Auditory Performance in Recovered SARS-COV-2 Patients

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Objective: While COVID-19 symptoms impact rhinology (anosmia) and laryngology (airways), two major disciplines of the otolaryngology armamentarium, the virus has seemed to spare the auditory system. A recent study, however, reported changes in otoacoustic emission (OAE) signals measured in SARS-COV-2 positive patients. We sought to assess the effect of COVID-19 infection on auditory performance in a cohort of recovered SARS-COV-2 patients and controls. To avoid a potential bias of previous audiological dysfunction not related to SARS-COV-2 infection, the study encompasses patients with normal auditory history. We hypothesized that if SARS-COV-2 infection predisposes to hearing loss, we would observe subtle and early audiometric deficits in our cohort in the form of subclinical auditory changes.
Study Design: Cross-sectional study.
Setting: Tertiary referral center.
Patients: The Institutional Review Board approved the study and we recruited participants who had been positive for SARS-COV-2 infection, according to an Reverse Transcription Polymerase Chain Reaction (RT-PCR) test on two nasopharyngeal swabs. The patients included in this study were asymptomatic for the SARS-COV-2 infection and were evaluated following recovery, confirmed by repeated swab testing. The control group comprised healthy individuals matched for age and sex, and with a normal auditory and otologic history.
Intervention(s): The eligibility to participate in this study included a normal audiogram, no previous auditory symptoms, normal otoscopy examination with an intact tympanic membrane, and bilateral tympanometry type A. None of our volunteers reported any new auditory symptoms following SARS-COV-2 infection. Ototacoustic emissions (OAE) and auditory brainstem response (ABR) measurements were used to evaluate the auditory function.
Main Outcome Measure(s): OAE and ABR measurements.
Results: We have found no significant differences between recovered asymptomatic SARS-COV-2 patients and controls in any of transitory evoked otoacoustic emission (TEOAE), distortion product otoacoustic emissions (DPOAE), or ABR responses.
Conclusions: There is no cochlear dysfunction represented by ABR, TEOAE, and DPOAE responses in recovered COVID-19 asymptomatic patients. Retrocochlear function was also preserved as evident by the ABR responses. A long-term evaluation of a larger cohort of SARS-COV-2 patients will help to identify a possible contribution of SARS-COV-2 infection to recently published anecdotal auditory symptoms associated with COVID-19. **Key Words:** Auditory brainstem response—Coronavirus disease—Hearing—Otoacoustic emission—Severe acute respiratory syndrome coronavirus 2.

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The rapid emergence of the COVID-19 pandemic has led to extensive global efforts to characterize the hallmarks of a previously unknown disease (1). During the early days of the pandemic, it was already clear that some symptoms such as fever, dry cough, respiratory distress, and fatigue were prominently linked to acute infection (2). With the global accelerated spread of COVID-19, additional associated symptoms such as anosmia (i.e., loss of the sense of smell) started to be reported in the literature (3), while additional symptoms were initially

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interpreted as incidental, with no clear causation or pathophysiological mechanism (4).

Viral infections are a well-known trigger for auditory and vestibular dysfunction and must be considered when taking the history of patients who present with sudden hearing loss or acute vestibular dysfunction. A number of viral pathogens, including cytomegalovirus (CMV), Herpes simplex virus (HSV), measles, and rubella, have been linked with sensorineural deafness (5–8). The pattern of hearing loss associated with these viral infections is variable and ranges from mild to profound hearing impairment, which can be unilateral or bilateral, and may appear from birth to adulthood (9). Viral-related auditory compromise may also present as progressive hearing loss with gradual deterioration of hearing over years following the initial insult, as is the case for congenital CMV infections (10). While the pathophysiological mechanisms underlying auditory sequelae of viral infections are not fully elucidated, some suggest direct infection of the inner ear, while others implicate an indirect deleterious effect on the auditory pathway or compromised microvasculature of the cochlea and vestibulo-cochlear nerve (CN VIII) (9).

A recent cross-sectional study reported a potential link between SARS-CoV-2 infection and hearing loss as shown by abnormal hearing thresholds at 4 to 8 kHz, and lower transient evoked otoacoustic emissions (t-OAE) amplitude (11).

In this study, we aimed to further assess the possible effect of SARS-CoV-2 infection on auditory performance.

MATERIALS AND METHODS

Participants

Inclusion criteria were: 1) recovered COVID-19 patients following asymptomatic infection 2) current normal hearing, 3) normal tympanometry, and 4) no audiological complaints or noise exposure. Exclusion criteria were previous auditory symptoms, abnormal otoscopy examination, medication use, and self-reported tinnitus either novel or long-standing. From an initial group of 12 patients recovered from asymptomatic COVID-19 infection, eight met the inclusion criteria (average age of 44; ranging from 32 to 61 yr). Another eight age and sex-matched subjects served as a control group (average age 45.75; range, 29–60).

Procedures

All participants underwent several assessments:

1). Pure tone threshold audiometry testing was used to assess each participant's threshold of hearing for pure tones. Pure tone threshold audiometry included air-conduction measurements at octave intervals from 250 Hz through 8 kHz. A GSI-61 (Grason-Stadler, MN) audiometer was used with supra-aural headphones TDH-50P (Telephonics, NY) in a sound-proof room. All subjects had normal hearing with thresholds less than or equal to 25 dB. (American National Standards Institute Standards, 2004).

2). Tympanometry testing at 226 Hz with an Interacoustics Titan Tympanometer System was used to exclude any external or middle ear pathology. All participants had a Type A (Jerger tympanometry classification) tympanogram with normal middle ear pressure (0–100 daPa), compliance (0.37–1.66 mmho/ml), and volume (0.9–2 cm^3).

3). Transient evoked otoacoustic emissions (TEOAE) data were collected using an Interacoustics Titan OAE platform. The recorded TEOAE signal was evoked by a non-linear click with an intensity of 83 dB peSPL. The analyzed TEOAE parameters were: response reproducibility more than or equal to 90% for the frequencies 0.5, 1, 2, 3, and 4 kHz; signal to noise ratio (SNR) is more than or equal to six. The TEOAE amplitude for each frequency was obtained for both ears (12).

4). Distortion product otoacoustic emissions (DPOAE) were collected using an Interacoustics Titan OAE platform. The recorded DPOAE signal was evoked by two pure tones: F1& F2 at a 1.22 ratio, intensity of L1 = 65 dB SPL, and L2 = 55 dB SPL. The analyzed DPOAE parameter was SNR is more than or equal to six for the frequencies 0.5, 1, 2, 3, 4, 6, and 8 kHz. DPOAE amplitude for each frequency was obtained for both ears (12).

5). Neurological auditory brainstem response (ABR) waveforms were recorded using a Biologic Navpro system in an acoustically quiet room. The subjects were asked to lie down in a supine position on a bed to allow them to relax. After cleaning the skin, surface Spes Medica electrodes were attached. The positive electrode was placed on the vertex (Cz), the negative electrode was placed on the ipsilateral mastoid, and the common electrode was placed on the contralateral mastoid. The electrode impedance was below 2 kΩ. A high-level click stimulus was presented through an inserted earphone at 80 dB nHL with a high pass of 100 Hz and a low pass of 3 kHz, duration of 100 μs, and alternating polarity. A resolution of ±10 μV was used as a threshold for artifacts and the stimulus presentation rate was 11.1 clicks per second. The waves were repeated to test reproducibility. The main parameters analyzed were the absolute latency values of the waves I, III, and V.

Comparisons of OAE data between the two groups were made by a two-way Analysis of variance (ANOVA) followed by a Holm- Šídák post-hoc test for multiple comparisons. ABR test results of SARS-CoV-2 recovered patients were compared with standard nomograms. All statistical tests and figures were generated in Prism 8 software (GraphPad, CA). A statistical power analysis on the DP amplitude values observed for 500 Hz in the right ear was performed. We observed a mean of 4.0 with a standard deviation of 7.5 in the control group. According to these data and a cohort size of eight subjects in each group, a mean of –4.39 in the test group would be detected as significant with an α of 0.05 and $1-\beta$ of 0.80. We performed a similar analysis on our TE amplitude data at 500 Hz. The mean of the control group was 7.8 and the standard deviation was 4.4. A mean of 2.62 in the test group would be detected with an α of 0.05 and $1-\beta$ of 0.80. Statistical power analyses were performed using http://powerandsamplesize.com/

RESULTS

There were no statistically significant differences observed between the study and control groups in TEOAE SNR for the frequencies 1, 2, 3, and 4 kHz

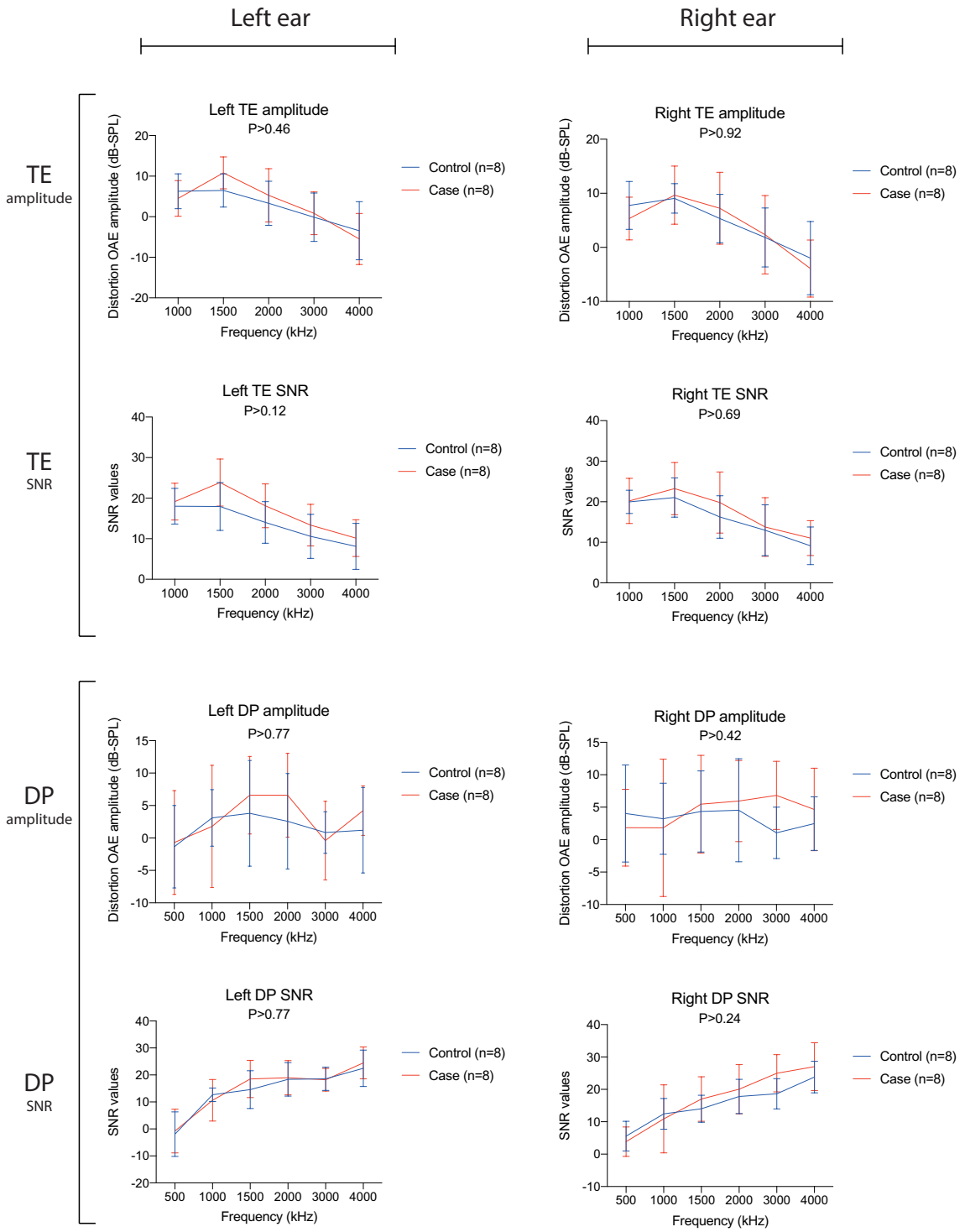

FIG. 1. No differences in TEOAE and DPOAE between SARS-CoV-2 recovered patients and controls. Distortion product and transient evoked OAE amplitudes and SNR values. Plots show mean ± SD. Statistical test by 2-way ANOVA with Holm-Šídák correction for multiple comparisons. *p* values noted are the lowest calculated for each test. DPOAE indicates distortion product otoacoustic emissions; TEOAE, transitory evoked otoacoustic emission.

(Fig. 1). Similarly, there were no statistically significant differences in TEOAE amplitude for the frequencies 0.5, 1, 2, 3, and 4 kHz by two-way ANOVA test with Holm-Šídák correction for multiple comparisons (Supplementary table 1, http://links.lww.com/MAO/B185). In addition, two-way ANOVA test with Holm-Šídák correction for multiple comparisons analysis did not detect any statistical significant differences from the

control in DPOAE SNR for the frequencies 1, 2, 3, and 4 kHz or DPOAE amplitude for the frequencies 0.5, 1, 2, 3, and 4 kHz (Supplementary table 1, http://links.lww.com/MAO/B185). ABR waveforms of all SARS-CoV-2 recovered patients were normal as compared with standard nomograms (Supplementary table 2, http://links.lww.com/MAO/B186).

DISCUSSION

SARS-CoV-2 is a newly emerged pathogen with far-reaching economic and healthcare consequences. The resultant COVID-19 disease is for the most part, a mild respiratory illness, but its long-term complications still need to be elucidated. An Austrian report suggested that even mildly symptomatic patients had severe pulmonary changes on radiography 5 to 6 weeks after recovery (13). As COVID-19 is a novel and evolving disease, high quality studies about long-term complications are scarce and speculations have been based on published reports concerning experience with similar viruses.

Previous corona virus outbreaks in recent years include the MERS-CoV and SARS CoV, both of which are genetically similar to Sars-CoV-2 and cause respiratory illness. Patients who recovered from these viruses displayed a higher tendency to hyperlipidemia, hyperglycemia, hypocortisolism, chronic fatigue, and depression than matched controls (14). Another study postulated that late manifestations of COVID-19 could be insomnia, cognitive decline, and even Parkinson or Alzheimer disease (15). None of these studies suggested a potential link between previous corona virus outbreaks and hearing impairment, either short or long-term following the infection.

Acute phase otolaryngology-related COVID-19 symptoms include sore throat, rhinorrhea, nasal congestion, throat congestion, tonsil edema, enlarged cervical lymph nodes, dizziness, and anosmia, all of which are expected to recede without sequelae (16). In addition, a number of reports have raised concerns that SARS-CoV-2 could have a long-lasting effect on the auditory system. Asymptomatic patients with COVID-19 were shown to have significantly lower hearing thresholds at 4, 6 and 8 kHz, as well as lower TEOAE averages compared with matched controls (11). However, the differences between the groups could be explained by preferential exclusion of patients with abnormal hearing from the control group. Another report described an elderly woman who recovered from severe COVID-19 infection and presented with sensorineural hearing loss (17). This case prompted speculation that COVID-19 could enhance oxidative stress and promote acute thrombosis, which in turn, could cause irreparable damage to the CNS hearing center (18). Another case report described a 29-year old man who presented with sudden sensorineural hearing loss (SSHNL) and was found positive for COVID-19 even though he displayed none of the known COVID-19 symptoms at diagnosis (19). In addition, an Iranian case series study concerned three patients who presented with SSHNL and were found positive for COVID-19 (20). It has yet to be clarified whether the COVID-19 infection in these patients was an incidental finding or whether SSHNL could be a presenting symptom of COVID-19.

The notion that viruses can damage the auditory system is by no means a new concept. Viruses such as mumps, cytomegalovirus (CMV), Epstein-Barr, and many others have long been linked to sensorineural hearing loss, mainly in the pediatric population (9,10,21). CMV was suggested to trigger an immune-mediated response that leads to profound hearing loss (10). Rubella, on the other hand, is thought to directly damage the cochlear epithelium and stria vascularis (22), and varicella zoster virus was shown to impair the vestibulocochlear nerve. The underlying mechanism responsible for the auditory damage by other viruses, remains unclear (23). If SARS-CoV-2 is indeed responsible for sensorineural hearing loss, this raises the question of the potential mechanisms involved.

Acquired auditory neuropathy (AAN) is a group of hearing disorders characterized by aberrant auditory conduction despite normal cochlear function. Demyelinating disorders have been suggested as the cause for AAN (24). Guillan-Barré syndrome (GBS), a demyelinating disorder, was shown to cause hearing loss with aberrant brainstem auditory evoked potentials, characteristic of AAN (25). A recent report described a possible causative relationship between COVID-19 and GBS (26), suggesting that COVID-19 could cause sensorineural hearing loss via auditory nerve dysfunction, as in AAN.

Another potential mechanism for AAN among patients with COVID-19 infection is the development of a brain ischemic infarct or hemorrhage. These are well-described complications of patients presenting with severe COVID-19 infection. It is possible that symptomatic COVID-19 infections may alter neurologic ABR signals and prolong interpeak wave latency. These in turn may be related to AAN if auditory pathways are involved, although this theory should be examined further in a cohort of patients with symptomatic severe COVID-19 infection.

Although not a routinely quantitative measurement, the normal OAE results obtained in the present study indicate that the participants' cochlear amplifier is at least at near normal function. The reason that this study did not replicate previously reported results (11), may be because the reduction in TEOAE previously reported in the COVID-19 group was a consequence of selection bias of hearing impaired individuals specifically in that group (11). Interestingly, the reported results do not support the AAN theory because in such cases we would expect a normal OAE response coupled with abnormal ABR testing, while the patients in this cohort demonstrated abnormal OAE signals (ABR tests were not done). The normal results of ABR testing and the OAE response of SARS-COV-2 recovered patients in the current study is consistent with auditory pathway integrity.

Although the present study advocates against a possible short-term auditory effect of asymptomatic COVID-19 infection, such an association cannot be entirely excluded

due to study limitations. Firstly, subtle differences between study groups could be missed owing to the small sample size. Secondly, only patients with asymptomatic SARS-COV-2 viral infection and no previous auditory dysfunction were recruited. It is possible however that patients with severe SARS-COV-2 infection may develop auditory deficits not seen in the asymptomatic patients. Likewise, patients with a known history of hearing impairment before SARS-COV-2 infection may experience an exacerbation of existing hearing impairment. Furthermore, during the early days of the COVID-19 pandemic, some treatment protocols proposed Plaquenil, a known ototoxic drug, that may lead to auditory dysfunction secondary to medical treatment. Patients' comorbidities, dependency on ventilation, impaired oxygenation, and prolonged intubation during SARS-COV-2 infection may potentially lead to long-term neurological sequela including hearing deficit. Lastly, it is possible that idiosyncratic hearing impairment may follow SARS-COV-2 viral infection in selected affected individuals. If that is the case, exploring the prevalence of hearing loss, rather than the mean OAE values, in a larger cohort, is more likely to identify such an effect.

CONCLUSION

This study was prompted by published reports that suggested COVID-19 could affect the auditory system, along with the proposed underlying mechanism. In the present study we found no difference in measurements of average OAE or ABR, between normal hearing asymptomatic COVID-19 recovered patients and matched controls. Further studies examining symptomatic COVID-19 patients and hearing-impaired individuals should be performed to examine the proposed correlation between hearing defects and COVID-19 infection further. Our current results suggest that large scale hearing screening of recovered asymptomatic patients may not be indicated, although further data regarding COVID-19 and hearing impairment should be collected for specific populations such as symptomatic patients who suffered severe infections, patients with neurological complications, children, and the elderly.

REFERENCES

1. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China - key questions for impact assessment. *N Engl J Med* 2020;382:692–4.
2. Tabata S, Imai K, Kawano S, et al. Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. *Lancet Infect Dis* 2020;20:1043–50.
3. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, Jacquerioz F. Clinical features of covid-19. *BMJ* 2020;369:m1470.
4. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? *New Microbes New Infect* 2020;35:100669.
5. Lee JY, Bowden DS. Rubella virus replication and links to teratogenicity. *Clin Microbiol Rev* 2000;13:571–87.
6. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The ''silent'' global burden of congenital cytomegalovirus. *Clin Microbiol Rev* 2013;26:86–102.
7. Schwarz ER. Consequences of perinatal infections with rubella, measles, and mumps. *Curr Opin Virol* 2017;27:71–7.
8. Westerberg BD, Atashband S, Kozak FK. A systematic review of the incidence of sensorineural hearing loss in neonates exposed to Herpes simplex virus (HSV). *Int J Pediatr Otorhinolaryngol* 2008;72:931–7.
9. Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. *Trends Hear* 2014;18:. 2331216514541361.
10. Schraff SA, Schleiss MR, Brown DK, et al. Macrophage inflammatory proteins in cytomegalovirus-related inner ear injury. *Otolaryngol Head Neck Surg* 2007;137:612–8.
11. Mustafa MWM. Audiological profile of asymptomatic Covid-19 PCR-positive cases. *Am J Otolaryngol* 2020;41:102483.
12. Hall JW, Dhar S. *Otoacoustic Emissions: Principles, Procedures, and Protocols (Core Clinical Concepts in Audiology)*, 1st ed. San Diego, CA: Plural Publishing; 2011.
13. Hartig F. Tauchen nach Covid-19-Erkrankung? Wetnotes.eu; 2020. Available at: https://www.wetnotes.eu/tauchen-nach-covid-19-erkrankung/. Accessed July 7, 2020.
14. Dasgupta A, Kalhan A, Kalra S. Long term complications and rehabilitation of COVID-19 patients. *J Pak Med Assoc* 2020;70:S131–5.
15. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis* 2020;76:3–19.
16. Krajewska J, Krajewski W, Zub K, Zatoński T. COVID-19 in otolaryngologist practice: a review of current knowledge. *Eur Arch Otorhinolaryngol* 2020;277:1885–97.
17. Sriwijitalai W, Wiwanitkit V. Hearing loss and COVID-19: A note. *Am J Otolaryngol* 2020;41:102473.
18. Cure E, Cumhur Cure M. Comment on ''Hearing loss and COVID-19: A note''. *Am J Otolaryngol* 2020;41:102513.
19. Kilic O, Kalcioglu MT, Cag Y, et al. Could sudden sensorineural hearing loss be the sole manifestation of COVID-19? An investigation into SARS-COV-2 in the etiology of sudden sensorineural hearing loss. *Int J Infect Dis* 2020;97:208–11.
20. Karimi-Galougahi M, Naeini AS, Raad N, Mikaniki N, Ghorbani J. Vertigo and hearing loss during the COVID-19 pandemic - is there an association? *Acta Otorhinolaryngol Ital* 2020. doi: 10.14639/0392-100X-N0820. [Online ahead of print].
21. Lindsay JR, Davey PR, Ward PH. Inner ear pathology in deafness due to mumps. *Ann Otol Rhinol Laryngol* 1960;69:918–35.
22. Töndury G, Smith DW. Fetal rubella pathology. *J Pediatr* 1966;68:867–79.
23. Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry* 2001;71:149–54.
24. Kaga K. Auditory nerve disease and auditory neuropathy spectrum disorders. *Auris Nasus Larynx* 2016;43:10–20.
25. Schiff JA, Cracco RQ, Cracco JB. Brainstem auditory evoked potentials in Guillain-Barré syndrome. *Neurology* 1985;35:771–3.
26. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. *J Clin Neurosci* 2020;76:233–5.