Original Research

Evaluation of the effects of Covid-19 on cochleovestibular system with audiovestibular tests

Kazım Bozdemir, MD[1], Elif Ersoy Çallıoğlu, MD[2] , **Yüce İslamoğlu, MD[2]** ,
**Mehmet Kadir Ercan, MD[3], Fatma Eser, MD[4], Birsen Özdem, MD[4], Arda Kıraç, MD[2],
Dilara Bayazıt, MD[5], Rahmet Güner, MD[6] and Mehmet ali Babademez, MD[1]**

Abstract

Purpose: The purpose of the present study was to investigate the effects of COVID-19 on audiovestibular system with Transiently Evoked Distortion Otoacoustic Emissions (TOAE), Distortion Product Otoacoustic Emissions (DPOAE), video head impulse test (vHIT) and caloric test.
Methods: Audiovestibular findings of 24 patients with moderate/severe COVID-19 and 24 healthy controls were compared using pure tone audiometry, tympanometry, TOAE, DPOAE, caloric test, and vHIT.
Results: On audiometry, the pure tone averages of the COVID-19 patients were higher than the controls ($P = .038$). The TEOAE amplitudes at 4000 and 5000 Hz ($P = .006$ and $P < .01$), and DPOAE amplitudes at 3000, 6000, and 8000 Hz ($P < .001$, $P = .003$ and $P < .001$) were significantly lower in COVID-19 patients compared to the controls. On vestibular tests, there was no significant difference between the caloric test results of the patients and the controls ($P > .05$). On vHIT testing, amplitudes of right semicircular canal was found to be significantly lower in COVID-19 group compared to the control group ($P = .008$).
Conclusion: COVID-19 may affect inner ear functions causing a subtle damage in the outer hair cells and lateral semicircular canals. It must be kept in mind that COVID-19 may cause cochleovestibular problems.

Keywords

COVID-19, SARS-CoV-2, inner ear, cochlea, video head impulse test

Introduction

Viral infections may result in different forms and severities of hearing loss. Hearing loss may be due to the direct effect of the virus on the inner ear structures, or due to an indirect effect through immune-mediated mechanisms.[1-3]

SARS-CoV-2 infection or COVID-19 has caused a pandemic, and its exact symptoms, diagnosis and treatment are not clear even after 2 years.[4] It has been reported that COVID-19 may cause vertigo and hearing loss,[5,6] however, the mechanisms are not clear. It was suggested that arterial and venous thrombosis as well as microvascular occlusion might be associated with the pathogenesis of the disease.[7,8] Since the microcirculation of cochlea is vulnerable to thrombotic events, cochleovestibular symptoms may also be associated with thrombovascular events.

[1]Department of Otolaryngology-Head and Neck Surgery, Yıldırım Beyazıt University, Ankara, Turkey
[2]Department of Otolaryngology-Head and Neck Surgery, Ankara Bilkent City Hospital, Ankara, Turkey
[3]Department of Audiology, Ankara Bilkent City Hospital, Ankara, Turkey
[4]Department of İnfectious Diseases and Microbiology, Ankara Bilkent City Hospital, Ankara, Turkey
[5]Deparment of Audiology, İstanbul Medipol University, İstanbul, Turkey
[6]Department of İnfectious Diseases and Microbiology, Yıldırım Beyazıt University, Ankara, Turkey

Corresponding Author:
Elif Ersoy Çallıoğlu, Department of Otolaryngology-Head and Neck Surgery, Ankara Bilkent City Hospital, Bilkent Sehir Hastanesi KBB Klinigi, Ankara 06800, Turkey.
Email: elifersoy78@hotmail.com

This study aimed to investigate the effects of COVID-19 on cochleovestibular system by using audiovestibular tests.

Materials and methods

This prospective case-control study was approved by the local ethical committee of our tertiary medical center (No: E1-20-718/718). A total of 24 patients with mild/moderate COVID-19 who admitted between July 1, 2020 and August 30, 2020, and 24 healthy age- and sex-matched controls were included in the study. The ages of the participants ranged between 18 and 65 years.

There were 10 female and 14 male COVID-19 patients with a mean age of 45.7 ± 6.7 years. The control group consisted of 14 female and 10 male individuals with a mean age of 48.9 ± 6.9 years. None of the patients had any history of neuro-otologic disorders, ototoxicity, or chronic systemic conditions including diabetes mellitus and autoimmune disorders.

The patients were hospitalized, and none of them were intubated in the intensive care unit. All patients received favipiravir and anticoagulants as the standard of care. Favipiravir was administered p.o. 1600 mg/day on the first day, then 600 mg b.i.d. for 4 days, and .1 mg/day enoxaparin was injected subcutaneously.

The patients and the controls were evaluated with audiovestibular tests. The tests were performed 2 weeks after the positive SARS-CoV-2 PCR test results, after the patients had become negative.

Audiovestibuler testing

The tests included pure tone thresholds (GN Otometrics, Madsen, Astera-2, Denmark), tympanometry (GN Otometrics, Madsen New Zodiac, Denmark), acoustic reflexes, transient-evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) (GN Otometrics, Madsen Capella Cochlear Emissions Analyzer, Denmark). The vestibular tests were performed with videonystagmography (GN Otometrics, ICS Charter 200, Denmark), video head impulse test (v-HIT) (Interacoustics, Denmark), and air caloric test.

Statistical analysis

The analysis of the data was performed with IBM SPSS Statistics version 25.0 software (IBM Corporation, Armonk, NY, USA). Shapiro-Wilk test was used to investigate whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentages (%) while quantitative data were presented as mean ± standard deviation (SD) and medians (25th–75th percentiles). The mean differences between the groups were compared with Student's t test, and the Mann–Whitney U test was applied for the comparisons of not-normally-distributed variables. Categorical data were analyzed with continuity corrected $\chi 2$ or Fisher's exact tests, when appropriate.

A P value less than .05 was considered as statistically significant. However, the Bonferroni correction was
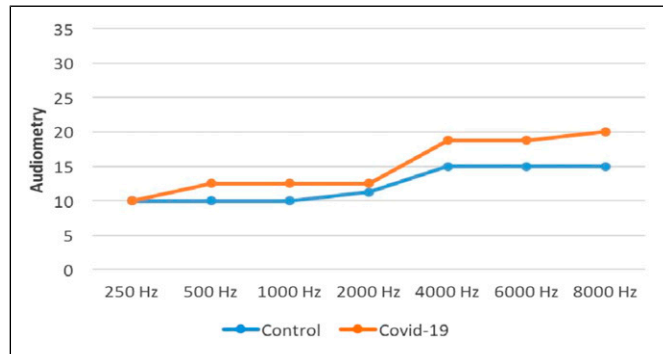
Figure 1. Pure tone audiometry results of COVID-19 patients and the controls.
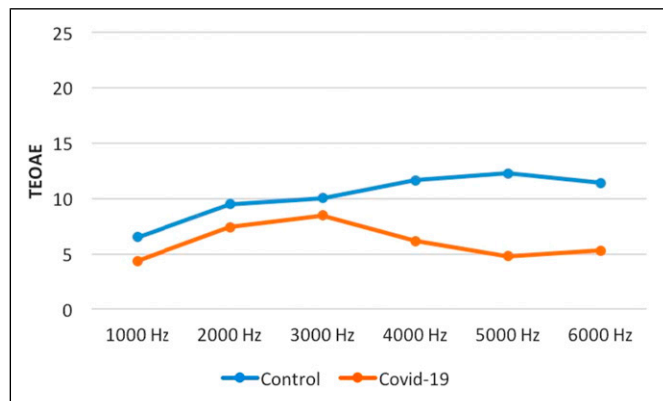
Figure 2. The results of TEOAEs in COVID-19 patients and the controls. TEOAE: Transient-evoked otoacoustic emissions.

performed for each possible multiple comparison, in order to control any Type I error.

Results

There was no significant difference between COVID-19 patients and the controls for their ages or genders ($P > .05$). All patients and controls had Type A tympanometries and normal acoustic reflexes.

The pure tone averages were 12.2 dBHL in COVID-19 patients and 13.1 dBHL in the controls. The pure tone averages of the patients were significantly higher than the controls ($P = .04$). The difference was due to the higher pure tone averages of the COVID-19 patients at 4 kHz ($P = .002$). Otherwise, there was no significant difference between the frequency-specific pure tones of the patients and the controls ($P > .05$) (Figure 1).

The amplitudes of TEOAEs were significantly lower in the patients compared to the controls at 4 kHz and 5 kHz ($P < .01$). The TEOAE amplitudes of the patients and the controls were similar ($P > .05$) except for the amplitudes at 4 kHz and 5 kHz (Figure 2 and Table 1).

There was no significant difference between the patients and the controls regarding the DPOAE amplitudes ($P > .05$)

Table 1. The results of TEOAEs in the study groups.

Frequencies, Hz	SNR of the Controls (n = 24)	SNR of the COVID-19 Patients (n = 24)	p †
1000	6.50 (4.69–8.99)	4.35 (2.86–8.73)	.205
2000	9.48 (5.00–13.06)	7.40 (4.56–13.79)	.404
3000	10.05 (7.53–15.30)	8.48 (5.64–12.58)	.252
4000	11.63 (9.30–15.23)	6.18 (2.06–12.21)	**.006**
5000	12.25 (9.80–15.36)	4.78 (1.45–8.20)	**<.001**
6000	11.40 (7.89–14.25)	5.30 (1.65–10.40)	.011

TEOAE: Transient-evoked otoacoustic emissions, SNR: Signal noise ratio.

except for the amplitudes at 3 kHz, 6 kHz, and 8 kHz. The DPOAE amplitudes were significantly lower in the COVID-19 patients compared to the controls at 3 kHz, 6 kHz, and 8 kHz ($P < .01$) (Figure 3 and Table 2).

Canal paresis was not evident in either in the COVID-19 patients or the controls on caloric testing. The caloric test results of the patients and the controls were not significantly different regarding the presence of canal paresis and directional preponderance ($P > .05$). The vHIT results did not indicate any significant difference between the study groups regarding the gains of the following semicircular canals: left anterior, right posterior, left lateral, right anterior, and left posterior ($P > .05$). The gains in the right lateral canals were .95 (range: .91–1.01) and .91 (range: .83–.94) in the controls and the COVID-19 patients, respectively. The gains of in right lateral semicircular canals were significantly lower in the patients compared to the controls ($P = .008$) (Table 3).

Discussion

COVID-19 may lead to multi-organ failure due possibly to inflammatory reactions or coagulopathy disorders.[8] It is also known that some viral infections may cause labyrinthitis and vestibular neuritis.[9] The inner ear damage may also be related to immune-mediated mechanisms.[1-3] There are limited number of reports regarding the effect of COVID-19 on audiovestibular system. Our study may help illuminating the effect of COVID-19 on inner ear functions.

The audiovestibular effects of COVID-19 have been reported.[6,10,11] Its effect on the cochlea was reviewed by Fancello et al.[10] Beukes et al.[11] reviewed the audiological symptoms of COVID-19, and reported the tinnitus rate as 8%. Mustafa et al.[6] reported elevated pure tone averages and decreased TEOAE amplitudes. The results of our study are comparable with the results of previous studies.

Unlike the studies mentioned above, Dror et al.[12] compared asymptomatic COVID-19 patients with a healthy control group using TEOAE, DPOAE, and ABR, and did not find any significant differences between the groups. However, their study group consisted of 12 cases who had asymptomatic SARS-CoV-2 infection. It may be supposed that different results may be
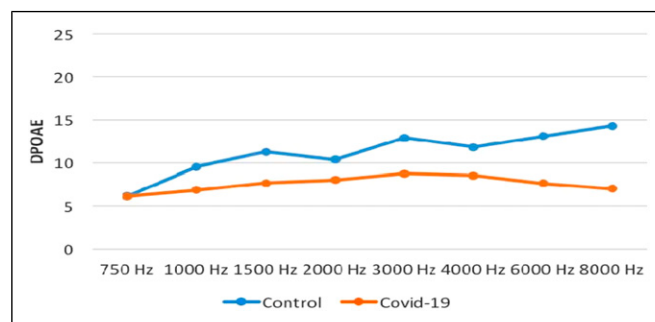
Figure 3. The DPOAE results in COVID-19 patients and the controls. DPOAE: Distortion product otoacoustic emissions.

obtained due to the inclusion of different patient groups into the study, and few number of patients may also affect the results.

Normal tympanometry results suggest that the middle ear is spared in COVID-19. That is, COVID-19 does not increase the probability of otitis media with effusion. Likewise, a normal functioning acoustic reflex arc suggests the integrity among the cochlear nerve, facial nerve, and their central connections in the brainstem.

We found significant differences between COVID-19 patients and controls for the TEOAE and DPOAE amplitudes. TEOAE shows the status of outer hair cells in a wide frequency range. DPOAEs may be helpful with regard to determination of subtle problems within the cochlea. In our study, the DPOAE amplitudes showed a tendency to decrease in the high frequencies. According to these findings, it is possible to say that COVID-19 may lead to outer hair cell damage mainly situated in the basal turn of the cochlea, and audiological problems associated with the disease are related to cochlea, rather than central auditory connections.

Dizziness was reported as the most common neurological symptom in the study of Mao et al,[13] indicating the neuroinvasive potential of SARS-CoV-2. Baig et al[14] suggested that the virus invades neural tissues via the angiotensin converting enzyme-2 receptors on the capillary endothelium. In addition to that, it was reported that viral invasion, hypoxia, hypercoagulopathy and immune-mediated reactions may play role in neuroinvasion.[15] A review published in 2021 reported the prevalence of hearing loss,

Table 2. The DPOAE results in COVID-19 patients and the controls.

Frequencies, Hz	SNR of the Controls (n = 24)	SNR of the COVID-19 Patients (n = 24)	p †
750	6.18 (3.98–9.31)	6.13 (5.14–6.81)	.628
1000	9.55 (3.71–12.73)	6.85 (6.36–7.19)	.080
1500	11.28 (6.80–13.80)	7.70 (6.74–9.70)	.083
2000	10.35 (8.88–14.04)	8.03 (6.58–10.33)	.007
3000	12.88 (10.43–14.90)	8.78 (7.15–11.03)	**<.001**
4000	11.80 (9.71–14.74)	8.53 (6.51–12.28)	.024
6000	13.10 (8.75–18.04)	7.65 (4.79–10.96)	**.003**
8000	14.30 (9.03–17.46)	7.03 (3.66–10.06)	**<.001**

DPOAE: Distortion product otoacoustic emissions, SNR: Signal-to-noise ratio. Data were expressed as median (25th–75th percentiles), † Mann–Whitney U test, a *P*-value less than .00625 was considered as statistically significant according to the Bonferroni correction.

Table 3. v-HIT results in the COVID-19 patients and the controls.

Semicircular Canals	Controls (n = 24)	COVID-19 Patients (n = 24)	p †
Left anterior	.95 (.90–.97)	.95 (.86–1.01)	.901
Right posterior	.93 (.90–.98)	.93 (.83–1.00)	.529
Right lateral	.95 (.91–1.01)	.91 (.83–.94)	**.008**
Left lateral	.97 (.90–1.01)	.90 (.83–.94)	.009
Right anterior	.93 (.88–.96)	.92 (.85–1.01)	.657
Left posterior	.92 (.90–.96)	.94 (.86–.97)	.804

v-HIT: Video head impulse test. Data were expressed as median (25th–75th percentiles), † Mann–Whitney U test, a *P*-value less than .0083 was considered as statistically significant according to the Bonferroni correction.

tinnitus and rotational vertigo as 6%, 14.8% and 7.2%, respectively.[16] Our study supports those findings.

On vestibular testing, no significant difference was found between the patients and controls regarding caloric test results, however decreased gain was found in 1 of the lateral semicircular canals on v-HIT. This was an interesting finding, because the caloric test helps in comprehending the activity of lateral semicircular canals. Thus, the findings of caloric test and v-HIT were not in agreement. However, it is also possible that the balance problems encountered in COVID-19 may be due to subtle changes in the semicircular canals or due to involvement of other parts of the vestibular apparatus.

Little et al.[17] have argued that agents like chloroquine, hydroxychloroquine, azithromycin, lopinavir, ritonavir, interferon, ribavirin and ivermectin which are used in COVID-19 treatment might have caused cochleovestibular symptoms. Therefore, cochleovestibular side effects of the medications should be kept in mind.

Our study has some limitations. Subjective vestibular assessment based on questionnaires was not carried out. We did so, since we wanted to evaluate the audiovestibular system with objective tests, because subjective evaluations may be misleading. The majority of COVID-19 patients complain of balance problems, as observed in the clinical practice. This subjective balance problem may be attributed to systemic effects of the viral disease rather than the audiovestibular effects of COVID-19. The patients who were included in this study had clinical data and audiograms in the database of our hospital. Therefore, the impact of a prior insult on the results could be eliminated.

Conclusion

COVID-19 may affect inner ear functions in the form of a subtle damage to the outer hair cells or lateral semicircular canals. The mild high-frequency sensorineural hearing loss encountered may remain unrecognized unless an audiogram is performed.

Author contribution

All authors declare that they all meet the author criteria.

Declaration of conflicting interests

Funding

Ethical Statement

Ethical approval was taken from the Ministry of Health and the local ethical committee. (protocol: E1-20-718).

Consent about participate and publication

All patients were informed about the study and their informed consents were obtained.

Data availability

Data is available on request from corresponding author.

ORCID iDs

Elif Ersoy Çallıoğlu 🔵 https://orcid.org/0000-0003-1860-0947
Yüce İslamoğlu, MD 🔵 https://orcid.org/0000-0002-1294-7088

References

1. Adler SP. Congenital cytomegalovirus screening. *Pediatr Infect Dis J.* 2005;24(12):1105-1106.

2. Budzilovich GN, Lieberman AN. Herpes zoster oticus and facial paralysis (Ramsay Hunt syndrome). *Clinicopathologic study and review of literatüre J Neurol Sci.* 1973;20(2):149-159.

3. Al Muhaimeed H, Zakzouk SM. Hearing loss and herpes simplex. *J Trop Pediatr.* 1997;43(1):20-24.

4. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun.* 2020;109:102433. doi:10.1016/.jaut.2020.

5. Trecca EMC, Gelardi M, Cassano M. COVID-19 and hearing difficulties. *Am J Otolaryngol.* 2020;41:102496. doi:10.1016/j. amjoto.2020.102496. [Epub ahead of print].

6. Mustafa MWM. Audiological profile of asymptomatic Covid-19 PCR-positive cases. *Am J Otolaryngol.* 2020;41:102483. doi: 10.1016/j.amjoto.2020.102483. [Epub ahead of print].

7. Petri M. Antiphospholipid syndrome. *Transl Res.* 2020;225: 70-81. doi:10.1016/j.trsl.2020.04.006. Epub 2020 May 12.

8. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med.* 2020 Jun;8(6):e46-e47.

9. Goddard JC, Fayad JN. Vestibular neuritis. *Otolaryngol Clin.* 2011;44:361-365. DOI: 10.1016/j.otc.2011.01.00.

10. Fancello V, Hatzopoulos S, Corazzi V, Bianchini C, Skarżyńska MB, Pelucchi S, et al. SARS-CoV-2 (COVID-19) and audio-vestibular disorders. *Int J Immunopathol Pharmacol.* 2021;35: 20587384211027373.

11. Beukes E, Ulep AJ, Eubank T, Manchaiah V. The Impact of COVID-19 and the pandemic on tinnitus: A systematic review. *J Clin Med.* 2021;10(13):2763.

12. Dror AA, Kassis-Karayanni N, Oved A, et al. Auditory performance in recovered SARS-COV-2 patients. *Otol Neurotol.* 2021;42(5):666.

13. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology.* 2020;77(6):683-690.

14. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* 2020;11(7):995-998.

15. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* 2020;87:18-22.

16. Almufarrij I, Munro KJ. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. *Int J Audiol.* 2021:1-11.

17. Little C, Cosetti MK. A narrative review of pharmacologic treatments for COVID -19: Safety Considerations and Ototoxicity. *Laryngoscope.* 2021;131(7):1626-1632.