.4 Hz measurements were compared between the groups (Table 3). In the study group, while gain values were obtained lower for both eyes at all frequencies, the gain values for the right eye at 0.1 Hz and for both eyes at 0.2 and 0.4 Hz were found to be significantly lower compared to the control group ($p<0.05$). In the study group, high asymmetry values were obtained in both directions and at all frequencies; however, there was no significant difference compared to the control group ($p>0.05$).

The gain values obtained in the optokinetic test were compared between the groups (Table 4). In the study group, the gain values for the eye movement in the right and left were found to be significantly lower compared to the control group ($p<0.05$).

Table 1. Mean semicircular canal gains and asymmetry values

		Study Group Mean ±SD	Control Group Mean ±SD	p value
Mean Gain of SCC	Right Anterior SCC	1.02 ±0.08	1.03 ±0.06	0.475
	Left Anterior SCC	0.95 ±0.13	1.01 ±0.05	0.029*
	Right Lateral SCC	0.90 ±0.16	0.99 ±0.05	0.017*
	Left Lateral SCC	0.94 ±0.13	0.99 ±0.05	0.295
	Right Posterior SCC	0.95 ±0.13	1.01 ±0.04	0.054
	Left Posterior SCC	0.95 ±0.19	1.01 ±0.05	0.325
Asymmetry Value	Lateral SCCs	4.00 ±5.29	2.20 ±1.61	0.603
	Anterior SCCs	6.11 ±5.76	2.40 ±1.54	0.002*
	Posterior SCCs	5.00 ±8.78	1.25 ±1.29	0.008*

*p<0.05

SCC: Semicircular canal

Table 1 shows the mean gain values and asymmetry values of each semicircular canals.

Table 2. Mean saccade velocity, latency and accuracy values for the eye movement to the right and left

	Study Group Mean ±SD	Control Group Mean ±SD	p value
Saccade Velocity Left Moving	339.00 ±46.81	351.02 ±55.84	0.544
Saccade Velocity Right Moving	277.74 ±52.35	316.88 ±72.55	0.072
Saccade Latency Left Moving	239.19 ±26.93	230.85 ±25.30	0.284
Saccade Latency Right Moving	221.67 ±22.51	218.93 ±22.39	0.679
Saccade Accuracy Left Moving	94.09 ±4.21	95.64 ±4.10	0.211
Saccade Accuracy Right Moving	95.76 ±8.26	99.78 ±4.53	0.044*

*p<0.05

Table 2 shows the mean values of saccade velocity, latency and accuracy for the eye movement to right and left.

Table 3. Mean pursuit gains for the right and left eye, mean pursuit asymmetry values for the eye movement in the right and left

		Study Group Mean ±SD	Control Group Mean ±SD	p value
Pursuit Gain	0.1 Hz Left	0.92 ±0.13	0.97 ±0.06	0.084
	0.1 Hz Right	0.91 ±0.09	0.96 ±0.06	0.033*
	0.2 Hz Left	0.95 ±0.12	1.01 ±0.04	0.018*
	0.2 Hz Right	0.94 ±0.13	1.00 ±0.06	0.036*
	0.4 Hz Left	0.92 ±0.13	1.00 ±0.03	0.009*
	0.4 Hz Right	0.91 ±0.14	0.98 ±0.07	0.049*
Pursuit Asymmetry	0.1 Hz Left Moving	3.45 ±6.87	1.60 ±1.83	0.847
	0.1 Hz Right Moving	2.66 ±5.57	1.10 ±1.64	0.499
	0.2 Hz Left Moving	3.68 ±7.40	0.70 ±1.09	0.178
	0.2 Hz Right Moving	3.48 ±7.57	1.08 ±1.38	0.921
	0.4 Hz Left Moving	3.41 ±6.63	1.53 ±2.08	0.413
	0.4 Hz Right Moving	3.98 ±11.90	1.48 ±2.57	0.656

*p<0.05

Table 3. shows the mean value of pursuit gain for both eyes, and asymmetry value for eye movement to right and left for 0.1 Hz, 0.2 Hz, 0.4Hz.

Table 4. Mean gain values in optokinetic test

	Study Group Control Mean ±SD	Control Group Control Mean ±SD	p value
Optokinetic Gain Left	0.83 ±0.15	0.93 ±0.15	0.025*
Optokinetic Gain Right	0.77 ±0.20	0.91 ±0.12	0.013*

*p<0.05

Table 4 shows the mean value of optokinetic gain for right and left eye.

DISCUSSION

The vestibular system can be affected by a variety of viruses like herpes zoster oticus, rubella, cytomegalovirus, measles and mumps, therefore these viruses are accepted as etiology of dizziness and balance disorders[14,15]. Individuals with Covid-19 have dizziness as common symptoms[4,9,16]. Also, Covid-19 has some effects on the hearing system[17]. Considering the anatomy and physiology of the hearing and balance system, Covid-19 can similarly affect the vestibular system.

In our study individuals were evaluated within 1-11 months after recovery from Covid-19. In the study group, only 1 individual mentioned dizziness during the course of Covid-19, and 1 individual reported dizziness after recovery from the disease. However, DHI for only 6 individuals scored between 2 and 48 (mean: 18 ± 10). It is assumed that this may be related to the difference between the questions asked while taking anamnesis and the question types in DHI.

The VOR gain measured by vHIT assessment provides information about the vestibular system and the VOR pathway. In healthy individuals, the VOR gain value is expected to be between 0.79-1.20[18]. In our study, it was observed that VOR gains in both groups were within normal limits, but there was a significant difference in only two VOR gains and asymmetry values in the comparison between the study and control groups. Although this difference is statistically significant, it is not considered to be clinically significant. Bozdemir et al. reported in their study that only right lateral SSK gains in vHIT were significantly lower in the control group compared to the study group[17].

Additionally in our study, the corrective saccades observed in 3 individuals in study group. In another study conducted with 48 individuals with Covid-19, no overt and covert saccades were observed; however, a significant difference was found only in the anterior canal gain[19]. In another study, vHIT gain values were found to be lower in all channels in the study group compared to the control group, and RALP and LARP asymmetry values were found to be significantly different compared to the control group. In the Covid-19 group, the rate of saccade was 15.4% in the right lateral SCC and 19.2% in the left lateral SCC, while no saccade was observed in the control group[20]. Due to the differences in this information in the literature, a more comprehensive evaluation of saccadic eye movements, which has an important place in peripheral vestibular lesions, in Covid-19 patients may help the diagnosis in vestibular pathologies. Abnormal vHIT and VNG records of our study were shown in Table 5.

Table 5. Abnormal eye recordings in study group

Test	Study Group
vHIT	7.14% RL overt saccade
	3.57% RL and LL covert saccade
Gaze horizontal	7.14% horizontal nystagmus
Gaze vertical	3.57% horizontal nystagmus
Sakkad	3.57% hypometric saccade
Pursuit	64.28% saccadic eye movements + 3.57% nystagmus
Spontaneous nystagmus	64.28% with no fixation nystagmus (22.22% with fixation nystagmus)

Tablo 5 shows the percentage of abnormal eye recordings in vHIT and VNG

In the oculomotor evaluation, nystagmus was observed in 2 individuals in the horizontal gaze test and in 1 individual in the vertical gaze test. In another study, no pathological condition was encountered in gaze vertical and gaze horizontal tests[20]. It's thought that this difference may be due to the individual differences in the effect of Covid-19.

In the spontaneous nystagmus test, nystagmus was observed in 18 individuals (64%) in the absence of fixation, and it was observed that nystagmus was not suppressed in the presence of fixation in 4 of these individuals. Patients who have central nervous system disorders have spontaneous nystagmus that is not supressed by fixation[21]. Since it is known that spontaneous nystagmus not suppressed by fixation can be observed in patients with central nervous system disorders[21], it may be associated with central involvement in these individuals. Significant differences were observed for both groups in the optokinetic and smooth pursuit tests; however, all values were within the normal limits. According to literature cerebral hemispheres, brainstem, cerebellum, peripheral oculomotor nerves, and muscles participate in saccade, smooth pursuit, and optokinetic eye movements, and it is known that abnormal eye movements are caused by impairments and lesions in these organs[22]. The fact that the data was within normal limits and there were generally no complaints of severe dizziness/imbalance in the study group suggests that these structures were not affected significantly. It was noteworthy that in these tests, the latency and asymmetry values were higher than in the control group. Whereas gain and velocity values in the study group were lower compared to the control group. In addition, saccadic eye movements in 18 individuals (64%) and nystagmus in 1 individual was observed in the video recordings of the smooth pursuit test. Additionally, hypometric saccade was observed in 1 individual in saccade test. This suggests that the oculomotor systems are affected in individuals with Covid-19. In another study, no significant difference was found between the Covid-19 group and the control group in terms of normal or pathological conditions in VNG saccade, optokinenic and spontaneous nystagmus tests[20].

The participants of our study with Covid-19 consisted of individuals who had no severe symptoms and received treatment at home. As the severity of infection increases, neurological involvement becomes more evident[4]. Therefore, future studies on individuals, who has more severe Covid-19 disease and receive treatment in the hospital, will shed light on the literature.

In our study 33% of participants did not use drugs for the treatment of Covid-19, 23% used Hydroxychloroquine and Oseltamivir for treatment. Despite the fact that there is no information about the effects of antiviral drugs used by 44% on the vestibulo-ocular system, there is not sufficient evidence in our study to rule out the vestibulotoxic effect. This is the limitation of our study since medical treatment was not classified in a separate category.

CONCLUSION

Although there is no obvious vestibular complaint in individuals with Covid-19, abnormalities can be observed in objective vestibular tests. The long-term follow-up of individuals with Covid-19 will help to determine the various effects on the vestibular system and whether they have a negative impact on the quality of life. Conducting studies on individuals with more severe disease and in different age groups will contribute to the literature in terms of the effect of Covid-19 on the vestibulo-ocular system. In addition, the inclusion of the VEMP test in the vestibular system evaluation of patients with Covid-19 will contribute to the literature by providing a more comprehensive examination.

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