EVALUATION OF COVID-19 IMPACT ON AUDITORY PATHWAY

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Received: 3/3/2023
Accepted: 17/3/2023

Online ISSN: 2735-3540

ABSTRACT:

Background: *Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection. The origin of COVID-19 was reported in December 2019 in Wuhan, China, where cases of unknown pneumonia were reported. A novel coronavirus was obtained from these cases and was suggested as the cause of this outbreak.*

Aim of the Work: *To detect presence or absence of auditory dysfunction and its type in COVID-19 patients. To investigate the possible site of lesion (up to the level of brain stem) in relation to COVID-19 infection.*

Patients and Methods: *The present study was conducted on a total of forty-five subjects in Audiology Unit-Ain Shams University Specialized Hospital and El-Demerdash hospital. The study was performed on two groups: a study group consisted of 30 post COVID-19 patients with mean age of 34.80 ± 9.81 years and a control group consisted of 15 normal hearing individuals without previous history of COVID-19 infection, their mean age was 32.80 ± 8.28 years. Both study and control groups underwent basic audiological assessment (PTA, acoustic immitancemetry & acoustic reflex), TEOAEsand neuro-otologic ABR.*

Results: *In the present study, Pure tone audiometry showed normal hearing in 28 (93.3 %) subjects of the study group subjects and documented mild high frequency sensorineural hearing loss in 2 (6.7%) subjects. Speech audiometry showed normal speech reception threshold and excellent speech discrimination in all subjects. Although the average of all frequencies was found within the normal limits in the hearing assessment of patients by PTA performed in patients who had COVID-19 and recovered, a significant higher thresholds was found, especially at 2, 4 and 8 KHz in comparison to the control group, Also there was significant lower (worse) TEOAEs signal to noise ratio (SNR) values at (2.8 and 4 KHz) in the study group in comparison to the control group and no significant difference between the study and control groups as regards low repetition rate & high repetition rate ABR parameters.*

Conclusion: *In conclusion, pure tone audiometry and transient evoked oto-acoustic emissions were affected in subjects infected with COVID-19 specially at the high frequencies.*

Key Words: *COVID-19, PTA, TEOAEs, ABR.*

INTRODUCTION:

In December 2019, a new human coronavirus (HCoV) infection has emerged in Wuhan, China. Unlike severe acute respiratory syndrome (SARS)-CoV-1 and middle east respiratory syndrome (MERS)-CoV outbreaks, according to WHO COVID 19 Dashboard, 20 February 2023, there have been 757,264,511 confirmed cases of COVID-19, including 6,850,594 deaths worldwide**(1).**

The most common symptoms that accompany COVID-19 include fever, cough, sore throat, headache, muscle pain, diarrhea, and dyspnea[(2)]. Nevertheless, there are various case reports referring to cranial nerves involvement, as it seems to be a reasonable neurotropic entity[(3&4)]. The vestibulocochlear system seems to be no exception, with reports concerning vestibular neuritis, disequilibrium, tinnitus and sudden hearing loss[(5, 6&7)].

Various theories explain the auditory system involvement following SARS CoV-2 infection. These include immune mediated damage, haematogenous spread, ischaemia theory, inflammation of auditory pathway components, Direct neural invasion of SARS-CoV-2 that affects cells through the angiotensin-converting enzyme 2 (ACE2) receptors in neurons and glial cells which is a critical step in the pathophysiology of clinical manifestations in COVID-19[(8)].

Hearing loss in COVID-19 era is one of the emerging areas of concern and calls for further research in the field for the better understanding of this entity. This study will focus on examining peripheral and central auditory pathways to the level of brain stem in post-covid-19 patients.

AIM OF THE WORK:

To detect presence or absence of auditory dysfunction and its type in COVID-19 patients. To investigate the possible site of lesion (up to the level of brain stem) in relation to COVID-19 infection.

PATIENTS AND METHODS:

Study population: The present study was conducted on a total of forty-five subjects in Audiology Unit-Ain Shams University Specialized Hospital and El-Demerdash hospital after approval of research Ethics Committee in September 2021. The purpose and design of the study were explained to all participants individually and informed oral consent was taken before starting the examination.

The subjects were divided into:

a) Study group: Thirty subjects with past history of COVID-19 infection.

Criteria for selection:

Inclusion Criteria:

1. Adults ranging from 18-60 years.
2. Post COVID-19 subjects diagnosed by laboratory tests, radiological investigations.
3. Subjects with past history of COVID-19 infection within the last 6 months.
4. Patients who were not older than 60 years old to avoid age related hearing loss.
5. Patients without neurological disorders prior to infection with COVID-19 (or any disease that may affect the central auditory pathway).
6. Patients who were not previously diagnosed with hearing loss or complained from signs of auditory dysfunction prior to infection with COVID-19.
7. Patients without systemic disorders like diabetes and hypertension (or any disease that may affect the peripheral or central auditory pathway).

b) Control group:

Fifteen normal hearing subjects age matched to study group. All subjects did not have any history suggestive of ear disease or central nervous system (CNS) disease or COVID-19 infection.

Methods:

All patients were subjected to the following; either in one or more than one session for about 2 hours:

Detailed audiological history including: presence of hearing loss, tinnitus, discharge, and ear ache/ ear fullness. **Full COVID-19 specific history** including: method of diagnosis, types of symptoms,

symptoms severity, number of attacks, investigations, treatment and vaccination. **Otological Examination**: to exclude any external or middle ear pathologies. **Basic Audiological Evaluation including**: Pure tone audiometry for frequencies 250-8000 Hz for air conduction and 500-4000 Hz for bone conduction, Speech audiometry including speech reception threshold (SRT) using Arabic spondee words[9] and speech discrimination scores using adult Arabic Phonetically Balanced monosyllabic words[10], Acoustic immittancemetry (Tympanometry, ipsilateral and contralateral Acoustic reflex threshold at 0.5, 1, 2 and 4 KHz). Transient evoked Otoacoustic emission and Neuro-otologic auditory brainstem response (ABR).

Ethical Considerations:

Verbal consent obtained from patients before testing after explaining the aim of the test and the procedure to be done. Also, approval from Ethical committee of Ain Shams University was obtained before start of this research.

Statistical Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using statistical package for social sciences (IBM SPSS) version 23. The quantitative data with parametric distribution were presented as mean, standard deviations and ranges. Also qualitative variables were presented as number and percentages. The p-value was considered significant as the following: P-value > 0.05: Non significant (NS), P-value < 0.05: Significant (S), P-value < 0.01: Highly significant (HS).

RESULTS:

The study was performed on two groups: A study group (group A) involved 30 post COVID-19 patients with mean age of 34.8 years and a control group (group B) constituted of 15 normal hearing individuals without previous history of COVID-19 infection, their mean age was 32.8 years.

Table 1: Age and gender distribution in the study and control groups:

		Group		Chi-square/ T test	P-value	Sig.
		Study Gr.	Control Gr.			
		No. = 30	No. = 15			
Gender	Male	13 (43.3%)	8 (53.3%)	X^2= 0.402*	0.526	NS
	Female	17 (56.7%)	7 (46.7%)			
Age	Mean ±SD	34.80 ± 9.81	32.80 ± 8.28	T= 0.677•	0.502	NS
	Range	21.0-58.0	22.0-52.0			

*•: Independent t-test; *: Chi-square test P>0.05: Non significant; P<0.05: Significant, P< 0.01: Highly significant SD is the standard deviation*

Table (1) showed that both study and control groups were age and gender matched.

Table 2: Distribution of study group as regards presenting symptoms of COVID-19:

		No. = 30
Pulmonary symptoms	Yes	26 (86.7%)
	No	4 (13.3%)
Systemic symptoms	Yes	24 (80.0%)
	No	6 (20.0%)
GIT symptoms	Yes	14 (46.7%)
	No	16 (53.3%)
ENT symptoms	Yes	26 (86.7%)
	No	4 (13.3%)
Auditory symptoms	Yes	13 (43.3)
	No	17 (56.7)

Table (2) revealed that the majority of cases presented with pulmonary (as cough and shortness of breath) and ENT symptoms (as loss of taste and loss of smell).

Table 3: Percentage of specific auditory complaints (Hearing Loss, tinnitus, earache and ear fullness) in the study group:

	No. (%)
Hearing loss	2 / 30 (6.7%)
Tinnitus	6 / 30 (20.0%)
Earache	3 / 30 (10.0%)
Ear fullness	6 / 30 (20.0%)
Total no. of patients with Auditory symptoms	13 / 30 (43.3%)

Table (3) revealed that the majority of patients complaining from tinnitus and ear fullness.

Table 4: Comparison between study and control groups as regards pure tone air conduction audiometric threshold at different frequencies.

		Study Gr. No. = 60 ears	Control Gr. No. = 30 ears	Test value	P-value	Sig.
0.25 KHZ	Mean±SD	14.58 ± 4.72	13.33 ± 4.22	1.225•	0.224	NS
	Range	5 - 20	5 – 20			
0.5 KHZ	Mean±SD	13.58 ± 5.05	11.67 ± 4.79	1.726•	0.088	NS
	Range	5 - 25	5 – 20			
1 KHZ	Mean±SD	14.42 ± 4.13	13.50 ± 2.33	1.128•	0.262	NS
	Range	5 - 25	10 – 15			
2 KHZ	Mean±SD	15.75 ± 5.19	13.33 ± 3.79	2.263•	0.026	S
	Range	5 - 30	5 – 20			
4 KHZ	Mean±SD	18.67 ± 4.50	13.83 ± 4.68	4.743•	0.000	HS
	Range	10 - 35	5 – 25			
8 KHZ	Mean±SD	20.75 ± 4.20	15.17 ± 4.04	6.017•	0.000	HS
	Range	15 - 35	10 – 25			

•: Independent t-test SD is the standard deviation

Table (4) showed that statistically significant higher PTA thresholds at higher frequencies (2, 4 and 8 KHz) in the study group.

Table 5: Comparison between study and control groups as regards TEOAEs SNR in dB across different frequencies:

			Group A No. = 60	Group B No. = 30	Test value•	P-value	Sig.
TEOAEs SNR	1 KHz	Mean±SD	17.05 ± 7.55	16.74 ± 6.07	0.197	0.844	NS
		Range	-9.4 - 32.7	-3.9 – 23			
	1.4 KHz	Mean±SD	21.43 ± 6.45	21.95 ± 5.09	-0.390	0.697	NS
		Range	-1.8 - 32.3	4.9 – 29			
	2 KHz	Mean±SD	19.31 ± 5.99	20.20 ± 4.34	-0.721	0.473	NS
		Range	-6 – 31	7.8 - 26.9			
	2.8 KHz	Mean±SD	14.34 ± 6.32	18.62 ± 7.01	2.914	0.005	HS
		Range	-5.9 - 26.6	6.3 – 32.9			
	4 KHz	Mean±SD	16.07 ± 5.14	18.65 ± 5.69	2.171	0.033	S
		Range	0.4 - 24.7	3.6- 28.3			

•: Independent t-test SD is the standard deviation

Table (5) showed that TEOAE SNR at 2.8 and 4 kHz measurements in the study group was statistically significantly lower (worse) than control group.

Table 6: Comparison between study and control groups as regards Neuro-otologic ABR results:

		Study Gr. No. = 60	Control Gr. No. = 30	Test value•	P-value	Sig.
LRR Wave I latency	Mean±SD	1.58 ± 0.19	1.52 ± 0.17	1.345	0.182	NS
	Range	1.2 - 1.9	1.2 - 1.9			
LRR wave III latency	Mean±SD	3.63 ± 0.21	3.61 ± 0.18	0.551	0.583	NS
	Range	3.1 - 4.1	3.1 - 3.9			
LRR wave V latency	Mean±SD	5.56 ± 0.23	5.57 ± 0.20	-0.137	0.892	NS
	Range	5.1 - 6	5.2 - 5.9			
LRR I-III inter-peak latency	Mean±SD	2.04 ± 0.22	2.09 ± 0.20	-0.961	0.339	NS
	Range	1.4 - 2.9	1.8 - 2.5			
LRR III-V inter-peak latency	Mean±SD	1.93 ± 0.20	1.95 ± 0.22	-0.362	0.718	NS
	Range	1.4 - 2.6	1.5 - 2.5			
LRR I-V inter-peak latency	Mean±SD	3.97 ± 0.24	4.05 ± 0.19	-1.505	0.136	NS
	Range	3.4 - 4.7	3.7 - 4.5			
HRR wave I latency	Mean±SD	1.78 ± 0.18	1.78 ± 0.18	-0.029	0.977	NS
	Range	1.3 - 2.1	1.3 - 2.1			
HRR WAVE III latency	Mean±SD	3.89 ± 0.22	3.85 ± 0.21	0.787	0.433	NS
	Range	3.2 - 4.6	3.3 - 4.2			
HRR wave v latency	Mean±SD	5.88 ± 0.26	5.93 ± 0.22	-0.776	0.440	NS
	Range	5.2 - 6.4	5.4 - 6.3			
HRR I-III inter-peak latency	Mean±SD	2.08 ± 0.24	2.06 ± 0.24	0.379	0.706	NS
	Range	1.3 – 3	1.5 - 2.6			
HRR I-V inter-peak latency	Mean±SD	3.94 ± 0.60	4.14 ± 0.25	-1.716	0.090	NS
	Range	1.9 - 4.8	3.6 - 4.6			
V lat. Difference with LRR	Mean±SD	0.33 ± 0.14	0.36 ± 0.13	-1.059	0.293	NS
	Range	0.1 - 0.7	0.1 - 0.6			

•: Independent t-test P>0.05: Non significant; P<0.05: Significant, P< 0.01: Highly significant
SD is the standard deviation

Table (6) showed that there was no statistically significant difference between the two groups regarding neuro-otologic ABR parameters.

DISCUSSION

On 30 January 2020, the world health organization (WHO) declared the coronavirus disease 19 (COVID- 19) as a public health emergency of international concern (PHEIC), and declared it as a pandemic on 11 March 2020[(11)].

Former members of the coronavirus family (MERS and SARS) have had effects on the auditory system. Similarly, the SARS-CoV-2 virus may also cause hearing loss. SARS-CoV-2 may have direct neurological involvement or inner ear involvement due to hyper-coagulation, which is common in recent COVID-19 patients[(12)].

The age group for the inclusion in the study was set from 18 to 60 years, the lower limit of age was set at 18 years. The upper age limit was set to 60 years to avoid the age-related hearing loss based on studies in the literature which suggest the occurance age related hearing from the 5th decade of life[(13)]. **Mustafa**[(14)] in their study included the COVID-19 patients aged between 20 and 50 years, for the similar reasons.

History taking was done for COVID-19 patients with details on the COVID 19 symptoms, ear related symptoms, with duration of onset not more than 6 months. As duration of onset more than 6 months will signify pathology other than COVID-19 infection.

In the present study, pulmonary symptoms were the most frequently encountered followed by systemic symptoms (table 2). Supporting this finding, another study conducted by **Huang et al.**[15] who stated that, pneumonia is the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging.

These findings may be explained by targeting the SARS-CoV-2 viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor which is highly expressed in the lung and appears to be the predominant portal of entry.

In contrast, this finding disagrees with **Burak et al.**[16] who reported systemic symptoms as the most frequently encountered.

Tinnitus and ear fullness were the main audiological complaint followed by ear fullness (table 3). **Burak et al.**[16] **reported** that, the most common audiological symptoms in the group with COVID-19 were tinnitus (33.3%) followed by hearing loss (23.4%), ear fullness (3.3%) and earache (3.3%) (table 3)**.** Another study conducting by **Almishaal and Alrushaidan**[17] reported aural fullness was the most common symptoms (18.94%) followed by tinnitus (9.97%) and hearing loss (6.31%).

Pure tone audiometry showed normal hearing in 28 (93.3 %) subjects of the study group and documented mild high frequency sensorineural hearing loss in only 2 (6.7%) subjects.Speech audiometry showed normal speech reception threshold and excellent speech discrimination in all subjects. The mean thresholds at each frequency were within normal range ≤ 25 dB HL however, significant statistical higher thresholds were found at 2, 4 and 8 KHz in the study group in comparison to the control group (table 4).

This finding is consistent with other studies reporting higher frequencies affection in post COVID-19 patients. **Mustafa**[14] reported that high-frequency pure-tone thresholds (4, 6, and 8 kHz) were higher (worse) in the asymptomatic COVID-19 patients compared to the control group Moreover, another study found a significant difference in high-frequency pure-tone thresholds (4 and 8 kHz) between the COVID-19 positive group and the control groups[12]**.**

Affection of the auditory system may be duo ischemic damage to the auditory structures by causing clot formation in the vessels feeding the auditory system because it enters the cell by binding to the ACE-2 receptor in the vessels. In addition, the ACE-2 receptor is abundant in the brain and brainstem, and therefore, the virus may affect the hearing centers in the brainstem[18]**.**

There was a significantly lower (worse) TEOAEs signal to noise ratio (SNR) values at (2.8 and 4 KHz) in the study group in comparison to the control group **(**table 5). This agrees with findings reported by **Burak et al.**[16] who reported that hearing thresholds were significantly worse at 4 kHz and higher frequencies in individuals diagnosed with COVID-19. In addition, TEOAE amplitudes at 1500 Hz, 2000 Hz and 4000 Hz frequencies and DPOAE amplitudes at 4000 Hz and higher frequencies were significantly lower in this group. Another study supporting the present study findings reported by **Gedik et al.**[19]**,** who found low signal-to-noise ratio in TEOAE at 4 kHz in the patient group.

According to these findings, it is possible to say that COVID-19 may lead to outer hair cell damage mainly situated in the basal turn of the cochlea, and audiological problems associated with the disease are related to cochlea, sparing central auditory connections [20]. In other studies, to be compared with the effects of ototoxic drugs and noise on hearing, it was observed that

the outer hair cells in the basal region of the cochlea were affected more than the outer hair cells in the apex. This was explained by the intrinsic sensitivity of hair cells in the basal region[21]**.** Likewise, in current study, we think that the high frequency lower SNR values of TEOAEs caused by the COVID-19 virus is related to the intrinsic sensitivity of the hair cells in the basal region.

In the current study, few patients reported hearing loss that may be associated with COVID-19. Although the comparison results of the audiological assessments in the test and control groups were significant, the differences were small. While COVID-19 appears to have effects on the auditory system, these effects are thought to be minor and the mechanism of these effects requires further research.

The ABR test can be used to evaluate the effects of COVID-19 on the brainstem. In current study, there was no significant difference between the study and control groups as regards low repetition & high repetition rates ABR parameters (table 6). This finding is consistent with a study conducted by **Hassani et al.**[22] who stated that there was no significant difference between the study and control groups as regards ABR parameters at high and low repetition rates.

In conclusion, pure tone audiometry and transient evoked oto-acoustic emissions were affected in subjects infected with COVID-19 specially at the high frequencies.

Conclusion:

Our study showed that Pulmonary symptoms were the most common complaint among COVID-19 patients. As regards audiological complaints, tinnitus and ear fullness were the most commonly encountered. Affection of PTA and TEOAEs in study group was encountered in high frequencies and sparing lower frequencies

The results of the present study also demonstrated that the absence of major symptoms may hide unknown impact on the delicate sensory organs taking the cochlea as an example.

Conflict Of Interest:

The authors declare that they have no conflict of interest.

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تقييم تأثير كوفيد-١٩ على المسار السمعي

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المقدمة: مرض فيروس كورونا ٢٠١٩ ناجم عن عدوى فيروس كورونا ٢ المتلازمة التنفسية الحادة الوخيمة الجديدة. تم الإبلاغ عن أصل مرض فيروس كورونا ٢٠١٩ في ديسمبر ٢٠١٩ في مدينة ووهان الصينية ، حيث تم الإبلاغ عن حالات التهاب رئوي غير معروف. تم الحصول على فيروس كورونا جديد من هذه الحالات واقترح على أنه سبب هذا التفشي. يشار إلى الفيروس باسم فيروس كورونا ٢ المتلازمة التنفسية الحادة الوخيمة ، والمرض المصاحب له باسم مرض فيروس كورونا ٢٠١٩. أعلنت منظمة الصحة العالمية في ١١ مارس ٢٠٢٠ أن مرض فيروس كورونا ٢٠١٩ أصبح وباءً منتشرًا في جميع أنحاء العالم.

المرضي وطرق البحث: أجريت هذه الدراسة للكشف عن وجود أو عدم وجود خلل سمعي لدى مرضى فيروس كورونا ٢٠١٩ وللتحقق من الموقع المحتمل للآفة (حتى مستوى جذع الدماغ) فيما يتعلق بعدوى مرض فيروس كورونا ٢٠١٩. تم إجراء الدراسة على مجموعتين: مجموعة دراسة تتكون من ٣٠ مريضًا بعد الإصابة بفيروس كورونا ٢٠١٩ بمتوسط عمر ٣٤,٨٠ + ٩,٨١ سنة ومجموعة ضابطة مكونة من ١٥ فردًا سمعًا طبيعيًا دون تاريخ سابق للإصابة بمرض فيروس كورونا ٢٠١٩ ، وكان متوسط أعمارهم. ٣٢,٨٠ + ٨,٢٨ سنة. خضعت كل من مجموعتي الدراسة والمجموعة الضابطة لتقييم سمعي أساسي (رأب الأوعية الدموية عبر الجلد ، قياس المناعة الصوتية وردود الفعل الصوتية) ، وأثار الانبعاث الصوتي العابر في وجود وغياب الكبت المقابل ، وضوح الكلام العربي في اختبار الضوضاء للبالغين واستجابة جذع الدماغ السمعي العصبي.

النتائج: في هذه الدراسة ، أظهر قياس السمع النظيف سمعًا طبيعيًا في ٢٨ (٩٣,٣٪) من أفراد مجموعة الدراسة ووثق ضعف السمع الحسي العصبي الخفيف عالي التردد في ٢ (٦,٧٪) موضوعين. أظهر قياس سمع الكلام عتبة استقبال الكلام الطبيعية وتمييزًا ممتازًا في الكلام في جميع الموضوعات. على الرغم من العثور على متوسط جميع الترددات ضمن الحدود الطبيعية في التقييم السمعي للمرضى بواسطة رأب الأوعية الدموية عبر الجلد الذي تم إجراؤه في المرضى الذين أصيبوا بمرض فيروس كورونا ٢٠١٩ وتعافوا ، فقد تم العثور على عتبات أعلى بشكل ملحوظ ، خاصة عند ٢ و ٤ و ٨ كيلو هرتز مقارنةً بـ المجموعة الضابطة ، لا يوجد فرق معنوي بين مجموعتي الدراسة والضابطة فيما يتعلق بوضوح الكلام في اختبار الضوضاء ، كما كان هناك انخفاض معنوي (أسوأ) إشارة انبعاث صوتية انتقالية إلى نسبة ضوضاء عند (٢,٨ و ٤ كيلو هرتز) في مجموعة الدراسة بالمقارنة للمجموعة الضابطة ولا يوجد فرق معنوي بين الدراسة ومجموعات المراقبة فيما يتعلق بانخفاض معدل التكرار ومعدل التكرار المرتفع لمتغيرات استجابة جذع الدماغ السمعي.في دراستنا ، تمت مقارنة ثلاثين أذنًا في المجموعة الضابطة وستين أذنًا في مجموعة الدراسة. وجد أن ٧٦,٧٪ من آذان المجموعة الضابطة و ٤٢,٤٪ من آذان مجموعة المرضى يعانون من كبت طبيعي وكانت هناك علاقة معنوية بين المجموعتين.

الخلاصة:. وكشفت دراستنا أنالجهاز السمعي يمكن أن يتأثر في مرضى فيروس كورونا ٢٠١٩.