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Assessment of cochlear functions in hospitalized patients with SARS-CoV-2 infection

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Abstract

SARS-CoV-2 infection intensely increases thromboembolic events and inflammation. The inner ear can be easily damaged as a result of circulatory disorders and inflammation. Therefore, SARS-CoV-2 may negatively affect the cochlea. Outer hairy cell damage in the inner ear is one of the first signs of sensorineural hearing loss. Otoacoustic emissions use is an effective, objective, and non-invasive method for early detection of hearing loss. Our study aims to determine whether the cochlea is affected in hospitalized patients with SARS-CoV-2 infection who did not need intensive care treatment by using Distortion product otoacoustic emission (DPOAE) measurements. This study was conducted on 26 hospitalized patients with SARS-CoV-2 infection (patient group) and 25 healthy volunteers (control group). DPOAE measurements were performed on all participants in an audiometric test room. The DP-grams were obtained between 498Hz and 10000Hz. The DPOAE measurements were compared between two groups. When evaluated as a cluster, DP1 and the SNR values were found to be significantly lower in the patient group at frequencies 498, 996, 2002, 7998, 10000 Hz and frequencies 498, 996, 2002, 4004, 6299Hz, respectively. When the right and left ears of the patient group were compared, DP1 and SNR values were found to be similar at all frequencies. SARS-CoV-2 infection can cause damage to the outer hair cells and the regions of the cochlea belonging to a wide range of frequencies according to our DPOAE measurements and due to the specific characteristics of the virus.

Keywords: Cochlear, inflammation; outer hairy cell, sensorineural, thromboembolic

Introduction

Since the day it was first described in Wuhan, the new coronavirus identified as SARS-CoV-2 (COVID-19), has become a serious health problem affecting the whole world. COVID-19 related deaths are increasing day by day as there is still no clear medical treatment. Vaccination studies have begun, but still do not have sufficient efficiency globally. Clinical signs in patients, initial symptoms, and the course of the disease, also vary from country to country. This virus, which is spread by droplets, and direct contact, has an incubation period from 2-7 days to 14 days. For COVID-19, the entrance to the body is the upper respiratory tract. COVID-19 has been isolated from human airway epithelial cells [1,2].

The symptoms of the COVID-19 infection are several ranging from mild and flu-like to severe and even fatal, acute respiratory distress syndrome symptoms. There are also so many asymptomatic viruses transmitting to people in the community [3–5]. The most common symptoms of COVID-19 infection are fever, cough, fatigue, muscle pain, dyspnea, sore throat, headache, gastralgia, nausea, vomiting, and diarrhea [1,6–9]. More than half of patients show symptoms related to Otorhinolaryngology such as a cough, sore throat, anosmia, ageusia, nasal congestion, runny nose, postnasal discharge, gingivitis, otalgia, hoarseness, facial paralysis, rotatory vertigo, dizziness, tinnitus, and sudden sensorineural hearing loss [1,10].

Some viruses can cause congenital or acquired hearing loss such as measles, cytomegalovirus (CMV), herpes simplex

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virus (HSV), varicella-zoster virus (VZV), mumps, and human immunodeficiency virus. Generally, virus-induced hearing loss is sensorineural and less frequently conductive, and mixed. These viruses can negatively affect the auditory system, especially the inner ear structures including inner ear hair cells and the organ of Corti by causing direct damage, inducing immune and inflammatory responses, or suppressing immunity. Several studies suggest that SARS-CoV-2 may be one of these pathogens [11–14].

Outer hairy cell damage in the inner ear is one of the first signs of sensorineural hearing loss. Otoacoustic emissions (OAEs) are light intensity acoustic energy emissions of cochlear origin that can be detected from the external auditory canal in humans and animals. OAEs show the activity of the outer hair cells and otoacoustic emission measurements use is an effective, objective, and non-invasive method for early detection of hearing loss [15,16]. OAEs are very sensitive in determining the effects of autotoxicity on cochlear functions, and hearing loss can be determined by OAEs before being detected in pure tone audiometry [17–19]. Distortion product otoacoustic emissions (DPOAEs), one of the evoked otoacoustic emissions, are frequently used clinically. DPOAEs stand out with their broad bandwidth, frequency specificity, and larger dynamic range within OAEs. DPOAEs are effective in the diagnosis of cochlear damage and cannot be detected in the ischemic damages of the cochlea [20].

COVID-19 intensely increases thromboembolic events and inflammatory responses. Inner ear structures can be easily damaged as a result of circulatory disorders and inflammation. COVID-19 might be neuro-invasive and can enter the cell through angiotensin-converting enzyme 2 (ACE-2) receptors. These receptors are common in the peripheral and central nervous systems and temporal lobe in the auditory center. Therefore, COVID-19 may negatively affect the hearing. Our study aims to determine whether the hearing is affected in hospitalized COVID-19 patients who did not need intensive care treatment by using Distortion product otoacoustic emission (DPOAE) measurements because of the specific features we mentioned above.

Material and Methods

Before the trial, consent from the Clinical Research Ethics Committee at Adıyaman University was received (No: 2020-7, 18.06.2020). Our study was conducted on hospitalized COVID-19 patients who had a positive PCR test and on healthy volunteers (control group). Patients with positive PCR tests for COVID-19 at the time of admission were hospitalized on the same day and included in the study. There was no indication for intensive care hospitalization in the patients. The patients whose duration of infection did not exceed 14 days were included in the study. The control group consisted of volunteers who applied to the otolaryngology outpatient clinic for screening purposes only, without any complaints or diseases, and had normal examination findings.

Those who smoked cigarettes, drank alcohol, and used an ototoxic drug, those with diabetes, those with a neurological disease affecting their hearing, those who work in professions that are chronically exposed to noise, patients who have undergone otological surgery, those who have a congenital hearing impairment, and those who had lost their hearing for any reason, were excluded from the trial. An ear, nose, and throat examination was performed on all the volunteers, and those with acute or chronic external or middle ear disease were not included in the study. A bilateral tympanometric evaluation was performed with an Interacoustics AT235 device (Manufactured by Interacoustics A/S DK-5610 Assens) with a probe tone frequency of 226Hz (sound pressure level, +300 to −600 daPa). The Jerger's classification was used when interpreting the tympanogram [21]. Those whose measurement result was not found as “type A” were not included in the study. The volunteers meeting the conditions for inclusion were divided into two groups. The first group was composed of hospitalized COVID-19 patients and the second group was composed of healthy volunteers. The measurements of the patients were made between days 1-5 of their hospitalization. DPOAE measurements were performed on participants with an Otometrics Madsen Capella2 device (Manufactured by Intelligent Hearing Systems 6860 SW 81st St. Miami, FL 33143 ABD) in an audiometric test room. For the DPOAEs, L1 and L2 were presented at 65 dB and 55 dB sound pressure levels. The f2/f1 ratio was kept at approximately 1.22. The DP-grams were obtained with primary tone frequencies f2 between 498Hz and 10000Hz (including 498-996-2002-4004-6299-7998-10000Hz frequencies) (Figure 1). The signal-to-noise ratio (SNR), defined as the amplitude of the distortion product minus noise floor, and the DPOAE (2f1-f2) (DP1) amplitude were recorded. All the necessary protective equipment against COVID-19 was used during the otorhinolaryngology examination, the tympanometric examination, and the DPOAE measurement. The room, equipment, and devices used during the procedures were disinfected after each patient. The DPOAE measurement results were compared between the groups, and the effects of the COVID-19 infection on hearing were attempted to be determined. Also, the DPOAE measurements of both ears in the patient group were compared to see whether the virus had any unilateral ear involvement.

Statistical Method

The data was obtained from a total of 51 patients. Because more than one ear (right and left) for any patient was measured, the structure of the data was considered as “clustered data.” Conventional statistical methods are not appropriate for the analysis of clustered data because the dependencies among observations within the same cluster were not taken into account. In our study, to compare both the patient and control groups overall, the statistical methods considering the clustered data structure of the sample were used. Therefore, the Wilcoxon Rank Sum test in a clustered data approach was used [22]. Because the shape of the data set was not normally distributed, the Mann-Whitney U test was used to compare the patient and control groups within the left and right sides of the ears. Descriptive statistics were given as median (minimum-maximum) for continuous variables and frequency (percentages) for categorical ones. A comparison of left and right measures within the patient group was done using the Wilcoxon signed-rank test. The mean ages of the patients and the control group were compared by using the independent sample t-test. The type-I error rate was taken as 0.05 to test statistical hypotheses. The SPSS 20.0 was used to run the basic statistical analyses (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). To test the hypotheses considering the clustered type of the data, Microsoft Excel was used (Microsoft Corporation (2018). Microsoft Excel).

Results

Of the 51 volunteers, 26 were in the patient group and 25 were in the control group. There were 15 men and 11 women in the patient group and 15 men and 10 women in the control group. The ages of the volunteers in each group ranged from 18-60 (mean±SD, 44.38±16.37) and 19-60 (mean±SD, 40.56±15) respectively. The ages of the volunteers in both groups were statistically similar (P>.05).

The hospitalized patients had complaints such as fever, cough, shortness of breath, fatigue, muscle pain, and sore throat at the time of admission that suggesting the COVID-19 infection. None of them had hearing loss, tinnitus, and vertigo complaints. The oxygen saturation (SpO_2) of the patients was ranged between 88-93 % on room air at the time of hospitalization. In computed thorax tomographies of the patients mild to moderate involvement were detected in lung parenchyma that was consistent with COVID-19 pneumonia. The hospitalization period of the patients was between 5-15 days. We prescribed to patients intravenous or oral prednisolone for 10 days (40mg/day), subcutaneous enoxaparin sodium for 10 days (40mg/day), and oral favipiravir for 5 days (first day 3200mg/day, next days 1200mg/day). In addition, all patients received high-flow nasal oxygen according to their needs during their hospitalization.

The DP1 values for the right ear were found to be significantly lower in the patient group at frequencies of 996 and 7998 Hz when compared to the control group (p=.01, p=.016). The DP1 values for the left ear were found to be significantly lower in the patient group at frequencies of 996, 2002, 7998, and 10000Hz when compared to the control group (p=.008, p=.008, p<.001, p=.004). The SNR values for the right ear were found to be significantly lower in the patient group at frequencies of 996, 2002, 4004, 6299 and, 10000 Hz when compared to the control group(p=.002, p<.001, p<.001, p<.001, p=.028). The SNR values for the left ear were found to be significantly lower in the patient group at frequencies of 996, 2002, 4004 and, 6299 Hz when compared to the control group (p=.001, p<.001, p<.001, p=.038). The DPOAE measurements are shown in Table 1 for both ears.

When the right and left ears of the patient group were compared, DP1 and SNR values were found to be similar at all frequencies (P>0.05) (Table 2).

When evaluated as a cluster (the right and left ears together), DP1 values were found to be significantly lower in the patient group at frequencies 498, 996, 2002, 7998 and, 10000Hz compared to the control group (p=.008, p<.001, p=.022, p<.001, p=.004). The SNR values were found to be significantly lower in the patient group at frequencies 498, 996, 2002, 4004 and, 6299 Hz when compared to the control group (p=.037, p<.001, p<.001, p<.001, p<.001). DPOAE measurements are shown as a cluster in Table 3.

Table 1. Comparison of DPOAE measurements as right ear and left ear in patient and control groups

Side	Right			Left		
Group	Patient (n:26)	Control (n:25)	P	Patient(n:26)	Control (n:25)	P
	Median (min/max) (dB)	Median (min/max) (dB)		Median (min/max) (dB)	Median (min/max) (dB)	
DP1 498Hz	6 (-3/20)	10 (-10/28)	0.086	7 (-6/20)	10 (-2/49)	0.091
DP1 996Hz	0 (-9/18)	8 (-5/23)	0.010	1.5 (-13/24)	9 (-10/21)	0.008
DP1 2002Hz	0.5 (-22/56)	6 (-17/23)	0.070	1.5 (-15/17)	6 (-10/26)	0.008
DP1 4004Hz	-3 (-17/13)	-5 (-16/6)	0.406	-3 (-17/18)	-3 (-18/12)	0.998
DP1 6299Hz	-4 (-25/5)	-8 (-21/12)	0.308	-1 (-16/21)	-5 (-22/11)	0.210
DP1 7998Hz	0.5 (-13/24)	-4 (-16/4)	0.016	-0.5 (-11/13)	-7 (-24/3)	<0.001
DP1 10000Hz	0 (-12/8)	-3 (-20/11)	0.144	-0.5 (-24/14)	-4 (-30/10)	0.004
SNR 498Hz	0 (-11/11)	3 (-18/12)	0.093	1 (-15/11)	2 (-3/11)	0.242
SNR 996Hz	4.5 (-20/14)	9 (0/24)	0.002	1.5 (-9/19)	11 (-13/20)	0.001
SNR 2002Hz	1.5 (-20/11)	11 (-3/33)	<0.001	2.5 (-6/19)	15 (-8/34)	<0.001
SNR 4004Hz	1 (-15/10)	12 (3/25)	<0.001	3.5 (-16/14)	11 (-5/29)	<0.001
SNR 6299Hz	0 (-18/11)	6 (-9/19)	<0.001	4 (-14/9)	8 (-12/27)	0.038
SNR 7998Hz	4 (-15/20)	7 (-4/15)	0.330	7 (-6/13)	6 (-11/14)	0.603
SNR 10000Hz	2 (-10/12)	7 (-9/19)	0.028	4.5 (-15/12)	5 (-18/16)	0.917

DP1: 2f1-f2; SNR: signal-to-noise ratio.

Table 2. DPOAE measurement results of the right and left ears of the patient group

Patient Group	Left	Right	P
	Median(min/max) (dB)	Median(min/max) (dB)	
DP1 498Hz	7 (-6/20)	6 (-3/20)	0,675
DP1 996Hz	1.5 (-13/24)	0 (-9/18)	0.840
DP1 2002Hz	1.5 (-15/17)	0.5 (-22/56)	0.757
DP1 4004Hz	-3 (-17/18)	-3 (-17/13)	0.577
DP1 6299Hz	-1 (-16/21)	-4 (-25/5)	0.165
DP1 7998Hz	-0.5 (-11/13)	0.5 (-13/24)	0.115
DP1 10000Hz	-0.5 (-24/14)	0 (-12/8)	0.276
SNR 498Hz	1 (-15/11)	0 (-11/11)	1.000
SNR 996Hz	1.5 (-9/19)	4.5 (-20/14)	0.501
SNR 2002Hz	2.5 (-6/19)	1.5 (-20/11)	0.676
SNR 4004Hz	3.5 (-16/14)	1 (-15/10)	0.746
SNR 6299Hz	4 (-14/9)	0 (-18/11)	0.178
SNR 7998Hz	7 (-6/13)	4 (-15/20)	0.345
SNR 10000Hz	4.5 (-15/12)	2 (-10/12)	0.207

DP1: 2f1-f2; SNR: signal-to-noise ratio.

Table 3. Results of DPOAE measurements in patient and control groups as a cluster

Group	Patient (n:26)	Control (n:25)	P
	Median(min/max) (dB)	Median(min/max) (dB)	
DP1 498Hz	6,5 (-6/20)	10 (-10/49)	0,008
DP1 996Hz	1 (-13/24)	8 (-10/23)	<0,001
DP1 2002Hz	1 (-22/56)	6 (-17/26)	0,022
DP1 4004Hz	-3 (-17/18)	-3,5 (-18/12)	0,395
DP1 6299Hz	-3 (-25/21)	-6,5 (-22/12)	0,148
DP1 7998Hz	0 (-13/24)	-5 (-24/4)	<0,001
DP1 10000Hz	0 (-24/14)	-3,5 (-30/11)	0,004
SNR 498Hz	1 (-15/11)	3 (-18/12)	0,037
SNR 996Hz	2,5 (-20/19)	10 (-13/24)	<0,001
SNR 2002Hz	2 (-20/19)	14 (-8/34)	<0,001
SNR 4004Hz	3 (-16/14)	11,5 (-5/29)	<0,001
SNR 6299Hz	1,5 (-18/11)	6,5 (-12/27)	<0,001
SNR 7998Hz	6,5 (-15/20)	7 (-11/15)	0,908
SNR 1000Hz	4 (-15/12)	6 (-18/19)	0,542

DP1: 2f1-f2; SNR: signal-to-noise ratio

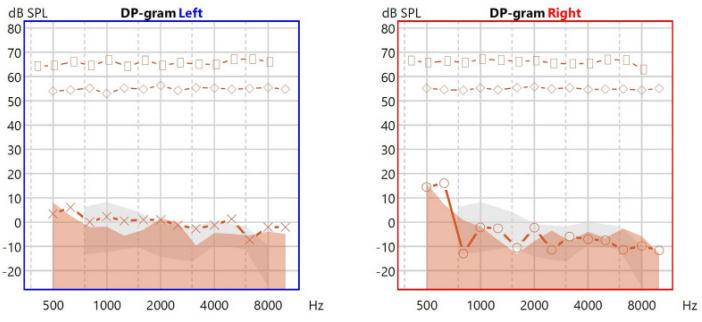

Figure 1. In the DP-gram of a randomly selected volunteer from the patient group, the frequency-specific distortion product amplitudes are seen

Discussion

In our study, we aimed to determine whether the SARS-CoV-2 had any effect on the cochlea by using DPOAE measurements. According to our data, when the right and left ears were evaluated separately, the DP1 and especially the SNR values were found to be significantly lower in many of the measured frequencies in the patient group when compared to the control group. In the cluster measurements, the DP1 and SNR values were found to be significantly lower in most of the frequencies in the patient group. We could not find a significant difference in the DPOAE measurements between the right and left ears of the patient group. These findings showed us that the COVID-19 infection

can bilaterally cause outer hair cell damage that will affect many frequencies in the cochlea.

Coronaviruses are neuroinvasive. In previous studies, viral RNA was found in the cerebrospinal fluid and brain tissue after coronavirus infections. These viruses may enter the central nervous system in various ways, such as through olfactory penetration and trans-synaptic transport of the virus [23–25]. It would not be surprising that the SARS-CoV-2 virus also exhibits similar characteristics. ACE2 receptors play an important role in the entry of SARS-CoV-2 into the cell [7]. The virus may affect all the tissues containing ACE2. Also, the central and peripheral nervous system and hearing center in the temporal lobe contains ACE2 [6]. The virus can create a cytokine storm and causes auditory damage, endotheliitis, and microcirculatory impairment, and the virus may directly invade the cochlear nerve and cochlea [26-28]. Although there are some publications about COVID-19 possibly causing hearing loss, it is still unclear whether COVID-19 affects the hearing system [13]. It is not known whether the exact cause of these reported hearing losses was the COVID-19 infection and whether the hearing loss was caused by the involvement of the central nervous system, cochlear nerve, or cochlea.

Otoacoustic emissions can give us objective information about cochlear outer hair cell activity. DPOAEs, which stand out among OAEs with their frequency specificity, can help in determining cochlear stress [29]. Their frequency specificity helps to identify the damages of certain areas of the cochlea [30]. Significant reductions in DPOAE amplitude after a cochlear injury have been detected in both animal and clinical studies [17,20,31,32]. In cochlear damage that may develop due to noise or ototoxicity, it can be demonstrated by detecting decreases in DPOAE amplitudes in the early period before any loss is found in pure tone audiometry [19,33]. In the study conducted by Mustafa on asymptomatic COVID-19 patients, in the audiometric evaluation, a significant increase especially in the high-frequency thresholds when compared to the control group and a significant decrease in TOAE amplitudes were found [13]. However, the findings described in the audiometric examination at frequencies higher than 4000Hz were the results of air conduction thresholds, and TOAE amplitudes were not frequency specific. The frequency-specific data we obtained in our study supports that SARS-CoV-2 can cause cochlear damage. We found that DPOAE amplitudes were significantly lower at frequencies of 996 and 7998Hz in the right ear and at frequencies of 996, 2002, 7998 and 10000Hz in left ear and at frequencies of 498, 996, 2002, 7998, and 10000Hz cluster evaluations.

One advantage of the DPOAE measurement is that it can provide SNR values. The signal-to-noise ratio is defined as the ratio of signal power to noise power that compares the level of the desired signal to the level of background noise. It is worth considering that emission amplitudes and noise thresholds can vary and DPOAE amplitudes can be affected by breathing sounds and ambient noise in measurements made at different times and conditions. Therefore, SNR may have a little advantage in DPOAE measurements. However, SNR and DPOAE amplitudes are not independent of each other and it is more appropriate to use both measurements as in our study [34,35]. Low SNR values can be detected due to cochlear outer hair cell damages. Significantly lower SNR values have been found in DPOAE measurements made on workers exposed to occupational noise [32,36]. Novanta et al. reported that significantly lower SNR values at 2kHz and 4kHz in DPOAE measurements performed on primary school teachers who were constantly exposed to in-school ambient noise were found [37]. Autoimmune diseases can also negatively affect hearing. In a study conducted on the effects of Celiac disease on hearing, a significant decrease was found in the SNR values of these patients [38]. Also, in another study on psoriasis patients, a significant difference was found in the TEOAE and DPOAE responses and SNR values in all the measured frequencies when compared to the control group [39]. The COVID-19 infection is also known to trigger excessive immune responses. With this feature, there is a possibility of causing cochlear damage. In our study, the SNR values at frequencies of 996, 2002, 4004, and 6299 Hz were found to be significantly lower in both the right ear, left ear, and cluster evaluations of the patient group. Also, the SNR values were significantly lower at frequencies of 10000 Hz in the right ear and 498 Hz in the cluster evaluation.

Virus-induced hearing loss can occur unilaterally or bilaterally. It is still unclear why this involvement is unilateral or bilateral. Among the viruses that can often cause unilateral hearing loss, the HSV, VZV, and Mumps viruses can be mentioned. Also, CMV, Rubella, and measles viruses, often bilaterally, can cause hearing loss [11,40]. Although there are publications about COVID-19 infection that can cause sudden unilateral hearing loss, bilateral sudden hearing loss has not been reported. Mustafa [13] reported that there may be hearing loss due to COVID-19 in his study, but did not mention whether there was a unilateral involvement. In our work, we found that the bilateral cochlear outer hair cells were negatively affected in the patient group. When we compared the right and left ear DPOAE amplitude and SNR values, we could not find any difference between the sides.

The limitations of our article include that we could not perform pure tone audiometry and ABR tests, as the need for closer contact time with patients in a closed environment may increase the risk of the COVID-19 transmission.

Conclusion

As a result, we think that COVID-19 may cause damage to the outer hair cells of the cochlea according to our DPOAE measurements and due to the specific characteristics of the virus. However, we do not know whether this damage could be permanent or whether COVID-19 affects any hearing-related areas other than the cochlea. For this reason, more studies will be needed to evaluate different localizations of the hearing system and to determine whether hearing loss is permanent or temporary.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Before the trial, consent from the Clinical Research Ethics Committee at Adıyaman University was received (No: 2020-7, 18.06.2020).

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