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BRAINSTEM AUDITORY EVOKED POTENTIAL FINDINGS IN SEVERE POST-COVID-19 PATIENTS

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ABSTRACT

Introduction: The severe acute respiratory syndrome called covid-19 has a broad clinical spectrum that can range from asymptomatic infections to severe conditions. It is hypothesized that covid-19 can cause neurological symptoms through direct and indirect mechanisms. The high amount of ACE2 in the brain and medulla oblongata can cause an increase in the viral load in the auditory center and a decrease in the concentration of oxygen in red blood cells. In this way, covid-19 can lead to cellular hypoxia and consequently damage the centers responsible for hearing. Objective: to analyze the findings of Brainstem Auditory Evoked Potential in severe post-COVID-19 patients. Method: This is a descriptive, cross-sectional, analytical study, which was carried out at the audiology outpatient clinic of the Speech Therapy Department. The study was carried out after approval by the Human Research Ethics Committee (CAAE: 61448422.7.0000.0217). Individuals who developed Covid-19 in a serious condition and who required medical intervention and follow-up participated in the study. This study is part of an umbrella project, CNPq Universal in which all individuals were submitted to evaluations of other skills related to language, swallowing and cognition. Meatoscopy, pure tone threshold audiometry, immittance testing, and brainstem auditory evoked potential (BAEP) were performed. Results: It was possible to observe according to the hearing thresholds, that most individuals did not present hearing loss. Regarding BAEP, all individuals underwent the test, and the waves were recordable, with the exception of waves I and III for four individuals. For the variable hypertension, the test identified a statistically significant difference between the findings in the interpeak interval I-III in both ears. Conclusion: Most BAEP tracings showed altered morphology, although latencies were preserved. In addition, a significant increase in interpeaks I-III was found in both ears in patients with hypertension.

Keywords: Covid-19. Auditory Evoked Potentials. Audiology.

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INTRODUCTION

In December 2019, the city of Wuhan, China, alerted the World Health Organization (WHO) about the several cases of pneumonia with unknown cause, arousing the interest of health authorities.[1] Shortly thereafter, in January 2020, Chinese researchers identified a new type of coronavirus (SARS-CoV-2) as the etiological agent of a severe acute respiratory syndrome called COVID-19.[2] The first case of COVID-19 recorded in Brazil was in February 2020 and a month later, on March 11, the WHO declared that the world was experiencing the first pandemic of the twenty-first century. [3.4]

COVID-19 has a broad clinical spectrum that can range from asymptomatic infections to severe conditions. Its transmission can occur directly, through contact with infected people, through respiratory droplets, and indirectly, through contact with contaminated surfaces and objects. [5] People infected with the coronavirus develop signs and symptoms that may include fever, accompanied by cough and sore throat. In more severe cases it can cause pneumonia and acute respiratory failure. [6.7]

The virus replicates when it enters the cell through the contact of its protein (S – Spike protein), with the ACE2 receptor, present in the cell membrane of some cells in human tissue, such as lungs, kidneys, heart and Central Nervous System (CNS). ACE2 is widely disseminated in human tissues, including the central nervous system, being expressed in the respiratory epithelium and vascular endothelium.[8] SARS-CoV-2 can cause damage to the host through four mechanisms that include: direct injury to host cells; dysregulation of ACE2-activated pathways, potentiating inflammatory activation; damage to endothelial cells, which can lead to obstruction of blood vessels and consequently tissue hypoxia and/or extravasation of fluid into tissues and dysregulation of the system. [9]

In addition to symptoms such as headache, dizziness, and neuropathic pain, common especially in more severe patients, studies have shown neurological manifestations associated with SARS-CoV-2 suggesting the development of possible complications. [10] Animal models of SARS and the Middle East respiratory syndrome caused by CoVs in the epidemics that occurred in 2002 and 2012 already considered the neurological impact of the coronavirus and the potential for its spread in the CNS.[11]

It is hypothesized that covid-19 can cause neurological symptoms through direct and indirect mechanisms. [12] The direct effect of the virus on the CNS occurs through the invasion of the respiratory virus, either through the bloodstream or through the retrograde neuronal route. The bloodstream mechanism infects endothelial cells at the blood-brain

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barrier (BBB) or epithelial cells at the blood-cerebrospinal fluid (CSF) barrier at the choroid plexus or even reaches the CNS through leukocytes.[13] The indirect effect through the neuronal pathway occurs through retrograde axonal transport through various cranial nerves (olfactory, trigeminal, glossopharyngeal and vagus) or peripheral nerves.[10]

A study conducted by Mao et al (2020) sought to identify the neurological manifestations of patients with coronavirus. The sample consisted of 214 patients, of whom 36.4% had neurological symptoms. These symptoms were more frequent in patients with severe infection, representing 45.5% of the individuals analyzed. In addition, the study showed that severe patients were the oldest and had more hypertension when compared to non-severe patients.[12]

The high amount of ACE2 in the brain and medulla oblongata can provide an increase in viral load in the auditory center, located in the temporal lobe.[14] In addition, the decrease in oxygen concentration in red blood cells due to covid-19 can lead to cellular hypoxia and consequently harm the centers responsible for hearing.[15] COVID-19 neuroinvasion involves the auditory centers in the brain, causing possible damage to the secondary auditory system and the auditory brainstem due to viral infections.[16]

In view of this, studies have shown that SARS-COV-2 can affect the auditory system, cause congenital or acquired hearing loss, of the uni or bilateral, progressive or stable sensorineural type.[17,18] The study by Mustafa (2020) showed in its results the impact of covid-19 infection on the outer hair cells of the cochlea, evidenced by the reduction in the amplitude of transient otoacoustic emissions in the test group when compared to the control group. Viral infections typically reach the auditory system intracochlearly, however, some viruses can expand to the auditory brainstem.[19]

As this is a recent epidemic, whose sequelae resulting from the disease and the treatments applied to patients are currently manifesting themselves in clinical practice, it is essential to carry out studies that highlight the impacts of COVID-19 on the auditory system of affected individuals. Therefore, the present study aimed to analyze the findings of Brainstem Auditory Evoked Potential in patients after severe covid-19.

MATERIALS AND METHODS

STUDY DESIGN

This is a descriptive, cross-sectional, analytical study, which was carried out at the audiology outpatient clinic of the Speech-Language Pathology and Audiology School Clinic

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of the Department of Speech-Language Pathology and Audiology, which is located at the Center for Simulations and Practices (CENSIP) of the Federal University of Sergipe on campus in the city of Lagarto.

The research was carried out after approval by the Human Research Ethics Committee (CAAE protocol: 61448422.7.0000.0217). Individuals who developed Covid-19 in serious condition, required intervention and medical follow-up, participated in the study. Individuals were invited to participate in the study after orientation on the research objectives and the Informed Consent Form (ICF) was signed, voluntarily accepting participation in the research, as recommended by Resolution 466/12 of the National Health Council.

This study is part of an umbrella project, CNPq Universal (Process: 402791/2021-5), in which all individuals were submitted to assessments of other skills related to language, swallowing, and cognition. After these evaluations, they were referred for audiological evaluation in which a specific interview was carried out related to complaints of the auditory system (previous history and evolution of the complaint, family history of disease, exposure to noise, general health status and complaints resulting from the post-covid episode); meatoscopy, in order to verify the conditions of the external acoustic meatus for the performance of auditory exams: pure tone threshold audiometry to verify auditory thresholds, immittance testing and Brainstem Auditory Evoked Potential (BAEP).

INCLUSION CRITERIA

Individuals of all genders, with a history of severe covid who have undergone some type of medical intervention; patients with normal hearing or mild hearing loss and type A curve hearing loss on tympanometry (Jerger, 1978) to ensure normal middle ear functionality; age over 12 years.

EXCLUSION CRITERIA

Individuals with no history of severe covid; people with moderate, severe and profound hearing loss; previous neurological changes unrelated to the covid episode; age under 12 years.

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BRAINSTEM AUDITORY EVOKED POTENTIAL

The BAEP evaluation was performed in a quiet room, with the patient lying comfortably on a stretcher and with his eyes closed (elimination of the artifact caused by eye movement). Disposable electrodes of the AG/AGCL type ECG with gel positioned on the skull were used, according to the international standard 10-20. Before positioning the electrodes, the skin was cleaned with NUPREP abrasive paste. To start the electrophysiological evaluation, the electrodes showed individual impedance less than 5KOhm and impedance between them less than 2KOhm. The equipment used was the *SMART-Interacoustic Intelligent Hearing System.*

The active electrodes were positioned in Fz and connected to input 1 of channels 1 and 2, respectively, of the preamplifier. The reference electrodes were positioned on the mastoids, at input 2 of each channel, of the preamplifier and the ground electrode was placed in the Fpz position.

Acoustic stimuli of *the Click type* with rarefied and condensed polarity, presentation rate of 21.1 stimuli per second, at an intensity of 80 dBnH, were used through the insertion earphone (EAR TONE 3A). The bandpass filters were set from 100 to 3000 Hz and gain at 100 thousand. The criterion for defining the response was the reproducibility between the tracings, which were collected more than once at the same intensity and polarity with 2048 promediations.

DATA ANALYSIS

After data collection and analysis of the exams, the results were submitted to descriptive statistical analysis (mean, standard deviation, median, maximum value and minimum value) and inferential analysis using the Mann-Whitney test to verify the correlation of BAEP findings in patients after severe covid and whether there was a correlation with any variable investigated in the initial interview.

RESULTS

The study included 26 individuals of both genders [10 females (38.5%) and 16 males (61.5%)], with a mean (± standard deviation) age in years of 53.4 ±14.1 (median of 52; minimum 30 and maximum 83) years. Most participants self-declared themselves as brown (20.80%), four people (16%) self-declared themselves white, and one person (4%) preferred not to answer.

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Regarding COVID-19-related symptoms, table 1 presents the relative and absolute frequency of each sign and symptom. It was possible to observe that the majority of the sample had difficulty breathing (57.7%) and cough (80.8%).

Table 1. Absolute and relative frequency of COVID-19 signs and symptoms

Signs and Symptoms	Yes or no	Absolute Frequency (N)	Relative Frequency (%)
Chest Pains	No	24	92,3%
	Yes	02	7,7%
Nasal congestion	No	23	88,5%
	Yes	03	11,5%
Saturation drop	No	20	76,9%
	Yes	06	23,1%
Tiredness	No	20	76,9%
	Yes	06	23,1%
Fever	No	16	61,5%
	Yes	10	38,5%
Lack of appetite	No	24	92,3%
	Yes	02	7,7%
Headache	No	21	80,8%
	Yes	05	19,2%
Cough	No	05	19,2%
	Yes	21	80,8%
Loss of smell	No	23	88,5%
	Yes	03	11,5%
Respiratory distress	No	11	42,3%
	Yes	15	57,7%
Diarrhoea	No	25	96,2%
	Yes	01	3,8%

Regarding the audiological evaluation data, it is possible to observe that, according to the hearing thresholds, most of them did not present hearing loss. Table 2 presents the

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descriptive data for the hearing thresholds of the right and left ears, as well as the comparison between both, for all 26 individuals evaluated.

Table 2: Descriptive statistical analysis for all frequencies tested in pure tone audiometry in both ears and static analysis when comparing the ears using the Mann-Whitney test.

	PURE TONE THRESHOLD AUDIOMETRY							
	RIGHT EAR				LEFT EAR			
	X±DP	Median	Max.	Min.	X±DP	Median	Max.	Min.
500 Hz	21.0±10.0	25,0	55,0	0,0	21.9±6.01	25,0	35,0	10,0
1 KHz	21.2±9.5	25,0	55,0	5,0	21.7±9.37	25,0	55,0	5,0
2 KHz	24.0±10.1	25,0	55,0	5,0	24.6±0.05	25,0	55,0	5,0
3 KHz	28.3±18.5	25,0	85,0	0,0	29.0±16.4	25,0	75,0	5,0
4 KHz	30.2±17.2	25,0	75,0	5,0	30.6±15.5	25,0	65,0	5,0
6 KHz	30.2±17.7	25,0	80,0	5,0	31.7±17.6	25,0	85,0	10,0
8 KHz	28.8±18.3	25,0	70,0	0,0	28.8±14.0	25,0	75,0	5,0

It was possible to perform BAEP in all individuals, however it was not possible to record waves I and III in four individuals. The descriptive statistical analysis for the absolute latencies of waves I, III, and V and interpeak latencies I-III, III-V, and I-V, as well as the difference between the ears, are described in Table 3.

Table 3: Descriptive analysis of brainstem auditory evoked potentials regarding the absolute latencies of waves I, III and V and interpeak latencies I-III, III-V and I-V, in ms, and the comparison between the right and left ears using the Mann-Whitney test.

	PEATE LATENCIES (MS)							
	RIGHT EAR				LEFT EAR			
	X±DP	Median	Max.	Min.	X±DP	Median	Max.	Min.
I	1.78±0.2	1,73	2,17	1,50	1.82±0.3	1,75	2,98	1,45
III	3.94±0.3	3,95	4,88	3,03	4.00±0.3	3,90	5,00	3,60
V	6.01±0.3	5,93	6,90	5,28	6.03±0.2	5,95	6,95	5,28
I-III	2.11±0.2	2,10	2,60	1,38	2.17±0.2	2,12	2,95	1,90
III-V	2.03±0.2	2,05	2,90	1,48	1.99±0.2	1,97	2,55	1,55
I-V	4.26±0.5	4,12	6,58	3,58	4.16±0.3	4,12	4,95	3,58

Another analysis investigated the relationship between BAEP findings and chronic non-communicable diseases, such as hypertension, diabetes, obesity, pneumonia, kidney disease, heart disease, and neurological diseases. For all these variables, except hypertension, no significant relationship was observed. In the case of hypertension, the test establishes a statistically significant difference between the findings in the I-III interpeak interval in both ears, as shown in Table 4

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Table 4. Comparison between BAEP results in people with and without hypertension

	HAS	Average	Median	Standard deviation	p-value
I (OD)	No	1,70	1,68	0,14	0,14
	yes	1,85	1,88	0,23	
III (OD)	No	4,00	3,85	0,32	1,00
	yes	3,90	3,98	0,32	
V (OD)	No	6,00	5,90	0,38	0,50
	yes	6,00	5,93	0,35	
I-III (OD)	No	2,21	2,15	0,17	0,01*
	yes	2,00	1,96	0,28	
III-V (OD)	No	2,00	2,05	0,21	0,36
	yes	2,10	2,07	0,33	
I-V (OD)	No	4,40	4,23	0,75	0,25
	yes	4,10	4,05	0,30	
I (OE)	No	1,80	1,70	0,39	0,07
	yes	1,90	1,88	0,19	
III (OE)	No	4,10	3,90	0,42	1,00
	yes	4,00	3,95	0,18	
V (OE)	No	6,00	5,98	0,47	0,98
	yes	6,00	5,95	0,34	
I-III (OE)	No	2,30	2,16	0,31	0,04*
	yes	2,10	2,02	0,14	
III-V (OE)	No	2,00	2,00	0,23	0,89
	yes	2,00	1,95	0,24	
I-V (OE)	No	4,30	4,20	0,40	0,25
	yes	4,10	4,10	0,34	
INTERAURAL DIFFERENCE OF WAVE V	No	-0,1	-0,03	0,27	0,16
	yes	0	0,05	0,21	
INTERAURAL DIFFERENCE OF INTERPICO I-V	No	0,2	0,02	0,55	0,78
	yes	0	0,05	0,28	

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The Mann-Whitney test verified the correlation between the presence of the following diseases: hypertension, diabetes mellitus, obesity, pneumonia, kidney disease, heart disease, and neurological diseases. After the correlation of the findings of the potentials, it was observed that only hypertension presented a statistically significant difference. This demonstrates that patients infected with covid-19 and hypertensive patients had greater alterations in BAEP findings.

DISCUSSION

There is still no clearly described mechanism on means for the installation of the virus in the CNS, but there is already a consensus that there is a neurotropism for the COVID 19 virus.[20] In this sense, studies that demonstrate the clinical findings of the effects of this virus on the auditory system, especially through procedures that evaluate the retrocochlear portion of the auditory system, are extremely important to elucidate the topodiagnosis of the alteration and propose rehabilitation that favors the affected region. BAEP is an electrophysiological test of the auditory system, which allows the evaluation of the conduction of the electrical response derived from an auditory event, both in its peripheral and central portions.

In this study, individuals from an umbrella research project participated, in which the inclusion criterion was to have contracted covid in a severe way in which hospitalization was necessary. Among the signs and symptoms presented by the sample, respiratory difficulty (57.7%) and cough were the ones with the highest incidence, demonstrating that the respiratory system seems to have been the most compromised in the acute phase of the disease. Although half of the sample showed symptoms associated with respiratory distress, only six people required intubation or remained in the ICU. For the others in this group, the intervention method was supportive treatment (oxygen therapy), non-invasive mechanical ventilation, and drug treatment. This is a relevant finding, since the CNS is particularly susceptible to the effects of hypoxia and can cause damage to several brain areas, including the auditory system.[21]

Regarding auditory symptoms, not all participants reported complaints, as this was not an inclusion criterion in the study. However, 23% of the sample reported some symptom, the most common being tinnitus (7.6%) and hypoacusis (15.3%).

All individuals underwent conventional audiological evaluation to verify auditory thresholds and middle ear conditions. In total, 28 individuals were referred for audiological evaluation, but two were excluded from the study because they had sensorineural hearing loss. Those who remained in the study (n=26) had mean ATL values lower than 32dBHL at least one frequency, demonstrating that most individuals did not present characteristics of disabling hearing loss.

The means and the highest standard deviations were observed in frequencies from 2kHz, with a slight increase in 8kHz. This finding may be related to the age of the participants, whose mean age was 53.4 years, ranging from 30 to 80 years. According to Portmann and Portmann (1993)[22], presbycusis can begin at 20/30 years of age, becoming more evident between 40 and 50 years of age. In addition, presbycusis initially affects high frequencies and later gradually affects medium and low frequencies [23], similar to what occurred in our study. However, it is important to emphasize that the individuals in this study reported not having auditory complaints before the COVID episode, but as most had normal hearing (84.6%) or mild hearing loss (15.3%), they could already have minimal changes in hearing thresholds, without Handcap changes.

Another point to be considered is the type of intervention required for the treatment of covid, since some individuals required drug treatment. Some drugs were administered to the individuals in this study, which in turn are already known for their ototoxic/neurotoxic potential, such as Azithromycin (ototoxic drug)[24], and Lopinavir (neurotoxic drug)[25]. The occurrence of Chronic Non-Communicable Diseases (NCDs) can also be pointed out as a causal or aggravating factor for changes in hearing thresholds. In our sample, 61.5% of the individuals had some type of CNCD, which can be cited as hypertension, diabetes mellitus, obesity, pneumonia, kidney disease, heart disease, and neurological diseases. Some studies have already been pointing to the high risk of complications from COVID-19 in patients with NCDs, which are presented in a severe form and with a higher prevalence of symptoms. [26,27,28]

More recent studies already show that SAH is the comorbidity most commonly associated with the severity or mortality from covid-19. Some authors29,12 explain that what may lead to a higher prevalence of SAH cases in patients with severe COVID is due to the fact that the ACE2 receptor has a greater expression in the lungs and heart. In the cases of patients with hypertension, there will be an increase in this receptor, which can lead to more severe cases of the disease when compared to the healthier population.[29,30,31,32]

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Regarding BAEP, the test was performed by all participants, and waves I, III and V could be recorded in 84.6% of the sample. The mean values found for waves I, III and V were 1.78; 3.94 and 6.01 for the right ear and 1.82; 4.00 and 6.03 for the left ear, respectively. The values of interpeak interval I-III, III-V, and I-V were 2.11; 2.03 and 4.26 for the right ear and 2.17; 1.99 and 4.16 for the left ear. The wave values are increased to those described in the literature as normal for a population of similar age and BAEP performed with the same equipment and similar parameters.[33,34,35] In this study, there was no control group, but the normal values for latency (ms), based on biological calibration for this age group, are 2.2 ms for interpeak I-III; 2.1 for interpeak III-V; and 4.2 for interpeak I-V.

Regarding the analysis of BAEP latencies, the values found are beyond those described in the literature, demonstrating that there was an increase in waves when compared to normal values.

Another relevant finding was the significant increase in interpeak I-III in both ears in individuals with arterial hypertension. The literature has shown that individuals who have severe COVID-19 are more likely to develop neurological manifestations, due to SARS-CoV-2-induced venous thromboembolism as a coagulation dysfunction, which would probably explain cerebrovascular manifestations of COVID-19 such as cerebral venous thrombosis or intracerebral hemorrhage, which are potentially more severe in individuals who have hypertension. In addition, neuronal cells are sensitive to cerebral hypoxia, which can lead to damage to the auditory pathways, which can be observed by increased interpeak I-III. Associated with this fact, there has been a clinically observed increase in cases of covid-related neuropathies, especially late, which may or may not be transient. In our findings, most of the BAEP tracings showed altered morphology, demonstrating when latencies are still preserved, the qualitative analysis of the tracing should be considered as a parameter for the decision to refer or monitor the post-covid patient, since most neurological changes that affect the auditory system have morphology alteration as the first clinical sign.

Thus, it can be inferred that BAEP is a useful test to assess how the auditory pathways are in post-covid patients. Considering the parameters of absolute latency and interpeak latency, based on the normality values of the equipment used, 46% of the participants presented altered results. In addition, the morphology of the auditory potentials shows a relevant parameter in the analysis.

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CONCLUSION

The results of the brainstem auditory evoked potential (BAEP) revealed that most of the tracings showed changes in morphology, although the latencies were permanently preserved. In addition, a significant increase in interpeak interval I-III was found in both ears in hypertensive individuals.

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