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No lasting impact of Covid-19 on the auditory system: a prospective cohort study

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Main Article

Dr Z Jafari takes responsibility for the integrity of the content of the paper

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Abstract

Objective. Otological complications are considered early symptoms of severe acute respiratory syndrome coronavirus-2; however, it is unknown how long these symptoms last and whether the virus leaves any hearing disorders post-recovery.

Methods. This prospective cohort study comprised 31 mild or moderate confirmed coronavirus disease 2019 patients and 26 age-matched control peers (21–50 years old). Patients were questioned about their otological symptoms, and their hearing status was assessed during one month post-diagnosis.

Results. Patients showed a significantly higher rate of otological symptoms (hearing loss, ear fullness, ear pain, dizziness or vertigo, communication difficulties, and hyperacusis) versus the control group ($p \leq 0.022$). The symptoms resolved early, between 2 and 8 days after their appearance. No significant differences were observed between the two groups in pure tone and extended high-frequency audiometry, transient evoked otoacoustic emissions, distortion product otoacoustic emissions, or auditory brainstem response following recovery.

Conclusion. The findings indicate that, in mild to moderate coronavirus disease 2019 cases, otological symptoms resolve within a week, and the virus has no lasting impact on the auditory system.

Introduction

Several viral epidemics of coronaviruses have been reported during the past two decades. Seven types of coronaviruses infect humans: 229E, NL63, OC43, HKU1, Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and, most recently, SARS-CoV-2). Existing evidence indicates that 229E, NL63, OC43 and HKU1 mainly lead to upper respiratory tract infections, with symptoms such as a runny nose, sore throat, fever and cough.[1] The other three coronaviruses (Middle East respiratory syndrome coronavirus, SARS-CoV and SARS-CoV-2) can cause life-threatening respiratory failure.[2]

Severe acute respiratory syndrome coronavirus-2 causes non-specific symptoms, and its presentation ranges from no symptoms (asymptomatic) to severe pneumonia. Real-time polymerase chain reaction is a diagnostic test for coronavirus disease 2019 (Covid-19), which consists of the collection of upper respiratory samples via nasopharyngeal and oropharyngeal swabs.[3] The typical signs and symptoms, which generally develop 5–6 days after infection (range, 1–14 days), include fever, dry cough, fatigue, shortness of breath, sore throat, headache, dizziness, myalgia or arthralgia, chills, nausea or vomiting, and nasal congestion. Regarding disease severity, whereas most patients with a confirmed diagnosis (80 per cent) show mild to moderate disease and recover, some patients develop severe (14.0 per cent) or critical (6.0 per cent) health conditions.[4,5] Overall, individuals aged over 60 years and those with underlying conditions (e.g. hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer) are at the highest risk of developing severe or critical symptoms and of dying.[6]

Coronavirus disease 2019 also can cause extrapulmonary complications, including sensory and neural symptoms such as otological manifestations (e.g. hearing loss, tinnitus, and dizziness or vertigo), olfactory and/or gustatory dysfunction,[7–9] and long-term neurological disorders.[10,11] The anosmia and ageusia symptoms have been recognised as key symptoms of the disease;[8] these last between 7 and 14 days after their appearance.[12] Mechanisms of neuro-invasion may result from direct brain invasion,[13] or from indirect effects of the virus on the peripheral and central nervous system.[10,14] The angiotensin-converting enzyme 2 (ACE2) receptor is characterised as a functional receptor for SARS-CoV.[15] This virus was found to be more pathogenic, potentially because of its 10- to 20-fold increased binding affinity to ACE2.[16,17]

According to two recent systematic reviews and meta-analysis papers, the event rate of otological symptoms (e.g. hearing loss, tinnitus and dizziness) is statistically significant in patients with SARS-CoV-2.[18,19] Both papers, however, underscore that the results should

be interpreted with caution given the low level of evidence (i.e. single-group prospective, cross-sectional or retrospective studies with no control group), weakness in data collection (i.e. using self-reports and/or medical records), high heterogeneity among studies, and no information regarding the rate of improvement after recovery. Likewise, apart from some case reports[20–25] and case series[26] of patients with sudden sensorineural hearing loss (SNHL) and tinnitus, no well-designed study using standard behavioural and objective hearing assessments in symptomatic patients has shown whether SARS-CoV-2 results in hearing disorders post-recovery. Two cross-sectional studies compared asymptomatic cases with a control group. In one of these studies, slight high-frequency SNHL and reduced transient evoked otoacoustic emissions (TEOAE) were observed;[27] in contrast, the other study showed no significant differences in TEOAE, distortion product otoacoustic emissions (DPOAE) or auditory brainstem responses (ABR).[28]

Considering the controversies and limitations of previous studies, we set up a prospective cohort study using standard behavioural and objective hearing assessments on confirmed mild or moderate cases of Covid-19 in order to address some fundamental questions. These questions were: (1) is the prevalence of early otological symptoms (e.g. hearing loss, ear fullness, ear pain, dizziness or vertigo, communication difficulties, hyperacusis, and tinnitus) significantly increased in patients with Covid-19 relative to the control group, and how long do these symptoms last?; (2) do the results of subjective and objective hearing assessments (e.g. pure tone audiometry, extended high-frequency audiometry, immittance audiometry, TEOAE, DPOAE and ABR) show a lasting effect of Covid-19 on the auditory system post-recovery?; and (3) how is the patients' general health compared with the control group following recovery?

Materials and methods

Participants

Fifty-seven individuals were included in this study. These consisted of: 31 symptomatic patients with a positive real-time polymerase chain reaction test result for SARS-CoV-2 (21 females, with a mean age (± standard deviation) of 33.87 ± 9.85 years, and an age range of 21–50 years), and 26 age-matched individuals (17 females, with a mean age of 32.28 ± 9.87 years, and an age range of 21–50 years) without a history of SARS-CoV-2 infection. Participants in the Covid-19 group had a mild or moderate level of the disease and were followed up within one month after diagnosis. These were non-pneumonia cases or mild pneumonia patients who recovered at home (mild disease) or were monitored closely for recovery (moderate disease: the presence of clinical or radiographic evidence of lower respiratory tract disease, but with a blood oxygen saturation of 94 per cent or higher).[4,5] All participants were healthcare workers at two hospitals (Ayatollah Kashani Hospital and Khorshid Hospital) affiliated with the Isfahan University of Medical Sciences, Iran, who were recruited through research flyers.

The annual records of basic medical examinations including hearing records (e.g. pure tone and speech audiometry) of participants were accessible at their workplace. In addition, a case history was taken from all participants, and only those with no previous record of the following symptoms or diseases were included in the study: hearing loss, tinnitus, dizziness, family or childhood history of hearing loss, chronic ear infection, ototoxic medication, ear diseases, ear surgery, diabetes, high blood pressure, stroke, hypertension, and cardiovascular diseases. In addition, none of the participants worked or had previously worked in noisy environments. The two groups were matched in terms of pre-coronavirus hearing thresholds within normal limits.[29]

Patients were monitored weekly for the appearance and permanence of otological symptoms (e.g. hearing loss, ear fullness, ear pain, dizziness or vertigo, communication difficulties, hyperacusis, and tinnitus) via telephone calls, and their hearing status was assessed through a comprehensive test battery in the fourth week post-diagnosis. A similar process was followed for the control group in the same period.

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional guidelines on human experimentation (Isfahan University of Medical Sciences, code number: IR.MUI.RESEARCH.REC.1399.349), and with the Helsinki Declaration of 1975, as revised in 2008. Participants were fully aware of the study content and gave their consent prior to participation.

Hearing assessments

Pure tone and extended high-frequency audiometry

The calibration of all hearing equipment was confirmed before beginning the study. Pure tone audiometry was conducted using Telephonics® TDH39 earphones at nine audiometric frequencies (0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 kHz). Extended high-frequency audiometry was performed using Koss R80 earphones at 12 and 16 kHz. The audiometry was carried out in both ears using a two-channel clinical audiometer (AC40; Interacoustics, Middelfart, Denmark), employing the modified Hughson–Westlake ascending–descending procedure as previously reported.[30]

Immittance audiometry

Tympanometry and ipsilateral and contralateral acoustic startle reflex tests at 0.5, 1, 2 and 4 kHz were conducted in both ears (with an AT235 device; Interacoustics) using a 226 Hz low-frequency probe tone.

Otoacoustic emissions

Transient evoked otoacoustic emissions (TEOAE) and distortion product otoacoustic emissions (DPOAE) are sensitive tests for the cochlear function that assess the integrity of the outer hair cells of the inner ear.[31]

Using a microphone located within a probe placed in the external auditory canal with an Integrity V500 device (Vivosonic, Ontario, Canada), TEOAE and DPOAE were recorded in a double-walled soundproof cabin with dimmed lights and a standard noise level.[32] Participants were asked to sit on a comfortable chair in a relaxed position and to breathe normally without any effort so as to produce the least possible additional noise during the recording session.

The eliciting stimulus was a non-linear click delivered at about 80 dB peak sound pressure level (SPL) in the ear canal. The spectrum analyser was triggered at 4 ms after stimulus presentation to prevent acoustic ringing of the input stimuli. The temporal window was set at 20 ms, and 260 averages were recorded in total.

The TEOAEs were analysed in frequency bands centred at 1, 2, 3 and 4 kHz, and were considered present when the

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reproducibility and signal-to-noise ratio were 70 per cent or greater and 6 dB, respectively. The DPOAEs were recorded using two pure tone stimuli (i.e. F1 and F2; F2/F1 = 0.5) at different intensities (L1: 65 dB SPL and L2: 55 dB SPL). The DPOAE amplitudes were analysed in frequency bands centred at 0.5, 0.75, 1, 1.5, 2, 3, 4 and 6 kHz, and responses with signal-to-noise ratios of 6 dB or greater were accepted.[33]

Auditory brainstem responses

The click ABR test, using insert earphones (model ER-3A; Etymotic Research, Elk Grove Village, Illinois, USA) and the Integrity V500 device, was conducted in a double-walled soundproof cabin with dimmed lights and a standard noise level.[32] Participants were asked to relax on a comfortable bed with their eyes closed during the test.

The electrode array was: site Fz for the non-inverting electrode, the earlobe for the inverting electrode and site FPz for the ground electrode.[34] The impedance of all electrodes was less than 3 kV and within 1.5 kV of each other.

A 100 ms click stimulus with alternate polarity at 80 dB SPL (peak equivalent), with a standard rate (21.1 Hz) and a high rate (51.1 Hz), was used for stimulus presentation. Two blocks of 2000 artefact-free sweeps were collected for each participant. The click ABR waves of two replications were visually marked as waves I, III and V.[35,36]

General Health Questionnaire

The 28-item General Health Questionnaire was completed by patients to assess their general health compared with that of the control group post-recovery. It is a self-administered instrument, based on an exploratory factor analysis of the original 60-item General Health Questionnaire.[37] This questionnaire is widely used for screening and assessing mental symptoms and psychosocial wellbeing, and can distinguish psychiatric patients from individuals who consider themselves to be healthy.[38] This questionnaire covers four main areas: somatic symptoms (questions 1–7), anxiety and insomnia (questions 8–14), social dysfunction (questions 15–21), and severe depression (questions 22–28).[37]

The participants were asked to rate their general health over the past few weeks, using a four-point scale: 0 = not at all; 1 = no more than usual; 2 = rather more than usual; and 3 = much more than usual.[39] The minimum and maximum total scores are 0 and 84, respectively, and higher General Health Questionnaire-28 scores indicate increased levels of distress. The Persian version of General Health Questionnaire-28 was used in this study.[40]

Statistical analysis

The statistical analyses were performed using SPSS Statistics 26.0 software, with a significance level of 0.05 or lower. The Kolmogorov–Smirnov test demonstrated a normal distribution of data in the study groups ($p \leq 0.113$). The Mann–Whitney U test was used to compare the two groups for otological symptoms during the past month. A multivariate analysis of variance test was applied to compare the two groups for: hearing thresholds; static compliance of the eardrum; middle-ear pressure; acoustic startle reflexes; TEOAE and DPOAE responses; absolute latencies, inter-peak intervals and peak amplitudes of ABR waves I, III and V; and total and subscale scores of the General Health Questionnaire-28. The F values, p values, estimations of the effect size (partial η^2) and observed power have been reported in statistical analyses. As no significant difference was observed between the right and left ears ($p \geq 0.163$), the data were pooled for the statistical analyses.

Results

Several patients with Covid-19 reported otological symptoms during their illness, including hearing loss ($n = 7$, 22.6 per cent: two right, three left and two bilateral), a feeling of ear fullness ($n = 7$, 22.6 per cent: two right, three left and two bilateral), ear pain ($n = 6$, 19.4 per cent: one right, three left and two bilateral), dizziness or vertigo ($n = 7$, 22.6 per cent), communication difficulties ($n = 3$, 9.7 per cent), hyperacusis ($n = 3$, 9.7 per cent: one left and two bilateral) and tinnitus ($n = 2$, 6.45 per cent: one right and one bilateral). The frequencies of experiencing hearing loss ($p \leq 0.001$), ear fullness ($p \leq 0.001$), ear pain ($p = 0.001$), dizziness or vertigo ($p \leq 0.001$), communication difficulties ($p = 0.022$), and hyperacusis ($p = 0.022$) were significantly increased in the Covid-19 group relative to the control group, which had no reports of such symptoms for the same period (Figure 1a). All otological symptoms lasted 2–8 days after their appearance, except for two cases with tinnitus that did not improve.

No significant differences were observed between the two groups, at either the standard or high rate of stimulus presentation, in any of the audiological assessments, including: pure tone and extended high-frequency thresholds ($F = 1.150$, $p = 0.339$, $\eta^2 = 0.165$, power = 0.570) (Figure 1b); static compliance of the eardrum ($F = 1.659$, $p = 0.201$, $\eta^2 = 0.015$, power = 0.248); middle-ear pressure ($F = 0.240$, $p = 0.625$, $\eta^2 = 0.002$, power =

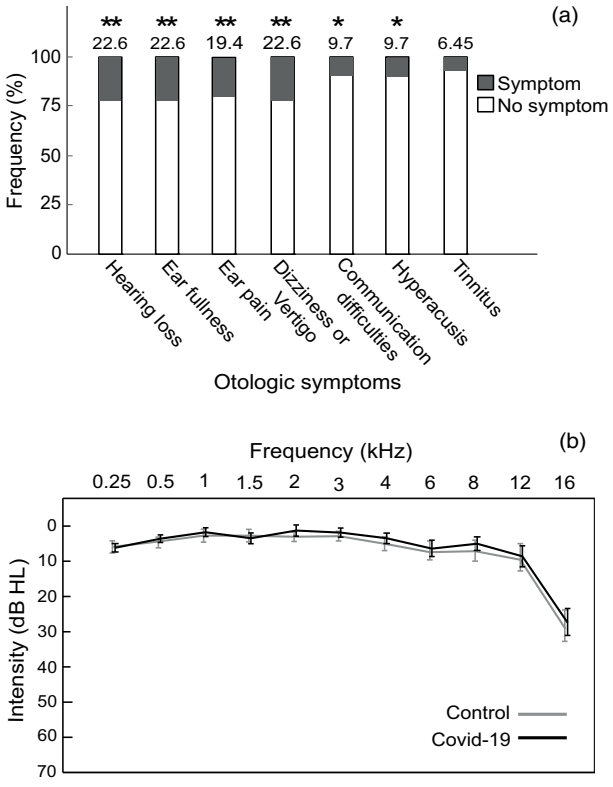

Fig. 1. Comparison between cases with coronavirus disease 2019 (Covid-19) and the control group in terms of otological symptoms and hearing thresholds. (a) The rate of otological symptoms was significantly increased in the Covid-19 group relative to the control group. (b) No significant difference was observed between the two groups in terms of audiometric hearing thresholds. The graph shows means ± 2 standard error. *$p < 0.05$; **$p < 0.01$

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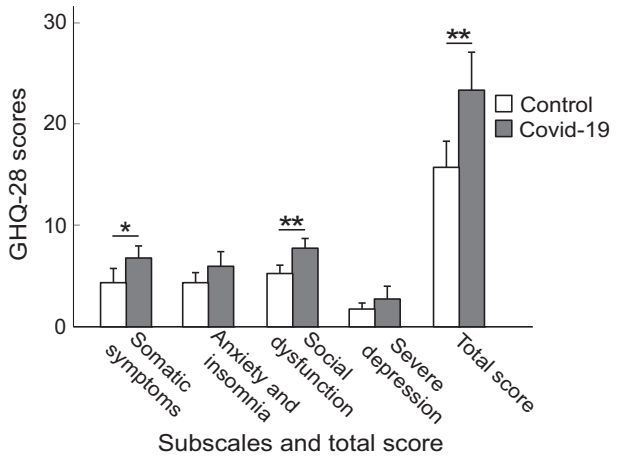

Fig. 2. General Health Questionnaire-28 (GHQ-28) scores for the coronavirus disease 2019 (Covid-19) group and the control group. The scores of the Covid-19 group were significantly increased compared to the control group for the somatic symptoms and social dysfunction subscales, and for the total scores. The graph shows means ± 2 standard error. *$p < 0.05$; **$p < 0.01$

0.077); acoustic startle reflexes (F = 0.418, $p = 0.903$, $\eta^2 = 0.075$, power = 0.172); transient evoked otoacoustic emissions (F = 0.723, $p = 0.578$, $\eta^2 = 0.034$, power = 0.224); distortion product otoacoustic emissions (F = 1.122, $p = 0.359$, $\eta^2 = 0.125$, power = 0.511); and ABR wave latencies (F = 0.283, $p = 0.596$, $\eta^2 = 0.003$, power = 0.082), inter-peak intervals (F = 0.315, $p = 0.576$, $\eta^2 = 0.003$, power = 0.086) and amplitudes (F = 1.898, $p = 0.092$, $\eta^2 = 0.107$, power = 0.678).

The two groups were also compared in terms of the total score and subscale scores of the General Health Questionnaire-28. In all measures, the scores of the Covid-19 group were higher than those of the control group. Significant differences were observed between the two groups in terms of the total score, as well as the somatic symptoms and social dysfunction subscales (F = 4.031, $p = 0.005$, $\eta^2 = 0.330$, power = 0.921) (Figure 2).

Discussion

This study aimed to investigate: (1) the frequency in occurrence of otological symptoms associated with SARS-CoV-2; (2) how long these symptoms last; (3) the effect of the virus on auditory responses; and (4) patients' general health post-recovery. Briefly, our findings demonstrated that: (1) the rates of experienced hearing loss, ear fullness, ear pain, dizziness or vertigo, communication difficulties, and hyperacusis were significantly increased in patients with Covid-19 compared with the control group; (2) the symptoms mostly resolved within a week (i.e. 2–8 days) after their appearance; (3) the virus left no significant impact on auditory responses post-recovery (i.e. within one month after diagnosis); and (4) patients with Covid-19 showed a higher distress level relative to the control group after recovery.

The appearance of otological symptoms in some of our patients is consistent with recent meta-analysis papers that suggest audio-vestibular complications as early symptoms of SARS-CoV-2.[18,19] A number of hypotheses have been raised regarding the potential mechanisms underlying otological manifestations. One such hypothesis is that they result from direct damage caused by the virus to the organ of Corti, stria vascularis and/or spiral ganglion.[27,41] For instance, inflammation and oxidative stress are tightly linked to one another, and their activation is simultaneously found in many pathological conditions, including infection with SARS-CoV-2.[42]

Inflammation is a natural defence mechanism against pathogens, and is involved in many autoimmune diseases.[43] Excessive production of reactive oxygen species in cells and tissues can lead to oxidative stress too, and can impair cellular molecules such as DNA, proteins and lipids. It can stimulate inflammatory processes, and the synthesis and secretion of pro-inflammatory cytokines (e.g. interleukins (ILs) 6 and 1β) and tumour necrosis factor-alpha. In Cazzolla and colleagues' study,[44] a correlation was found between the occurrence of smell and taste disorders and IL-6 levels. The recovery of olfactory and gustatory functions was also associated with reduced IL-6 levels, which points to the potential role of IL-6 in cell receptors infected by the virus at the peripheral level. A similar mechanism for the contribution of pro-inflammatory cytokines to early otological symptoms of SARS-CoV-2 is likely. The findings of past studies also support the role of reactive oxygen species and pro-inflammatory cytokines in initiating acute and chronic inflammation in SNHL and tinnitus.[45,46]

In addition, human evidence demonstrates that SARS-CoV-2 can spread throughout the body via the circulatory system because of the abundant expression of ACE2 in arterial and venous endothelial cells and arterial smooth muscle cells in many organs.[47] Thus, it is possible that the virus damages the blood–labyrinth barrier and invades the inner-ear structure by activating monocytes that may attack the vascular system.[13] In this regard, ACE2 gene expression has been observed in the mouse cochlea,[48] but the presence of SARS-CoV-2 in the human inner ear has not been reported yet. Virus attachment to haemoglobin and deoxygenating erythrocytes can also cause hypoxia and further damage to the inner ear.[49] Previous studies have shown prolonged latency and reduced amplitude of ABR waves in response to experimental temporary hypoxia in individuals with normal hearing.[50,51]

In our study, the results of behavioural audiometry (e.g. pure tone and extended high-frequency hearing thresholds), and of objective tests of middle-ear function (e.g. tympanometry and acoustic startle reflexes), inner-ear function (e.g. transient evoked and distortion product otoacoustic emissions) and the auditory peripheral nervous system (e.g. ABR with standard and high rates of stimulus presentation), were consistent with no long-term impact of SARS-CoV-2 on the auditory system post-recovery. This suggests that the impact of mild or moderate levels of the disease on the auditory system is transient. Those previously reported cases of sudden hearing loss, with or without tinnitus and dizziness, mostly occurred in patients with severe disease and/or in those with underlying conditions.[20–25]

Our finding of a transient effect is in line with recent publications on patients with early olfactory and/or gustatory dysfunction caused by SARS-CoV-2.[12,52,53] In a cross-sectional study, however, Mostafa reported slight high-frequency hearing loss in asymptomatic cases with Covid-19 compared with the control group.[27] This finding might result from a difference between the two groups in hearing thresholds before the disease. In our study, the two groups were matched for pre-coronavirus hearing thresholds within normal limits. Further studies, however, are necessary to shed light on the physiological mechanisms involved in auditory and vestibular symptoms in patients with Covid-19, especially in severe cases with partial or no improvement post-recovery, even after steroid therapy.[23–25]

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- Meta-analyses indicate a significantly higher rate of otological symptoms in severe acute respiratory syndrome coronavirus-2 patients
- Results of past studies should be interpreted with caution given low evidence levels, data collection weakness, high heterogeneity among studies, and no information about post-recovery improvement
- This study indicates a significantly increased otological symptom rate in mild to moderate coronavirus disease 2019 cases compared with age-matched controls
- However, symptoms resolve 2–8 days after their appearance, and the virus has no permanent impact on the auditory system

This study utilised the General Health Questionnaire-28 to examine the impact of Covid-19 on patients' general health post-recovery. This questionnaire assesses mental symptoms and psychosocial wellbeing in four main areas – somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression – suggested to be universal across cultures.[37] In our study, patients with Covid-19 had significantly increased scores for the somatic symptoms (6.77 *vs* 4.30) and social dysfunction (7.74 *vs* 5.25) subscales, as well as the total score (23.30 *vs* 15.70 out of 80), compared with the control group. It has been suggested that individuals with total scores of 23 or lower be classified as non-psychiatric, while those with scores above 24 be classified as psychiatric.[37,54] In our study, the total score was above 24 in 8 cases with Covid-19 (25 per cent) and in 1 case in the control group (3.8 per cent). Our participants were active healthcare workers during the pandemic. Studies during the pandemic have demonstrated that individuals under quarantine,[55] and those who lost their job or had their salary reduced,[56] showed a higher increase in General Health Questionnaire-28 scores (especially on the anxiety and insomnia subscale) relative to those without these experiences.

Conclusion

In our study, the frequency in occurrence of otological symptoms was significantly higher in mild or moderate Covid-19 cases compared with age-matched control peers. The symptoms, however, resolved early, within 2–8 days after their appearance. The results of standard behavioural and objective hearing assessments also demonstrated no significant differences relative to the control group almost one month post-diagnosis. The early resolution of otological symptoms is consistent with recent reports demonstrating the improvement of olfactory and gustatory dysfunction symptoms within one to two weeks after their appearance. Our findings suggest that, in patients with mild to moderate disease, the otological symptoms are transient. There are, however, case reports and series of sudden SNHL and tinnitus with partial or no recovery, mainly in severe cases, and their underlying mechanisms should be considered in future research.

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Competing interests. None declared

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