The effect of the severity of COVID-19 on the sequelae of the audiovestibular system

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Abstract

Objectives: The neurotropic and neuroinvasive properties of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been described. It remains unknown how SARS-CoV-2 affects the audiovestibular system when it causes mild or severe disease. In this study, the sequelae effect of SARS-CoV-2 on the audiovestibular systems of different patient groups was investigated using objective and subjective test batteries. Methods: In this present study, we evaluated vestibulocochlear functions of patients who previously had Coronavirus Disease-2019 (COVID-19) with pure tone audiometry, ocular vestibular-evoked myogenic potential (o-VEMP), and cervical vestibular-evoked myogenic potential (c-VEMP) tests to identify possible sequelae by comparing them with the control group. Results: We found that the amplitude of p13-n23 was lower in both groups of patients than in the control group (p < 0.001). In the results of the left ear c-VEMP, the amplitude of p13-n23 was statistically different between the outpatient, inpatient, and control groups. The amplitude of p13-n23 was lower in both groups of patients than in the control group (p < 0.001). In the evaluation of the o-VEMP in the left ear, we observed a statistically significant difference in the latency of n10 (p = 0.006) and the amplitude of n10-p15 (p < 0.001) between the groups. The n10 latency was prolonged in both groups of patients compared to the control group and there was no statistically significant difference between groups of patients. Furthermore, the amplitude of n10-p15 was lower in both groups of patients compared to the control group and there were no statistically demonstrable differences between the groups of patients. Conclusions: In conclusion, our results suggest that SARS-CoV-2 may affect the vestibulocochlear system. But we could not find a direct relationship according to the severity of the disease.

Keywords

COVID-19, vestibular-evoked myogenic potentials, vestibulocollic reflex, vestibuloocular reflex

Introduction

Some pneumonia cases of unknown origin were detected in Wuhan, China, and reported to the World Health Organization. In January 2020, a new type of coronavirus was determined as the pathogen of the cases. The virus was defined as acute respiratory syndrome coronavirus-2 (SARS-CoV-2). On January 30, 2020, the Organization defined the disease as Coronavirus Disease 2019 (COVID-19). COVID-19 spread rapidly all over the world. The disease has a wide variety of clinical symptoms ranging from asymptomatic to shortness of breath, taste and smell dysfunctions, fever, and dry cough. In addition to these symptoms, a large number of neurological involvements have been declared including stroke, unconsciousness, and visual disturbances, although it is uncertain whether the symptoms are a direct complication of the disease. It is well understood

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that viruses can cause hearing loss. Hearing impairment may be congenital or acquired, affecting one or both ears, and can vary from mild to severe. Sahin et al. reported the neuroinvasive and neurotrophic features of the coronavirus. Based on these characteristics of the virus, it can be suggested that COVID-19 may cause auditory neuropathy spectrum disorder (ANS). ANSD is characterized by disconnection between outer hair cells and ascending neural pathways.

Vestibular-evoked myogenic potential (VEMP) test plays a notable role as a component of vestibulometry and is used to assess the task of the utricle and saccule. Ocular VEMP (o-VEMP) tests the entirety superior vestibular nerve and utricle. Cervical VEMP (c-VEMP) tests the entirety of the inferior vestibular nerve and the saccule. The elongation of the positive peak, the increase in latency, or the low amplitude are the indicator of abnormal c-VEMP and are considered a marker of saccular impairment.

From the beginning of the pandemic, many authors have attempted to report a detailed clinical definition of the disease, covering its audiological findings. Based on the smell and taste dysfunctions reported in SARS-CoV-2 positive patients, neurotrophic and neuroinvasive characteristics of the virus have been discussed. Neurological symptoms have been declared in approximately 30% of patients who had COVID-19.

The inner ear is one of the areas affected by the virus, and this effect can manifest itself with clinical findings that include sensorineural hearing loss (SNHL), tinnitus, and/or vertigo. Vestibulocochlear dysfunctions related to SARS-CoV-2 have been reported, but a detailed vestibulocochlear evaluation is rarely available.

In this study, our objective was to evaluate vestibulocochlear functions of patients with COVID-19 who were treated outpatient and inpatient with pure tone audiometry, o-VEMP, and c-VEMP tests, and to identify possible sequelae by comparing them with the control group.

**Patients and methods**

This cross-sectional study was carried out at Malatya Training and Research Hospital, Otorhinolaryngology-Head and Neck Surgery Clinic between May and July 2021. Ethical approval was obtained from the Clinical Research Ethics Committee of Malatya Turgut Özal University before starting the study (ethical number 2021/14). When conducting the research, all the principles of the Declaration of Helsinki were adhered to and followed. Before inclusion in the study, patients were verbally informed about the study and written informed consent was obtained from all of them. In this study, our objective was to evaluate the vestibulocochlear functions of patients who previously had COVID-19 with pure tone audiometry, o-VEMP and c-VEMP tests and to identify possible sequelae by comparing them with the control group. A total of 105 patients were included in the study; the group that experienced the COVID-19 disease in the hospital and support of oxygen needed during the recovery period (35 patients), and the control group matched other groups in terms of age and gender (35 patients). All patients included in the study were examined by an ENT specialist. The age, comorbidities, audiological and neurological histories of the patients were questioned in detail. The symptoms of the patients in the group who had COVID-19 and the drugs they used during the COVID-19 process were interviewed and recorded. COVID-19 patients were selected from patients diagnosed and followed in our hospital. Patients who were diagnosed with COVID-19 by PCR test from an oro-nasopharyngeal sample and an average of 3 months passed from diagnosis were included in the study. All patients included in the study were selected from the age range of 20–50 years.

Patients with a history of otological (vertigo, tinnitus, surgery history, and hearing loss complaints before COVID-19) and neurological disease, muscle nerve disease, neck trauma or surgery, periorbital surgery, or ocular disease were excluded from the study. Patients with ear-related complaints during and after the COVID-19 period were not excluded from the study as they were the subject of the study. Patients who could not achieve a complete response on c-VEMP and o-VEMP tests were excluded from the study (6 patients (14.6%) in the inpatient group, four patients (10.3%) in the outpatient group, and four patients (10.3%) in the control group). Patients who did not require oxygen after the diagnosis of COVID-19 formed the outpatient group, who needed oxygen during the illness and were hospitalized; but did not reach a critical condition enough to be admitted to the intensive care unit constituted the inpatient group. Pure tone audiometry, c-VEMP, and o-VEMP procedures were performed for all patients included in the study after their otoscopic examinations. Audiological examination and VEMP tests were performed and evaluated by an experienced audiologist and ENT specialist. Audiological tests were performed with the Interacoustics AC40 device (Middelfart, Denmark) to evaluate six different frequencies (250 Hertz (Hz), 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz) in a conventional silent cabin. All frequencies were recorded separately and used in statistical analysis.

**Cervical VEMP procedure**

The c-VEMP test was performed with Interacoustics Eclipse EP25 (Middelfart, Denmark). Tone burst stimuli were administered to the ear with IP30 insert earphones (RadioEar, Middelfart, Denmark). Electromyography (EMG) signals were enhanced and bandpass-filtered among the 30 and 2000 Hz frequencies. Tone burst stimuli (105 dB nHL, 500 Hz, each has a 2 ms rise fall and a 0-ms plateau time, stimuli at an intensity of 5.1/second) were administered to each ear. c-VEMP measurements were made when the intensity of muscle contraction was between 100 microvolt (µV) root mean square (RMS) and 150 µV RMS. The peak and interpeak latencies and peak-to-peak amplitudes of the p13
Ocular VEMP procedure

The o-VEMP test was performed with an Interacoustics Eclipse EP25 device (Middelfart, Denmark). The EMG signals were enhanced and bandpass-filtered between 1 and 1000 Hz frequencies. Sound stimuli were administered to the contralateral side of the active electrode with an intensity level of 105 dB nHL. The peak latencies and peak-to-peak amplitudes of wave n10 and p15 were saved for each ear. The value of the asymmetry ratio was obtained using the formula defined by Murofushi et al. between the right and left ears.10 According to our normative data, we accepted asymmetry rates greater than 39%, as asymmetry existed between the two ears according to our normative data.

Statistical analysis

Data were given as median (min-max), mean (standard deviation), and count (percent). Compliance with normal distribution was checked with the Kolmogorov–Smirnov test. The Pearson chi-square test, Kruskal-Wallis test, and the one-way analysis of variance test were used where appropriate in statistical analysis. The LSD test was used for the one-way analysis of variance test and the Conover test was used for the Kruskal-Wallis test in multiple comparisons. The p-value of <0.05 was considered statistically significant. IBM SPSS Statistics 26.0 program was used in the analysis.

Results

Demographic analysis including gender and age was given in Table 1. The distribution of males and females among the groups was similar. In the audiological evaluation, although the mean values of all frequencies were observed as in the normal range, a statistically significant difference was detected particularly at 4000 Hz for the right ears (p= 0.009) and 8000 Hz for the left ears between the groups (p= 0.016) (Figure 1 and Figure 2).

In the c-VEMP calculations based on the control group, the asymmetry value was determined to be 25%, and there are 2 participants with this value in the control group. Similarly, there are nine participants in the outpatient group. Finally, there is one participant in the inpatient group. In the o-VEMP calculations based on the control group, the asymmetry value was
Table 2. Comparison of the right ear c-VEMP and o-VEMP parameters between groups

|                   | Control Group | Outpatient Group | Inpatient Group |
|-------------------|---------------|------------------|-----------------|
| **c-VEMP p13 (ms)** | 15.41±2.14a   | 15.43±3.02a      | 14.33(12.67–25.76) |
| **c-VEMP n23 (ms)** | 24.45±6.26a   | 24.09±10.33a     | 23.67±9.13a(19.33–29.67) |
| p13-n23 latency (ms) | 9.04±2.05a    | 8.81±2.36a       | 8(5.67–12.67)    |
| p13-n23 amplitude (mV) | 166.48±42.62a | 111.14±57.52b    | 96.97(18.79–279.30) |
| o-VEMP n10 (ms)    | 9.58±0.806a   | 9.33±8.67–13     | 9.67±8.67–12.67  |
| o-VEMP p15 (ms)    | 14.69±0.196a  | 14.81±1.098a     | 14.67±13.0–18.0  |
| n10-p15 latency (ms) | 5.11±0.862a   | 4.96±0.96a       | 4.67±0.30–7.67   |
| n10-p15 amplitude (mV) | 13.07±7.327a  | 10.72±9.529a     | 6.94±1.46–37.59  |

*p-values in bold indicate statistically significance, **: Kruskal-Wallis (Mann-Whitney-U with Bonferroni Correction in pairwise comparison); ***: One-Way ANOVA (Tamhane T2, Tukey Test in pairwise comparison).

c-VEMP: Cervical vestibular-evoked myogenic potential, o-VEMP: Ocular vestibular-evoked myogenic potential, SD: Standard deviation, ms: millisecond, mV: millivolt; *p-values in bold indicate statistically significance, **: Kruskal-Wallis (Mann-Whitney-U with Bonferroni Correction in pairwise comparison); ***: One-Way ANOVA (Tamhane T2, Tukey Test in pairwise comparison).

determined as 39%, and there were three participants with this value in the control group. Similarly, there are six participants in the outpatient group. Finally, there are six participants in the inpatient group.

In the c-VEMP test, p13 latency, n13 latency, p13-n23 latency, and the amplitude values of p13-n23 were analyzed for the right and left ears and compared between groups. In the results of the right ear c-VEMP, the latency of n23 (p = 0.002) and the amplitude of p13-n23 (p < 0.001) were significantly different between the groups. The mean latency of n23 was 22.65 ± 1.53 ms in the inpatient group, and this value was lower compared to the inpatient group. Finally, there are six participants in the inpatient group. In the o-VEMP test, n10 latency, p15 latency, n10-p15 latency, and the amplitude of n10-p15 were analyzed and compared between the groups. We did not observe any differences in the right ears on the o-VEMP test (p > 0.005). In the assessment of the o-VEMP of the left ear, we observed a statistically significant difference in the latency of n10 (p = 0.006) and the amplitude of n10-p15 (p < 0.001) between the groups. The mean n10 latency value was 9.56 ± 0.48 in the control group, which was lower than in other groups. The mean amplitude of n10-p15 was calculated as 7.76 ± 5.83 mV for inpatients, which was lower than the other two groups (Table 2 and Table 3).

The use of medications during COVID-19 was given in Figure 3. We observed that the use of favipiravir was high in both groups and that acetylsalicylic acid was used only in outpatients. Low molecular weight heparin (LMWH) was used mainly in inpatients. We found that corticosteroids were only used in hospitalized patients and antibiotics were mainly used in hospitalized patients.

The complaints observed in patients during COVID-19 were given in Figure 4. Tiredness was the most common symptom in both groups of patients. Additionally, dyspnea had been exist in all individual of inpatient group.

Discussion

The excessive number of papers published regarding SARS-CoV-2 infection have caused an infallion in the literature and made it difficult to determine a relationship between the virus and the injury in the inner ear. An exact history, including previous audiological conditions, is essential to help the physician determine the etiology. Previous exposure to noise, cranial trauma, ototoxic drugs, autoimmune events, and Meniere disease should be considered before establishing a relationship between SARS-CoV-2 and inner ear injury.

In this present study, we evaluated vestibulocochlear functions of patients with COVID-19 with pure tone audiometry, o-VEMP, and c-VEMP tests to identify possible sequelae by comparing them with the control group. We found that the pure tone averages of both the outpatient and inpatient groups were worse than those of the control group. In the audiological evaluation, although the mean values of all frequencies were observed as in the normal range, a statistically significant difference was detected particularly at 4000 Hz for the right ears (p = 0.009) and at 8000 Hz for the left ears between groups (p = 0.016).

M.W.M. Mustafa performed pure tone audiometry in asymptomatic patients with COVID-19 and compared them with the control group. In this study, the results of the patient group were worse at 4000 Hz, 6000 Hz and 8000 Hz, and he interpreted this situation as damage to the hair cells in the
Similarly, in our study, the thresholds were statistically worse in the patient groups at 4000 Hz in the right ear and 8000 Hz in the left ear. VEMP responses have been shown to be affected by some pathologies. Conductive hearing loss could be the cause of the lack of VEMP responses due to inadequate access to the sound intensity in the oval window. On the other hand, sensorineural hearing loss does not influence VEMP responses. In people older than 60 years, VEMP responses may indicate alterations. Therefore, we excluded patients with conductive hearing loss and sensorineural hearing loss, although it is known that sensorineural hearing loss does not affect the results of VEMP. The p13-n23 amplitude differed significantly between the groups in the right ear c-VEMP results. We found that the amplitude of p13-n23 was lower in both groups of patients than in the control group. Although we did not detect a statistically significant difference between the inpatient and outpatient groups, we observed a statistically significant difference between the patient and control groups (p < 0.001). When we analyzed the left ear c-VEMP results, we found that the amplitude of p13-n23 was statistically different between the outpatient, inpatient, and control groups. The p13-n23 amplitude was lower in both groups of patients than in the control group. We found that this decrease was more pronounced in the outpatient group (p < 0.001). In the assessment of the o-VEMP of the left ear, we observed a statistically significant difference in the latency of n10 (p = 0.006) and the amplitude of n10-p15 (p < 0.001) between the groups. The n10 latency was prolonged in both groups of patients compared to the control group and there was no statistically significant difference between the groups of patients. Furthermore, the amplitude of n10-p15 was lower in both groups of patients compared to the control group and there were no statistically demonstrable differences between the groups of patients. In c-VEMP responses, we found that the n23 latency value in the right ear was the highest in the control group and lower in the patient groups. Furthermore, the latency of p13 for the left ear was highest in the outpatient group and lowest in the inpatient group.

Table 3. Comparison of the left ear c-VEMP and o-VEMP parameters between groups

|                | Control Group | Outpatient Group | Inpatient Group | p-value* |
|----------------|---------------|------------------|-----------------|----------|
|                | Mean±SD | Median (Min-Max) | Mean±SD | Median (Min-Max) | Mean±SD | Median (Min-Max) | p-value** |
| c-VEMP p13 (ms) | 15,801±2,385a | 15a(12,67–23,33) | 16,115±2,405a | 15,67a(12,33–20,00) | 14,275±1,521b | 13,67b(12,33–19) | 0,001** |
| c-VEMP n23 (ms) | 23,857±2,96a | 23,33a(18,33–33) | 24,515±3,735a | 24,33a(19,33–36,33) | 22,79±1,726a | 22,67a(19,67–28,67) | 0,998** |
| p13-n23 latency (ms) | 8,058±2,32a | 8,67a(4,33–14) | 8,4±2,671a | 7,67a(5–17,33) | 8,51±1,03a | 8,67a(6–9,67) | 0,397** |
| p13-n23 amplitude (mV) | 163,247±49,994a | 170,5a(69,11–271,8) | 86,426±49,924b | 72b(23,37–247,20) | 112,604±43,769c | 112,4c(50,17–210,8) | <0,001** |
| o-VEMP n10 (ms) | 9,562±0,484a | 9,67a(9–10,67) | 10,202±1,207b | 9,67b(8,67–13,33) | 10,19±1,017b | 10b(9–14) | 0,006** |
| o-VEMP p15 (ms) | 14,771±0,82a | 14,67a(13–16,33) | 15,162±1,261a | 15,33a(13–17,33) | 15,248±1,278a | 15a(13,33–19,33) | 0,115** |
| n10-p15 latency (ms) | 5,21±1,007a | 5a(3,67–7,33) | 4,961±0,852a | 5a(3,33–6,67) | 5,057±0,951a | 4,67a(2,67–7,33) | 0,537** |
| n10-p15 amplitude (mV) | 14,571±7,706a | 12,82a(3,04–37,58) | 10,116±9,928b | 6,721b(1,37–35,30) | 7,768±5,835b | 5,605b(1,44–23,28) | <0,001** |

c-VEMP: Cervical vestibular-evoked myogenic potential, o-VMEP: Ocular vestibular-evoked myogenic potential, SD: Standard deviation, ms: millisecond, mV: millivolt, *p-values in bold indicate statistically significance, **: Kruskal-Wallis (Mann-Whitney-U with Bonferroni Correction in pairwise comparison).

Figure 3. Use of medications during COVID-19
The latency of n23 for the right ear and p13 for the left ear was statistically different between the three groups. We cannot fully explain this inverse ratio, especially for n23, but only this difference in p13 and/or n23 latency can be considered insignificant in our other results.

The functions of the vestibular system can be determined by testing reflex arcs of the cervical and extraocular muscles using c-VEMP and o-VEMP tools. The c-VEMPs test the vestibulo-collic reflex arc, and o-VEMPs assess the functions of the vestibulo-ocular reflex arc. Abnormal c-VEMP or o-VEMP measurements, including amplitude and latency, may indicate dysfunctions of the vestibulo-collic or vestibulo-ocular reflex arcs. The lack of o-VEMP and c-VEMP responses can demonstrate the damage that occurred in the vestibular system. Central diseases or demyelinating disorders of the vestibular nerve can cause delayed latencies of the vestibulo-collic or vestibulo-ocular reflex arcs. Today, VEMP tests are an essential component of the vestibular measurement battery and maintain a clinical evaluation of frequent vestibular diseases, including Meniere’s disease, vestibular neuritis, and superior canal dehiscence syndrome.

Since the beginning of the COVID-19 pandemic, case reports, reviews, brief clinical reports, and a limited number of clinical studies have been published on audiovestibular symptoms such as vertigo, tinnitus, and hearing loss in COVID-19 positive individuals. Aljasser et al. reported that the number of patients suffering from recognizable alterations in auditory symptoms was low and they could not find a statistically significant difference between COVID-19 patients and controls. They observed a high percentage of dizziness and vertigo among patients with COVID-19 compared to the control group. Malayala et al. declared six patients suffering from vestibular dysfunctions, but SARS-CoV-2 was detected in only four of the six cases. Nystagmus was defined in only two subjects. In this study, one or more audiovestibular complaints developed in 10 patients in the outpatient group. Most patients’ complaints regressed without the need for any treatment. In the inpatient group, 16 patients developed audiovestibular complaints. Although most of these patients returned to normal after COVID-19, when patients were called for control, hearing loss and tinnitus in one patient, dizziness in two patients, and vertiginous complaints in three patients continued.

A detailed vestibular examination is difficult to perform in cases of COVID-19, as complete protective equipment and careful disinfection of all surfaces are essential. On the other hand, the possibility of triggering vomiting during the evaluation increases the risk of contamination. The audiovestibular damage relevant to SARS-CoV-2 infection may be due to direct viral invasion of the inner ear or to a virus-activated immune mechanism. Our first study on the effects of COVID-19 on cochlear functions showed a reduced amplitude of TEOAEs in newborns exposed to the virus intrauterine. Our results supported the hypothesis of direct viral damage on cochlear hair cells. Another pathological mechanism has been considered to be the existence of a resistant inflammatory process with the generation of pro-inflammatory cytokines that could disrupt inner ear functions and the concurrent presence of an autoimmune mechanism.

Alterations in c-VEMP latencies and amplitudes in cases with COVID-19 may indicate that COVID-19 may influence the brainstem and vestibulo-collic arc and causes retardation in transmission on the arch. The absence of greater differences in gain asymmetries in VEMP tests indicates the critical compensation role of the central vestibular system.

Articles on vestibular system symptoms related to COVID-19 have been published in the literature. In a study conducted...
by Viola et al. based on a questionnaire, balance disturbances were observed in 34 patients after their diagnosis of COVID-19. They reported dizziness in 32 patients and acute vertigo attacks in 2 patients.20 SARS-CoV-2, similar to hepatitis B and C viruses, can directly affect the inner ear due to hypercoagulation observed in cases with COVID-19.21 Audiovestibular disturbances appear to develop due to vascular injury because the inner ear is structurally vulnerable to ischemia.22

Vestibular complaints are frequently observed in patients with COVID-19 during the recovery period, and these complaints are expected to be encountered more frequently in patient groups receiving intensive care treatment and inpatient group. This study is the first to measure the sequelae effects of COVID-19 on the audiovestibular system by considering disease severity. It has been shown that SARS-CoV-2 can leave permanent damage on the audiovestibular system. Considering our study, vestibular diseases should not be ignored in patients admitted after COVID-19 in outpatient clinic conditions. Vestibular rehabilitation methods should be discussed in the recovery period of these patients after COVID-19.

The limitations of this study are the limited number of patients and the lack of other tests to further evaluate the vestibular system.

In conclusion, SARS-CoV-2 may affect the inner ear and vestibular system. The study showed a statistical significance in the patient group compared to the controls, but we could not find any difference between the patient groups. The c-VEMP and o-VEMP tests are suitable and reliable test materials for evaluating audiovestibular sequelae of COVID-19.

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