The Journal of Laryngology & Otology

cambridge.org/jlo

Does coronavirus disease 2019 affect peripheral and central auditory systems? Matched group cross-sectional study and six-month follow up

Merve Deniz-Sakarya[1] and İrfan Yorulmaz[2]

[1]Department of Audiology, Faculty of Health Sciences, Baskent University, Ankara, Turkey and [2]Department of Otorhinolaryngology—Head and Neck Surgery, Faculty of Medicine, Ankara University, Ankara, Turkey

Main Article

Merve Deniz-Sakarya takes responsibility for the integrity of the content of the paper

Cite this article: Deniz-Sakarya M, Yorulmaz İ. Does coronavirus disease 2019 affect peripheral and central auditory systems? Matched group cross-sectional study and six-month follow up. *J Laryngol Otol* 2024;1–7. https://doi.org/10.1017/S0022215124000355

Received: 15 August 2023
Revised: 29 January 2024
Accepted: 5 February 2024

Keywords:
Covid-19; hearing loss; hearing tests; audiometry; electrophysiology

Corresponding author:
Merve Deniz-Sakarya;
Email: mervedeniz91@gmail.com

Abstract

Objective. This study aimed to compare the peripheral-to-central auditory systems of people with coronavirus disease 2019 to a well-matched control group and examine the long-term effects of coronavirus disease 2019 on the auditory system.

Method. Participants who were outpatients of coronavirus disease 2019 ($n = 30$) were compared with a well-matched control group ($n = 30$). Behavioural and electrophysiological tests were performed, and tests were repeated at six months in the coronavirus disease 2019 group.

Results. Statistically significant differences were observed in the right ear at 10 kHz ($p = 0.007$) and 12.5 kHz ($p = 0.028$), and in the left ear at 10 kHz ($p = 0.040$) and 12.5 kHz ($p = 0.040$) between groups. The groups had no difference regarding the other audiological test results ($p > 0.05$).

Conclusion. Extended high-frequency thresholds were affected in the coronavirus disease 2019 patients. No other findings indicated that the peripheral-to-central auditory system was affected. The effect on extended high-frequency thresholds appeared permanent, but no clinically significant new, late-onset auditory system effects were observed.

Introduction

Several neurological and neuro-otological manifestations have been reported in association with coronavirus disease 2019 (Covid-19).[1–3] In particular, the number of cases or case series of sudden sensorineural hearing loss associated with Covid-19 has been widely reported in the literature.[4] While some studies have found an increase in the incidence of hearing loss during the pandemic compared to the pre-pandemic period,[5] controlled studies investigating the effect of Covid-19 on the hearing system have shown inconsistent results. Some controlled studies have suggested a decrease in high-frequency (4–8 kHz) hearing thresholds during and shortly after a positive reverse transcription polymerase chain reaction.[6–12] In some studies, extended high-frequency thresholds were also included in the analysis, and an effect of Covid-19 on the 10–16 kHz thresholds was shown.[8,10,13] In contrast to these findings, several other studies detected no statistical or clinical differences in hearing thresholds compared to control measurements.[14–19] However, most of these cross-sectional studies examined only short-term auditory effects.

Although the underlying mechanisms are not fully known, it has been reported in the literature that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may be neurotropic.[20] However, only a few studies investigating the relationship between Covid-19 and the auditory system have included audiological tests that can provide information about the central auditory system. In studies comparing the auditory brainstem response (ABR) findings of individuals with Covid-19 with those of a control group, no difference could be detected for the absolute latency and amplitude of waves I, III and V.[8,14] Only one study showed a significant difference between the groups in absolute latency of waves I, III and V, which was interpreted as a peripheral hearing loss effect.[10]

The effect of Covid-19 on the peripheral-to-central auditory system still needs to be clarified, as cross-sectional studies in the literature have been conducted using limited audiological test tools (often only with pure tone audiometry and/or otoacoustic emissions) and have presented inconsistent results. Furthermore, the long-term effects of Covid-19 on hearing have not been sufficiently investigated. This study aimed to examine the peripheral-to-central auditory systems of patients following their recovery from Covid-19 with a comprehensive audiological test battery and to reveal the long-term auditory effects of the disease.

Materials and methods

This study involves data collected between August 2021 and September 2022 at the Audiology Unit of the ENT Department, Faculty of Medicine, Ankara University. The

study was conducted following the principles of the Declaration of Helsinki, and approval was granted by the Ethics Committee of Ankara University (Date: 12 August 2021/No: İ7-495-21).

The study group consisted of 30 Covid-19 patients (11 males and 19 females), with a mean age of 34.57 ± 11.56 years and a control group of 30 healthy individuals without Covid-19 (11 males and 19 females), with a mean age of 34.50 ± 11.83 years. The two groups were matched on age range and gender (Table 1). Covid-19 was diagnosed by reverse transcription polymerase chain reaction. None of the patients required hospitalisation. The audiological assessments were performed 46.10 ± 16.53 days after the reverse transcription polymerase chain reaction diagnosis (minimum 39 days, maximum 89 days). Sixteen (53.33 per cent) patients with Covid-19 received favipiravir treatment, while the remaining 14 (46.67 per cent) had no antiviral treatment. The inclusion criteria were normal otoscopic findings and normal tympanogram (Type A). The exclusion criteria were history of ear surgery, noise exposure, neurological and/or psychiatric disease, ototoxic drug use, self-report hearing loss and tinnitus before Covid-19, and being treated in intensive care for Covid-19.

Instruments: questionnaire

Information about the demographic characteristics of the participants (e.g. age, gender) and their Covid-19-related hearing and/or communication difficulties (e.g. reduced hearing, difficulty understanding speech, tinnitus) was collected.

Behavioural tests

Pure tone audiometry and extended high-frequency audiometry

Pure tone air and bone conduction thresholds were recorded using an Interacoustic AC 40 clinical audiometer (Assens, Denmark) using Telephonics TDH-39 supra-aural headphones (Farmingdale, New York, USA) at 0.25–8 kHz frequencies. Bone conduction hearing thresholds were determined using a RadioEar B71 bone vibrator (Middelfart, Denmark) at 0.5–4 kHz frequencies. Extended high-frequency audiometry thresholds at 10–14 kHz frequencies were determined with an AC 40 Interacoustics clinical audiometer using Sennheiser HDA300 headphones (Wedemark, Germany). Thresholds were determined using the Hughson–Westlake method.

Speech audiometry and speech recognition in noise tests

Speech reception thresholds and speech recognition scores were calculated for each ear. In addition, speech recognition in noise tests were performed by simultaneously presenting a monosyllabic phonetically balanced word list at 40 dB sensation level and white noise at 40 dB sensation level to the subjects' ipsilateral test ear.

Masking-level difference test

Masking-level difference is a behavioural test to detect lower brainstem lesions. Narrowband noise was presented continuously at 50 dB sensation level, while 500 Hz pure tone was presented in homophasic (S_0N_0) and antiphasic ($S_\pi N_0$) listening conditions starting at 70 dB HL. The masking-level difference score was obtained by calculating the difference between S_0N_0 and $S_\pi N_0$.

Electroacoustic and electrophysiological tests

Immitansmetric measures

Tympanometry and acoustic reflex threshold were performed using a GSI TympStar Pro middle ear analyser (Grason–Stadler, Eden Prairie, MN, USA). Tympanograms were obtained by presenting a 226 Hz probe tone at 85 dB SPL to the ear while the ear canal pressure was varied from +200 to −400 daPa. Acoustic reflex threshold was performed between 500 Hz and 4000 Hz frequencies, ipsilaterally and contralaterally.

Transient evoked oto-acoustic emissions

Transient evoked oto-acoustic emissions (TEOAE) was used to evaluate the integrity of the participants' inner ear outer hair cells. Transient evoked oto-acoustic emissions testing was performed with the Echoport ILO 292 USB-II, version 6 (Otodynamics, London, UK). signal-to-noise responses were recorded at 1, 1.4, 2, 2.8, and 4 kHz frequencies. Each record consists of an average of 260 sweeps. Wave reproducibility of 70 per cent and above and stimulus stability of 80 per cent and above were accepted in both measurements.

Auditory brainstem response and middle latency response

Auditory brainstem response (ABR) and middle latency response (MLR) were used to evaluate auditory pathways at the brainstem and midbrain levels. Interacoustics Eclipse EP 25 (Interacoustics, Middelfart, Denmark) was used for ABR and MLR recordings recorded in 2 channels: the disc electrodes were placed between the vertex and right mastoid for channel 1, and between the vertex and left mastoid for channel 2, with the forehead as ground. Electrode impedances were maintained below 5.0 kΩ. Stimuli were delivered via insert earphones for the right and left ear. The ABR test was recorded at 80 dB normal hearing level in rarefaction polarity, using 21.1 click stimuli per second, averaging up to 1000 sweeps. The bandpass filter range was adjusted at 30 Hz and 3000 Hz high-frequency cut-off, respectively. The MLR test was recorded at 70 dB normal hearing level in alternate polarity, using 7.1

Table 1. Characteristics of participants

			Covid-19 Group (n = 30)	Control Group (n = 30)	Total (n = 60)	p-value
Age	mean ± SD		34.57 ± 11.56	34.50 ± 11.83	34.53 ± 11.60	0.90
	min–max		20–55	20–55	20–55	
Gender	Female	n (%)	19 (63%)	19 (63%)	38 (63%)	1.00
	Male	n (%)	11 (37%)	11 (37%)	22 (37%)	

SD = standard deviation

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press

rate of 500 Hz tone burst stimuli per second, averaging up to 1000 sweeps. The bandpass filter range is adjusted at high- and low-frequency cut-offs of 30 and 3000 Hz, respectively.

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). To evaluate the normality of distribution Shapiro–Wilk test and, in order to assess equality of variances, Levene's test were used. Comparisons were analysed using either the independent samples *t*-test or the Mann–Whitney U test. The difference between the first and second measurements of the patient group was made with the dependent sample *t*-test or Wilcoxon signed rank text. All reported *p*-values are two-tailed, with a *p*-value ≤ 0.05 indicating statistical significance.

Results

Questionnaire results

After Covid-19, 8 out of 30 participants (26.7 per cent) reported at least one hearing or communication difficulty. Four participants (13.3 per cent) had more than one complaint. Five participants (16.6 per cent) reported difficulty understanding speech in noise, three participants (10 per cent) reported new-onset tinnitus, three participants (10 per cent) had annoyance with loud sounds, two participants (6.6 per cent) reported difficulty understanding speech in quiet, and two participants (6.6 per cent) reported fullness in the ear. In three (10 per cent) patients with Covid-19 and tinnitus, the onset of symptoms was within 5–7 days following diagnosis of Covid-19. At the first evaluation, the mean visual analogue scale (VAS) annoyance was 2.33 ± 1.53 (minimum 1, maximum 4), and the mean VAS-tinnitus loudness was 3.66 ± 1.53 (minimum 2, maximum 5).

Behavioural test results

No significant difference was observed between the two groups for 0.25–8 kHz air-conduction thresholds, pure tone average (PTA), and 0.5–4 kHz bone-conduction thresholds. However, a statistically significant difference was observed for extended high-frequency thresholds in right ears at 10 kHz ($p = 0.007$) and 12.5 kHz ($p = 0.023$), and in left ears at 10 kHz ($p = 0.040$) and 12.5 kHz ($p = 0.040$). Participants with a history of Covid-19 had higher extended high-frequency thresholds for the right and left ears (Table 2). No significant difference was found between groups in right speech-reception thresholds ($p = 0.362$), left speech-reception thresholds ($p = 0.612$), right speech-recognition scores ($p = 0.068$), left speech-recognition scores ($p = 0.449$), right speech-recognition scores in noise tests ($p = 0.652$) and left speech-recognition scores in noise tests ($p = 0.380$).

In the masking-level difference test, the mean $S_0N_0-S_\pi N_0$ value was 10.53 ± 2.67 for the patient group and 10.80 ± 2.38 for the control group. There was no significant difference in masking-level difference score between groups (U = 489.5, $p = 0.545$).

Electroacoustic and electrophysiological test results

There was no statistically significant difference between the middle ear peak pressure, static admittance, and volume values in both ears between groups ($p > 0.05$). Bilateral ipsilateral and contralateral acoustic reflex threshold was evaluated between 0.5 kHz and 4 kHz, and no statistically significant difference was obtained between the groups. Also, no significant differences were observed between the two groups in 1.0, 1.4, 2.0, 2.8, and 4.0 kHz TEOAE values in both ears ($p > 0.05$) (Table 3).

The ABR test compared the groups' absolute latencies and amplitudes of I, III, and V and interpeak latencies and amplitudes of I–III, III–V, and I–V for both ears. No significant difference was found in all measurements ($p > 0.05$) (Table 4). In the middle latency response test, absolute latencies of the components Pa, Na, Pb, and interpeak latencies of Na-Pa for both ears were compared between the groups, and no significant difference was found in all measurements ($p > 0.05$).

Comparison of extended high-frequency thresholds of treatment and non-treatment groups

Sixteen (53 per cent) individuals in the study group received favipiravir (treatment group), and 14 (47 per cent) did not receive any drug treatment (non-treatment group). Although bilateral 10, 12.5, and 14 kHz extended high-frequency thresholds were higher in the treatment group, no statistically significant difference was observed between the treatment and non-treatment groups ($p > 0.05$). There was also no age difference between the groups (treatment group mean = 35.38 ± 11.40; non-treatment group mean = 33.64 ± 12.10; $p = 0.690$).

Follow-up results

Twenty-five of 30 participants were followed up after six months post-polymerase chain reaction. The eight participants who self-reported hearing or communication complaints at the first evaluation continued to have problems in the six-month follow up except for ear fullness. None of the participants experienced new-onset hearing or communication problems.

Tinnitus persisted in all participants (10 per cent) six months after the disease, but the VAS-annoyance and VAS-tinnitus loudness decreased for all participants. The mean VAS-annoyance was 1.33 ± 0.58 (minimum 1, maximum 2), and VAS-tinnitus loudness was two for all participants. A statistically significant difference was obtained between the initial and follow-up measurements of only the right ear 500 Hz air-conduction hearing threshold ($p = 0.020$). The mean threshold value was 2.40 ± 5.02 in the first measurement and 4.40 ± 5.06 in the follow-up measurement. In the follow-up study, intra-group comparisons of other audiological evaluations did not show a significant difference ($p > 0.05$).

Discussion

This study showed a significant difference only in 10 kHz and 12 kHz extended high-frequency thresholds, bilaterally, between Covid-19 patients and healthy individuals. No other significant peripheral and central auditory effects were found. In addition, no clinically significant changes in hearing were detected during the six-month follow-up study.

Our study found no evidence to support the peripheral effect of Covid-19 with 250–8000 Hz PTA and transient evoked oto-acoustic emissions (TEOAE). Some studies have shown an increase in high-frequency pure tone thresholds (2/4–8 kHz) and a decrease in TEOAE amplitudes.[7,9–11] In contrast, others had unchanged PTA results with a significant decrease in TEOAE amplitudes.[6] These studies support that there is cochlear damage due to Covid-19. However, other

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press

Table 2. Comparison of pure-tone and extended high-frequency audiometry test results in groups

Ear	kHz	Covid-19 Group		Control Group		Test Statistic	*p*-value
		Min–max	mean ± SD	Min–max	mean ± SD		
Right	0.25	−5–30	3.67 ± 8.50	−10–30	5.17 ± 8.76	396.0[U]	0.416
	0.50	−5–25	3.17 ± 6.23	−5–25	4.17 ± 7.08	419.0[U]	0.631
	1.0	0–35	8.67 ± 7.18	−5–30	8.17 ± 8.15	417.0[U]	0.615
	2.0	0–35	10.33 ± 8.40	0–30	10.17 ± 6.50	449.0[U]	0.988
	4.0	−5–30	8.50 ± 8.52	−10–25	7.17 ± 7.27	0.652[t]	0.517
	6.0	−10–35	4.83 ± 10.38	−10–20	2.50 ± 7.96	0.977[t]	0.333
	8.0	−10–40	4.67 ± 11.67	−10–20	2.50 ± 9.63	409.0[U]	0.538
	10	0–85	25.33 ± 19.43	0–60	14.00 ± 11.40	270.0[U]	*0.007**
	12.5	−10–95	33.33 ± 30.83	−5–75	16.00 ± 20.78	302.0[U]	*0.028**
	14	−5–90	37.33 ± 33.57	−5–90	25.83 ± 25.19	381.5[U]	0.310
	PTA	−1–29	7.74 ± 6.55	−1–25	7.87 ± 6.13	446.0[U]	0.953
Left	0.25	−5–15	5.83 ± 6.03	−5–20	7.50 ± 5.98	378.0[U]	0.273
	0.50	−5–15	4.50 ± 5.31	−5–20	6.17 ± 5.03	377.5[U]	0.262
	1.0	0–20	7.33 ± 5.21	−5–25	6.33 ± 6.15	391.5[U]	0.363
	2.0	−5–25	9.33 ± 7.74	−5–25	9.83 ± 7.13	−0.260[t]	0.796
	4.0	−5–30	8.00 ± 9.06	−10–25	7.17 ± 7.95	435.5[U]	0.826
	6.0	−10–35	5.83 ± 10.18	−20–25	5.00 ± 8.91	439.5[U]	0.875
	8.0	−10–35	3.50 ± 11.53	−10–50	4.83 ± 12.56	423.0[U]	0.686
	10	−5–80	23.33 ± 21.83	0–75	13.17 ± 14.77	312.5[U]	*0.040**
	12.5	−10–90	32.33 ± 28.55	0–75	17.17 ± 20.11	312.0[U]	*0.040**
	14	0–90	39.00 ± 32.49	−5–90	25.00 ± 28.01	333.5[U]	0.083
	PTA	−3–21	7.40 ± 5.79	−3–21	7.53 ± 5.33	−0.093[t]	0.926

[U] = Mann–Whitney U test; [t] = independent sample *t*-test; * significant difference ($p < 0.05$); PTA = pure tone average

studies either found no significant difference in hearing thresholds or TEOAE[14,15,17–19] or both, or stated that the difference was not statistically significant.[16]

Bilateral 10 kHz and 12.5 kHz extended high-frequency threshold values of the patient group after Covid-19 were higher than the control group. The patient group's bilateral 10 kHz and 12.5 kHz extended high-frequency thresholds exceeded 20 dB HL. Although normal values of extended high-frequency thresholds are not standardised, many studies show that the average threshold values for these frequencies in adults with normal hearing do not exceed 20 dB HL.[21] The mean extended high-frequency thresholds of the patient group is higher than the control group and deviates from this norm value by approximately 5–10 dB HL.

Table 3. Comparison of transient evoked oto-acoustic emissions (TEOAE) values in groups

Ear	kHz	Covid-19 Group		Control Group		Test Statistic	*p*-value
		Min–max	mean ± SD	Min–max	mean ± SD		
Right	1.0	0–28.2	12.67 ± 8.04	3.1–30.5	13.23 ± 7.10	−0.284[t]	0.777
	1.4	0–28.9	15.50 ± 6.87	2.3–27.8	16.57 ± 6.72	−0.613[t]	0.542
	2.0	0–31.1	14.48 ± 7.95	1.1–26.7	14.86 ± 6.68	−0.200[t]	0.842
	2.8	0–24.4	13.41 ± 7.03	0–21.4	12.75 ± 5.35	0.411[t]	0.683
	4.0	0–26	8.09 ± 6.26	0–25.4	9.60 ± 5.78	−0.974[t]	0.334
Left	1.0	0–30.5	12.49 ± 8.51	0–26.6	12.92 ± 7.48	−0.204[t]	0.839
	1.4	0–30.6	15.68 ± 7.42	0–26.6	16.03 ± 6.2	−0.189[t]	0.850
	2.0	0–31.2	14.04 ± 7.07	0–31.8	13.55 ± 5.87	0.294[t]	0.770
	2.8	0–27.9	11.74 ± 7.22	0.1–22	12.75 ± 5.75	−0.599[t]	0.552
	4.0	0–25.5	8.43 ± 6.55	0–19.6	8.70 ± 5.24	−0.176[t]	0.861

[t] = independent sample *t*-test

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press

Table 4. Comparison of ABR wave latencies and amplitudes in groups

	Wave	Covid-19 Group		Control Group		Test Statistic	*p*-value
		Min–max	Mean ± SD	Min–max	mean ± SD		
Right Latency (ms)	I	1.27–1.87	1.52 ± 0.14	1.27–2.67	1.47 ± 0.08	390.0^{U}	0.365
	III	3.13–4.13	3.64 ± 0.20	3.33–4.00	3.61 ± 0.16	0.618^{t}	0.539
	V	5.00–6.00	5.48 ± 0.26	5.00–6.20	5.48 ± 0.25	−0.129t	0.898
	I–III	1.73–2.60	2.12 ± 0.19	1.87–2.60	2.13 ± 0.17	470.0^{U}	0.765
	III–V	1.40–2.20	1.83 ± 0.20	1.60–2.20	1.87 ± 0.14	−0.790^{t}	0.433
	I–V	3.60–4.47	3.96 ± 0.19	3.53–4.53	4.01 ± 0.24	−0.786^{t}	0.435
Left Latency (ms)	I	1.13–1.80	1.45 ± 0.14	1.20–1.80	1.44 ± 0.12	0.384^{t}	0.702
	III	3.13–4.00	3.61 ± 0.18	3.27–3.93	3.59 ± 0.18	0.539^{t}	0.592
	V	5.07–6.13	5.48 ± 0.27	5.00–6.20	5.47 ± 0.26	0.148^{t}	0.883
	I–III	1.87–2.40	2.16 ± 0.14	1.73–2.47	2.14 ± 0.18	0.259^{t}	0.796
	III–V	1.40–2.47	1.87 ± 0.22	1.47–2.60	1.88 ± 0.22	−0.250^{t}	0.804
	I–V	3.67–4.53	4.03 ± 0.22	3.67–5.60	4.08 ± 0.38	460.0^{U}	0.882
Right Amplitude (μV)	I	0.044–0.576	0.31 ± 0.15	0.077–0.706	0.35 ± 0.16	−1.055^{t}	0.296
	III	0.098–0.634	0.28 ± 0.13	0.047–1.012	0.33 ± 0.24	461.0^{U}	0.871
	V	0.163–1.067	0.56 ± 0.25	0.20–0.91	0.52 ± 0.15	0.769^{t}	0.446
	I–III	0.005–0.338	0.12 ± 0.08	0.014–0.828	0.19 ± 0.16	575.0^{U}	0.065
	III–V	0.005–0.839	0.30 ± 0.24	0.006–0.743	0.26 ± 0.17	428.5^{U}	0.751
	I–V	0.005–0.610	0.27 ± 0.19	0.001–0.541	0.19 ± 0.14	337.0^{U}	0.095
Left Amplitude (μV)	I	0.075–0.736	0.33 ± 0.14	0.082–0.744	0.37 ± 0.17	511.0^{U}	0.367
	III	0.028–0.646	0.27 ± 0.17	0.002–0.920	0.31 ± 0.22	480.5^{U}	0.652
	V	0.087–0.986	0.52 ± 0.24	0.266–0.971	0.54 ± 0.21	−0.310^{t}	0.758
	I–III	0.010–0.578	0.17 ± 0.13	0.005–0.460	0.18 ± 0.12	494.5^{U}	0.511
	III–V	0.000–0.943	0.29 ± 0.26	0.008–0.792	0.29 ± 0.21	471.0^{U}	0.756
	I–V	0.006–0.847	0.22 ± 0.19	0.005–0.603	0.20 ± 0.15	433.0^{U}	0.802

^{t} = independent sample *t*-test; ^{U} = Mann–Whitney U test

This finding supports a peripheral effect at the most basal region of the cochlea. In the literature, some studies support a difference in extended high-frequency thresholds between the patient and control groups.[8,10,13] It is unknown whether inner-ear involvement is a viral effect, or an effect of Covid-19 drug treatment. It is known that the SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a key receptor for cell entry, and transmembrane serine protease 2 facilitates cell fusion.[22] Uranka et al. (2020) detected ACE2 and transmembrane serine protease 2 in various cells in the organ of Corti and stria vascularis of the mouse cochlea, suggesting that the inner ear is sensitive to SARS-CoV-2.[23] Jeong et al. (2021) demonstrated the relationship between SARS-CoV-2 and hair-cell damage in the inner ear with *in vitro* cell models.[24] Although studies do not explain why the virus mainly affects only high frequencies, they show that it may affect the peripheral hearing system.

Aging, noise exposure and ototoxic drugs also affect extended high-frequency thresholds. In the study, these variables were controlled, and only the effect of Covid-19 drug treatment on extended high-frequency thresholds was analysed. Sixteen favipiravir users who were similar in age range were compared to fourteen non-drug users. Extended high-frequency thresholds were higher in the drug group, but this difference was not statistically significant. Although it has been suggested that favipiravir may have had a potential ototoxic effect when first used to treat Covid-19,[25] it is still unknown. Favipiravir is among the nucleoside analogues that some nucleoside antilogues of antiviral drugs are known to affect the inner ear.[26] A study that examined the direct drug effect by comparing hydroxychloroquine users, non-drug users, and control groups showed that TEOAE amplitudes were lower in the drug group. However, there was no difference in the 0.25–8 kHz hearing thresholds. This finding suggests hydroxychloroquine use may cause inner ear damage that is not reflected in conventional audiological thresholds.[11]

In a controlled study using an extensive audiologic test battery like our study, extended high-frequency threshold results differed, although our other test results were similar. The researchers also found no difference in extended high-frequency thresholds between groups.[27] The possible reason may be that factors other than Covid-19 that will affect extended high-frequency thresholds become more common with advanced age and the variation in extended high-frequency thresholds increases, or the possible effect of favipiravir use by some of the participants in our study. For this reason, it is recommended that drug users, non-drug users, and control-group studies be examined in a large sample and with an extensive audiological test battery, including extended

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press

high-frequency audiometry, to examine a similar effect for favipiravir in a more controlled manner.

In our study, which included ABR for a brainstem level assessment, no significant differences were observed for ABR latencies and amplitudes between groups. In the literature, no evidence supports that Covid-19 affects the auditory system at the brainstem level in studies conducted with ABR.[8,12,27] One study reported that mild latency prolongation might be insignificant and may be due to peripheral hearing loss rather than possible brainstem damage.[10] Masking-level difference, a behavioural test that provides information at the lower brainstem level, was also added to the test battery in this study. There was no difference in masking-level difference score between the groups. As SARS-CoV-2 has been observed to be able to affect other cranial nerves (ophthalmoparesis, optic neuritis, anosmia), it was considered that SARS-CoV-2 may directly affect the vestibulocochlear nerve[28] and, in general, possible brainstem involvement in symptoms also has been considered.[29]

Nevertheless, as a result of ABR and masking-level difference test results, there is no auditory impairment at the brainstem level in Covid-19 patients in our study. Auditory pathways were also examined at the midbrain level; no difference was observed between the two groups regarding MLR test results. As a result of these assessments, no findings in this study supported that Covid-19 affects the central auditory system at the brainstem and midbrain levels.

In the six-month follow-up study, a statistically significant difference was observed between the first and second measurements only in the right ear 500 Hz hearing threshold. The mean hearing threshold was 2.40 in the first measurement and 4.40 in the second measurement. Since the difference between the two measurements was less than 5 dB HL, this difference was not clinically significant. No statistically or clinically significant new auditory changes with late onset were detected. Only one study with a control group examining the long-term auditory effect was found in the literature. Our results support this finding.[19] It was observed that the extended high-frequency thresholds determined in the first measurement was similar in the follow-up study, and the decrease in extended high-frequency thresholds was thought to be persistent at six months.

- The long-term effects of coronavirus disease 2019 on hearing have not been sufficiently investigated with an extensive audiological test battery
- In this study, only 10 kHz and 12.5 kHz extended high-frequency thresholds were affected in coronavirus disease 2019 patients compared to the control group (no results support that the peripheral auditory system is affected, except for the difference in extended high-frequency thresholds)
- Behavioural and electrophysiological audiological test results do not provide evidence that the central auditory system is affected in individuals with COVID-19
- In the six-month follow-up study, the effect on extended high-frequency thresholds appeared permanent, but no clinically significant new, late-onset auditory system effects were observed
- The possible effect of coronavirus disease 2019 on extended high-frequency thresholds may have been missed because studies mostly included conventional thresholds
- The results of this study are valuable in that they present both behavioural and electrophysiological audiological test results in a relatively large sample

One of the limitations of this study is that a polymerase chain reaction test was not requested from the individuals in the control group as it was thought that polymerase chain reaction-negative results in the control group would not eliminate the limitation. Meta-analysis studies have reported that the polymerase chain reaction test can give false negative results and that a negative result does not completely exclude SARS-CoV-2 infection.[30,31] As in other studies with the control group features, this was considered one of the limitations of the study. In addition, some virus-specific features (such as variants) may affect auditory outcomes. In the literature, there are differences in ENT symptoms according to variants.[32] While hearing loss is a rare symptom in patients with the Alpha variant of Covid-19, it has been reported that hearing loss is more common as a symptom in the Delta variant.[33] Since the study also had a follow-up component, data were collected over a wide period. Therefore, it is not possible to draw inferences about auditory outcomes specific to the dominant variant.

Conclusion

In the Covid-19 group aged 20-–55 with mild symptoms, only 10 kHz and 12.5 kHz extended high-frequency thresholds were higher than the healthy group. No auditory effects were found at the brainstem and midbrain levels. The effect on extended high-frequency thresholds appeared permanent in the six-month follow-up study, but no clinically significant new late-onset auditory system effects were observed. The results of this study are valuable in that they present both behavioural and electrophysiological audiological test results in a relatively large sample.

Acknowledgements. We would like to thank Eda Çakmak (PhD) for her assistance in the statistical analysis, and Kübra Özmen (PhD) for critical review.

Funding. The authors declared that this study received no financial support.

Competing interests. The author(s) declare none.

References

1 Collantes MEV, Espiritu AI, Sy MCC, Anlacan VMM, Jamora RDG. Neurological manifestations in COVID-19 infection: a systematic review and meta-analysis. *Can J Neurol Sci* 2021;**48**:66–76.
2 Deva FAL, Gupta A, Manhas M, Kalsotra P. Neuro-otological symptoms: an atypical aspect of covid-19 disease. *Indian J Otolaryngol Head Neck Surg* 2022;**74**(suppl 2):3273–82.
3 Eravci FC, Alafifi M, Dündar MA, Korkmaz C, Demirbaş S, Vatansev H *et al.* Neurotological manifestations of patients with Covid-19. *Kulak Burun Bogaz Ihtis Derg* 2021;**29**:168–75.
4 Umashankar A, Prakash P, Prabhu P. Sudden sensorineural hearing loss post coronavirus disease: a systematic review of case reports. *Indian J Otolaryngol Head Neck Surg* 2022;**74**(suppl 2):3028–35.
5 Wagatsuma Y, Daimaru K, Deng S, Chen JY. Hearing loss and the COVID-19 pandemic. *BMC Res Notes* 2022;**15**:228.
6 Daikhes, NA, Karneeva OV, Machalov AS, Kuznetcov AO, Sapozhnikov YM, Balakina AV *et al.* Audiological profile of patients with SARS-CoV-2-PCR-positive cases [in Russian]. *Vestn Otorinolaringol* 2020;**85**:6–11.
7 de Sousa FA, Costa RP, Xará S, Pinto AN, Almeida E, Sousa C. SARS-CoV-2 and hearing: an audiometric analysis of COVID-19 hospitalized patients. *J Otol* 2021;**16**:158–64.
8 Gedik Ö, Hüsam H, Başöz M, Tas N, Aksoy F. The effect of coronavirus disease 2019 on the hearing system. *J Laryngol Otol* 2021;**135**:810–14.
9 Mustafa MWM. Audiological profile of asymptomatic Covid-19 PCR-positive cases. *Am J Otolaryngol* 2020;**41**:102483.
10 Öztürk B, Kavruk H, Aykul A. Audiological findings in individuals diagnosed with Covid-19. *Am J Otolaryngol* 2022;**43**:103428.

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press

11 Rahimi V, Rouhbakhsh N, Manshadi SAD. Slight high-frequency hearing loss, the effect of Covıd-19 or hydroxychloroquine usage? *Otol Neurotol* 2022;**43**:944–50.
12 Tan M, Cengiz DU, Demir İ, Demirel S, Çolak SC, Karakaş O *et al.* Effects of Covid-19 on the audio-vestibular system. *Am J Otolaryngol* 2021;**43**:103173.
13 Emekci T, Dündar MA, Kirazlı G, Men Kılınç F, Cengiz DU, Karababa E *et al.* Evaluation of the efferent auditory system in Covid-19 adult patients. *Acta Otolaryngol* 2022;**142**:509–14.
14 Dror AA, Kassis-Karayanni N, Oved A, Daoud A, Eisenbach N, Mizrachi M *et al.* Auditory performance in recovered SARS-CoV-2 patients. *Otol Neurotol* 2021;**42**:666–70.
15 Durgut O, Karataş M, Çelik Ç, Dikici O, Solmaz F, Gencay S. The effects of SARS-CoV-2 on hearing thresholds in Covıd-19 patients with non-hospitalized mild disease. *Am J Otolaryngol* 2022;**43**:103320.
16 Gallus R, Melis A, Rızzo D, Piras A, De Luca LM, Tramaloni P *et al.* Audiovestibular symptoms and sequelae in Covid-19 patients. *J Vestib Res* 2021;**31**:381–7.
17 Kokten N, Celik S, Mutlu A, Pektas E, Icten S, Kalcıoglu MT. Does Covid-19 have an impact on hearing? *Acta Otolaryngol* 2022;**142**:48–51.
18 Kökoğlu K, Tektaş N, Baktir-Okcesiz FE, Şahin M. Mild and moderate Covid-19 disease does not affect hearing function permanently: a cross-sectional study involving young and middle-aged healthcare givers. *Eur Arch Otorhinolaryngol* 2021;**278**:3299–305.
19 Yıldız E. Comparison of pure tone audiometry thresholds and transient evoked otoacoustic emissions (TEOAE) of patients with and without Covid-19 pneumonia. *Am J Otolaryngol* 2022;**43**:103377.
20 Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of Covıd-19 to potential neurotropic mechanisms. *J Neurol* 2020;**267**:2179–84.
21 Oppitz SJ, Silva LCLD, Garcia MV, Silveira AFD. High-frequency auditory thresholds in normal hearing adults. *Codas* 2018;**30**: e20170165.
22 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**:271–80.
23 Uranaka T, Kashio A, Ueha R, Sato T, Bing H, Ying G *et al.* Expression of ACE2, TMPRSS2, and Furin in mouse ear tissue, and the implications for SARS-CoV-2 infection. *Laryngoscope* 2021;**131**:2013–17.
24 Jeong J, Choi HS. Sudden sensorineural hearing loss after Covid-19 vaccination. *Int J Infect Dis* 2021;**113**:341–3.
25 Ciorba A, Corazzi V, Skarżyński PH, Skarżyńska MB, Bianchin, C, Pelucchi S *et al.* Don't forget ototoxicity during the SARS-CoV-2 (Covid-19) pandemic! *Int J Immunopathol Pharmacol* 2020;**34**:2058738420941754.
26 Cianfrone G, Pentangelo D, Cianfrone F, Mazzei, F, Turchetta R, Orlando MP *et al.* Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. *Eur Rev Med Pharmacol Sci* 2011;**15**:601–36.
27 Visram AS, Jackson IR, Guest H, Plack CJ, Brij S, Chaudhuri N *et al.* Pre-registered controlled comparison of auditory function reveals no difference between hospitalized adults with and without COVID-19. *Int J Audiol* 2023;**62**:1–13.
28 Cherchi M. Otovestibular symptoms of Covid-19 and its vaccines/treatments. *Encyclopedia* (*Basel*) 2022;**2**:1200–9.
29 Machado C, DeFina PA, Chinchilla M, Machado Y, Machado Y. Brainstem dysfunction in SARS-CoV-2 infection can be a potential cause of respiratory distress. *Neurol India* 2020;**68**:989–93.
30 Pecoraro V, Negro A, Pirotti T, Trenti T. Estimate false-negative RT-PCR rates for SARS-CoV-2. A systematic review and meta-analysis. *Eur J Clin Invest* 2022;**52**:e13706.
31 Pu R, Liu S, Ren X, Shi D, Ba Y, Huo Y *et al.* The screening value of RT-LAMP and RT-PCR in the diagnosis of Covıd-19: systematic review and meta-analysis. *J Virol Methods* 2022;**300**:114392.
32 Hagemann J, Onorato G, Seifen C, Becker S, Huppertz T, Olze H *et al.* Presentation of airway and general symptoms in Covid-19 caused by dominant SARS-CoV-2 variants: a follow-up on ARIA consensus. *Allergy* 2022;**77**:3440–4.
33 Umashankar A, Prakash P, Prabhu P. Delta variant of Covid-19 and hearing loss. *Indian J Otolaryngol Head Neck Surg* 2023;**75**:2634–6.

https://doi.org/10.1017/S0022215124000355 Published online by Cambridge University Press