Acıbadem Univ. Sağlık Bilim. Derg. 2025; 16 (1)
https://doi.org/10.31067/acusaglik.1413949

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Audiology / Odyoloji

Can Auditory Brainstem Responses Be a Screening Tool to Assess the Brainstem for Post-Covid-19 ?

Merve Bengisu Başyurt[1], Didem Şahin Ceylan[2*], Elifnur Taşdemir[3]

[1] Institute of Health Sciences, Neuroscience MSc. Program, Uskudar University, Istanbul, Turkey

[2] Department of Audiology, Faculty of Health Sciences, Uskudar University, Istanbul, Turkey

[3] Vocational School of Health, Audiometry Program, Uskudar University, Istanbul, Turkey

Merve Bengisu BAŞYURT
0000-0003-2496-6371

Didem ŞAHİN CEYLAN
0000-0003-4729-9524

Elifnur TAŞDEMİR
0000-0002-0752-657X

Correspondence: Didem Şahin Ceylan
Department of Audiology, Faculty of Health Sciences, Uskudar University, Istanbul, Turkey
Phone: +90 216 400 22 22
E-mail: didem.sahinceylan@uskudar.edu.tr

Received: 03.01.2024
Accepted: 26.09.2024

ABSTRACT

Purpose: The aim of this study was to investigate whether auditory pathways at the brainstem level are affected in volunteers with normal hearing infected with SARS-CoV-2 virus, which is thought to localize in the brainstem and cause symptoms such as loss of smell and taste.

Methods: A total of 60 volunteers (120 ears), 30 (21 females and 9 males; M: 24.5±5.5) infected (study group) and 30 (18 females and 12 males; M: 20.7±2) never infected (control group), aged 17-45 years, were included in the study. The study group consisted of individuals who had Covid-19 and had at least one of the symptoms known to occur with the localization of the virus in the brainstem, such as nausea-vomiting, loss of smell-taste, weakness-fatigue.

The latency and amplitude values of auditory brainstem responses elicited at 80 dB nHL with LS-CE chirp stimuli were compared between the two groups. I, III, and V-wave latencies, I-III, III-V, and I-V interpic latencies, I, III, and V-wave amplitudes, and V/I amplitude ratio parameters were evaluated in the ABR test.

Results: Although no statistically significant difference ($p>0.05$) was observed between the study group and the control group in all parameters, it was found that the amplitudes of the waves were lower in the study group compared to the control group.

Conclusion: Although the findings did not show any significant results, the study group's worse amplitudes may indicate the presence of brainstem damage.

Keywords: Covid-19, Auditory Brainstem Responses, LS-CE-Chirp, SARS-CoV-2.

ÖZET

Amaç: Bu çalışmanın amacı, beyin sapında yerleşerek koku ve tat kaybı gibi semptomlara neden olduğu düşünülen SARS-CoV-2 virüsü ile enfekte olan normal işitmeye sahip gönüllülerde beyin sapı seviyesindeki işitsel yolakların etkilenip etkilenmediğini araştırmaktır.

Yöntemler: Çalışmaya yaşları 17-45 arasında değişen 30 (21 kadın ve 9 erkek; Ort: 24.5±5.5) enfekte (çalışma grubu) ve 30 (18 kadın ve 12 erkek; Ort: 20.7±2) hiç enfekte olmamış (kontrol grubu) olmak üzere toplam 60 gönüllü (120 kulak) dahil edildi. Çalışma grubu Covid-19 geçiren ve virüsün beyin sapında lokalizasyonu ile ortaya çıktığı bilinen bulantı-kusma, koku-tat kaybı, halsizlik-yorgunluk gibi semptomlardan en az birine sahip bireylerden oluşmuştur.

LS-CE chirp uyaranlarla 80 dB nHL'de ortaya çıkan işitsel beyin sapı yanıtlarının latans ve amplitüd değerleri iki grup arasında karşılaştırıldı. ABR testinde I, III ve V dalga latansları, I-III, III-V ve I-V interpik latansları, I, III ve V dalga amplitüdleri ve V/I amplitüd oranı parametreleri değerlendirildi.

Sonuçlar: Çalışma grubu ile kontrol grubu arasında tüm parametrelerde istatistiksel olarak anlamlı bir fark ($p>0.05$) gözlenmemesine rağmen, çalışma grubunda dalga amplitüdlerinin kontrol grubuna göre daha düşük olduğu saptandı.

Sonuç: Bulgular anlamlı sonuçlar göstermemekle birlikte, çalışma grubunun daha kötü amplitüdlere sahip olması beyin sapı hasarının varlığına işaret edebilir.

Anahtar Kelimeler: Covid-19, İşitsel Beyin Sapı Yanıtları, LS-CE-Chirp, SARS-CoV-2.

Severe Acute Respiratory Syndrome Coronavirus 2- SARS-CoV-2 (1), which emerged in Wuhan, China, in December 2019, caused an illness with symptoms such as fever, fatigue, dry cough, sore throat, and nasal congestion, with a clinical picture similar to that of influenza and the common cold: Coronavirus Disease-19 (Covid-19) (2). Over time, SARS-CoV-2 was observed to affect not only the respiratory center but also the central nervous system, causing neurological symptoms such as loss of taste and smell, headache, nausea, and vomiting (3).

The cellular target of SARS-CoV-2 is angiogensin converting enzyme 2 (ACE-2)(4). The immune system damage caused by SARS-CoV-2 has led to many theories, including vascular invasion, ischemia, infection of the auditory pathway, and that neurons and glia contain the ACE-2 receptor (5). Consistent with these theories, studies have suggested that the SARS-CoV-2 virus may affect the auditory and vestibular systems (6). It was thought that it may be possible to use the auditory brainstem response-ABR to assess brainstem damage caused by SARS-CoV-2 using auditory pathways (7). Our study was designed to investigate the impact of ABR testing on the hearing of Covid-19 survivors at the brainstem level, which causes significant neurological symptoms such as nausea and vomiting, muscle pain, headache, fatigue, and taste and smell disturbances.

Materials and Methods

Our cross-sectional study was conducted in the laboratory of the Department of Audiology, Faculty of Health Sciences, Üsküdar University with the approval of Üsküdar University Ethics Committee with decision number 2021-34 and date of 25.02.2021. Inclusion criteria;

- Age between 18-45 years to minimize the possible effects of aging on the hearing system(8),
- Bilateral type A (9) and 0.3-1.4 cc compliance; tympanogram with ±50 daPa values (10)
- Obtaining ipsilateral and contralateral reflexes in the range of 500-4000 Hz bilaterally was considered normal (11),
- Bilateral pure tone average (500-4000 Hz) obtained as ≤ 15 dB HL (12),
- Normal *Distortion product otoacoustic emissions (*DPOAE) test results (13)
- No diagnosed neurological, genetic, or systemic disease,

Different from the control group;

- The study group had a history of at least 1 "PCR test positive" in the previous 3 months,
- Mild to moderate illness and not hospitalized
- Experienced at least one of the symptoms of nausea-vomiting, muscle pain, headache, weakness, loss of taste and smell, which are thought to occur with the involvement of the brainstem pons region in the disease (14),
- Voluntary subjects who agreed to participate in the study were included in the study.

Data Collection Tools

A detailed medical history was obtained from all participants, and otoscopic examination, immittance evaluation, pure tone audiometry test, otoacoustic emission measurement (DPOAE), and ABR test were performed**.**

Acoustic Immittancemetry

Otoscopic control was performed prior to tympanometric assessment. Tympanometry and acoustic reflex testing were performed using the Interacoustics® Titan Handheld (Denmark). Bilateral type A tympanogram (0.3-1.6 cc compliance; ±100 daPa) (9) and bilateral ipsilateral and contralateral reflexes between 500-4000 Hz (10) were considered normal.

Pure Tone Audiometry Test

Participants' air conduction thresholds at frequencies of 125-8000 Hz were measured with supraaural headphones using an Interacoustics® AC40 clinical audiometer (Denmark). For all air conduction thresholds between 125-8000 Hz, it was ensured that there was no difference of 15 dB or more between consecutive thresholds and that all thresholds were within normal hearing limits (-10-15 dB). Bilateral pure tone averages (500-4000 Hz) ≤ 15 dB HL were considered normal (12).

Distortion Product Otoacoustic Emissions

The functionality of the receptor cells in the inner ear was assessed by DPOAE measurement using the Otodynamics/ Echoport ILO292 USB=2 device. The result was considered normal if the signal-to-noise ratio was 6 dB or greater at 4 of the measured frequencies (13)

Auditory Brainstem Response

The ABR test was performed in all participants with the lights off, with the patient in a calm supine position and/or in natural sleep. In the test using Ambu NeurolineTM 720 electrodes, the resistance difference between the electrodes was 2 kΩ or less and the resistance value at each electrode was 3 kΩ or less. The ER-3A insert headphones were placed in the ear canal, and a LS-CE-Chirp stimulus was sent at an intensity of 80dB nHL. The responses were recorded as a minimum of 3000 sweeps at the rate of 21.1 per second in alternating polarity. Double-trace records were taken in order to ensure the reliability of the response. Absolute latencies of waves I, III and V, inter-wave latencies, amplitudes of wave I and V, and the amplitude ratios V/I were determined.

Statistical Analysis

SPSS 25.0 package programme was used for statistical data analysis in the study. In this study, G*Power 3.1.9.4 program was used to calculate the sample size. According to the program, assuming an effect size = 0.8, significance level = 0.05 and power = 0.80, the minimum sample size was found to be at least 21 for each group.

The normality analysis of the distributions of I., III. and V. wave latency and amplitude values and I-III, III-V and I-V interpic latency measurements was performed with the Kolmogorov-Smirnov test and it was found that they did not fit the normal distribution. Therefore, Mann Whitney U test was used in the comparisons between the experimental and control groups. Significance level (α=0.05) was accepted in statistical comparisons (15).

Results

Gender differences were not analyzed due to non-homogeneous data distribution. Figure 1 presents the observed symptoms in the study group.

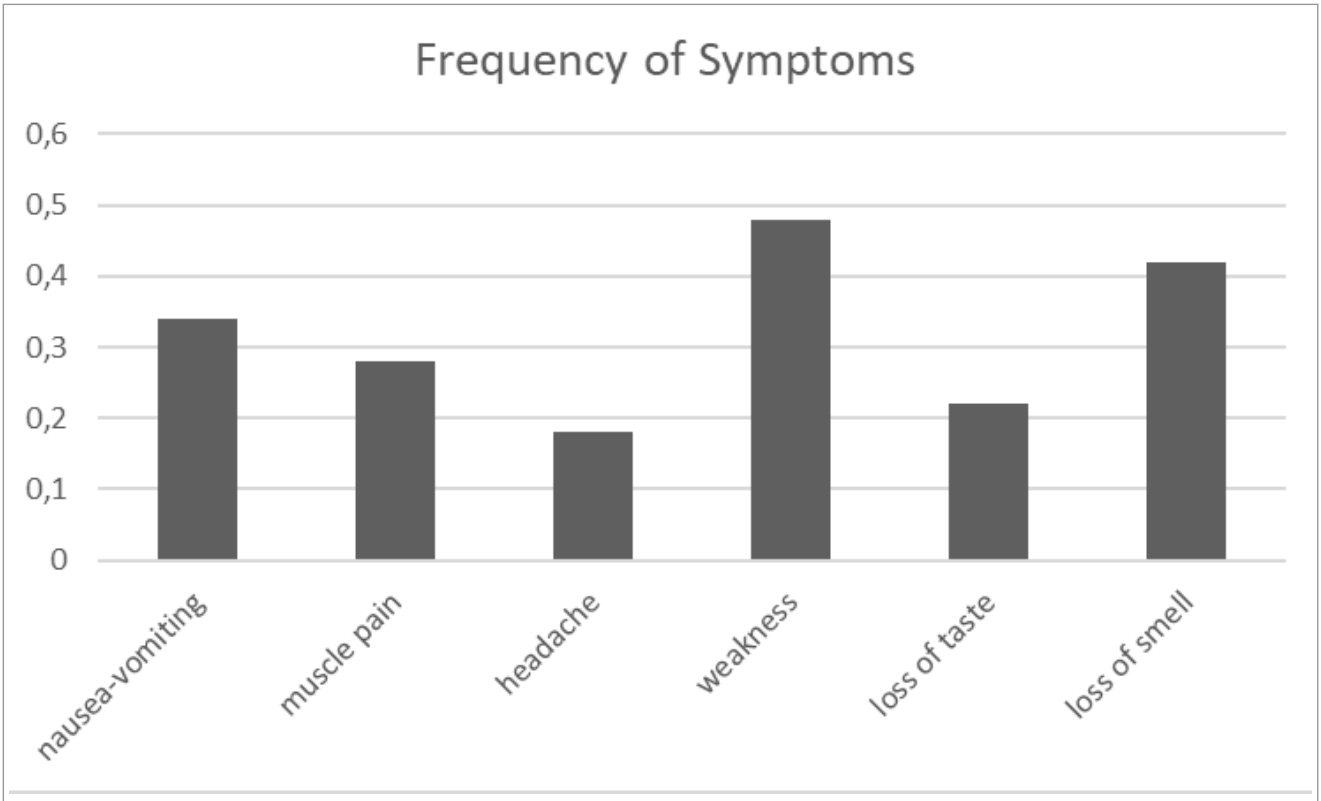

Figure 1: Frequency of neurological symptoms and other symptoms in the study group

Table 1: Latency and interpic latency values of I., III. and V. waves in the study and control groups

Parameter Latency (ms)	Control Group (M ± SD) (N:30)		Test Group (M ± SD) (N:30)		P-value**	
	Right	Left	Right	Left	Right	Left
Wave I	1.45 ± 0.13	1.48 ± 0.14	1.41 ± 0.18	1.44 ± 0.09	0.224	0.213
Wave III	3.57 ± 0.16	3.59 ± 0.17	3.53 ± 0.13	3.54 ± 0.15	0.438	0.311
Wave V	5.19 ± 0.20	5.21 ± 0.28	5.14 ± 0.19	5.16 ± 0.18	0.522	0.322
I–III interpeak latency	2.11 ± 0.19	2.10 ± 0.13	2.11 ± 0.20	2.07 ± 0.22	0.970	0.382
III–V interpeak latency	1.63 ± 0.16	1.62 ± 0.17	1.67 ± 0.17	1.69 ± 0.19	0.342	0.447
I–V interpeak latency	3.74 ± 0.22	3.72 ± 0.25	3.79 ± 0.21	3.77 ± 0.16	0.527	0.958

*Mann Whitney U test SS: standard deviation N: number of individuals **Significant difference (p<0.05).*

Table 2: Amplitude values of I., III. and V. waves in the study and control groups

Parameter	Control Group (M ± SD) (N:30)		Test Group (M ± SD) (N:30)		P-value**	
	Right	Left	Right	Left	Right	Left
Wave I	0.32 ± 0.12	0.31 ± 0.12	0.29 ± 0.13	0.28 ± 0.11	0.387	0.280
Wave III	0.37 ± 0.11	0.33 ± 0.11	0.33 ± 0.13	0.31 ± 0.11	0.135	0.496
Wave V	0.80 ± 0.23	0.74 ± 0.19	0.77 ± 0.13	0.78 ± 0.14	0.988	0.171
V/I	2.85 ± 1.34	2.91 ± 1.47	3.30 ± 1.61	3.51 ± 1.85	0.379	0.257

*Mann Whitney U test SS: standard deviation N: number of individuals **Significant difference (p<0.05).*

In ABR test; latency values of I., III. and V. waves, I-III, III-V, I-V interpic latency values, amplitudes of I., III. and V. waves and V/I amplitude ratio parameters were evaluated (see Table 1 and Table 2). No statistically significant difference was observed between the study group and the control group (p>0.05).

However, lower results were obtained in the I. and III. wave amplitudes in the right and left ears and in the V. wave amplitude in the right ear in the study group compared to the control group.

Discussion

Viral infections affect the peripheral hearing and vestibular system by involving the corti, stria vascularis and spiral ganglia (16). Viral infections such as cytolamegalovirus, rubella and measles can cause both acquired and congenital hearing loss (17). There have been many studies suggesting that coronaviruses can also cause hearing loss (18,19). However, most of the studies are related to peripheral hearing and vestibular system.

In many autopsy studies, it has been reported that RNA residues of the virus are found intensively in the brainstem region (14). The same studies have emphasized the brain stem damage's potential lethality level. However, our observations of brainstem damage in patients with varying degrees of disease with today's technological capability reveal multiple queries requiring resolution.

The extensive damage to the brainstem raises the probability of impacted central auditory pathways in the area. In this study, our aim was to exclude cochlear pathologies and concentrate solely on the brainstem by incorporating the requirement of normal DPOAE outcomes in our inclusion criteria. Although no statistically significant difference in latencies of I, III, and V waves and latencies between I-III, III-V, and I-V waves was observed between the experimental and control groups in ABR testing studies conducted in individuals with Covid-19 (20), Groiss et al., (2020) argued that the patient should be evaluated for brainstem involvement even if the disease is asymptomatic (21). One of the studies conducted before the Covid-19 pandemic stated that brainstem function can be assessed with ABR. Gedik et al., (2021) evaluated I, III and V wave latencies, I-III, III-V, I-V inter-wave latencies, I and V wave amplitude values and V/I amplitude ratio (22) . Significant difference was found only in prolongation of III-V inter-wave latency (p<0.05). On the other hand, although they did not find a statistically significant

difference, they stated that there were prolongations in the latency values of the study group compared to the control group.In our study, latencies of I, III, and V waves, latencies between I-III, III-V, I-V waves, amplitudes of I, III, and V waves, and V/I amplitude ratios were examined. Although no statistically significant difference was observed between the two groups (p>0.05), the study group had lower amplitudes of I and III waves in the right and left ears and of V wave amplitude in the right ear compared to the control group.

It was thought that the lack of significant differences between groups may be due to the fact that individuals in the study group survived the disease without any medical intervention and support (such as the need for intensive care and the use of ototoxic drugs). Although not significant, this difference in amplitudes suggests the presence of brainstem damage, albeit not at a significant level, in participants whose cochlea was considered healthy by DPOAE. A study evaluating otoacoustic emissions after COVID-19 infection reported that the absence of symptoms does not guarantee that the cochlea is functioning properly (23) while another of the following studies also confirmed damage to the cochlea using otoacoustic emissions testing (24). Another study showing prolongation of latency in brainstem evoked potentials in people who developed sensorineural hearing loss after Covid-19 attributed this to neuronal damage caused by the disease. Öztürk et al. (2022), also reported a similar association (8). Celesia, (2015) reported that in the case of brainstem dysfunction, wave morphology, amplitude, and latency may be affected, and outcomes associated with a weak (<0.5) amplitude ratio between V/I waves may be observed (24). In our study, no significant difference was observed in the V/I amplitude ratio between individuals in the study group with symptoms that can be considered neurological symptoms, such as loss of taste and smell, and individuals in the control group. This, as well as other results of the ABR, suggests that the study group may have survived the disease at a mild to moderate level.

Conclusion

This study investigated the effect of possible damage in the pons region of the brainstem, where the auditory pathways and nuclei are located, on ABR responses in individuals with Covid-19. The biggest difference of our study from other studies in the literature is the presence of at least one neurological symptom thought to originate from the pons region in all individuals included in the study. As a result, it was revealed that the auditory brainstem responses of adult volunteers who had undergone Covid-19 with neurological symptoms were not different from those of people who had not previously undergone Covid-19. However, the low amplitudes of the study group suggest the onset of brainstem damage. The study may be supported by other studies with more participants and may allow us to have an idea about the brainstem of people who have had Covid-19 with ABR scanning.

Limitation

The emergence of new variants of the virus causing the disease every day causes changes in the diversity and frequency of symptoms. In this study, since the variants that the study group was infected with were not questioned, no comparison between variants was made. In addition, since the distribution was not homogeneous, comparison between genders was not analysed.

Declarations

Funding

this study received no funding support

Conflict Of Interest The authors

have no conflict of interest to declare.

Author Contribution

MBB: Project development, data collection, manuscript writing,

DŞC: data analysis, literature review, critical review, manuscript writing,

ETE: data collection, literature review.

References

1. She J, Jiang J, Ye L, Hu L, Bai C, Song Y. 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. Clin Transl Med. 2020;9(1).
2. Qu JM, Cao B, Chen RC. Clinical features of COVID-19. Covid-19. 2021;13–39.
3. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: Mechanisms and manifestations. J Neurol Sci. 2020;412.
4. 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(2):271-280.e8.

5. Iroegbu JD, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2. Neurological Sciences. 2020;41(6):1329–37.
6. Almufarrij I, Munro KJ. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. Int J Audiol. 2021;60(12):935–45.
7. De Santis G. SARS-CoV-2: A new virus but a familiar inflammation brain pattern. Brain Behav Immun. 2020;87:95–6.
8. Öztürk B, Kavruk H, Aykul A. Audiological findings in individuals diagnosed with COVID-19. American Journal of Otolaryngology - Head and Neck Medicine and Surgery. 2022;43(3).
9. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol. 1970 Oct;92(4):311–24.
10. Grais EM, Wang X, Wang J, Zhao F, Jiang W, Cai Y, et al. Analysing wideband absorbance immittance in normal and ears with otitis media with effusion using machine learning. Sci Rep. 2021;11(1).
11. Kalcioglu MT, Sallavaci S, Hrncic N, Beishenova M, Davcheva Cakar M, Vlaski L, et al. Prevalence of and factors affecting otitis media with effusion in children in the region from Balkans to Caspian basin; A multicentric cross-sectional study. Int J Pediatr Otorhinolaryngol. 2021;143.
12. G CJ. Uses and abuses of hearing loss classification. ASHA. 1981;23(7):493–500.
13. Harris FP. Distortion-product otoacoustic emissions in humans with high frequency sensorineural hearing loss. J Speech Hear Res. 1990;33(3):594–600.
14. Yong SJ. Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. ACS Chem Neurosci. 2021;12(4):573–80.
15. George D, Mallery P. IBM SPSS Statistics 26 Step by Step. IBM SPSS Statistics 26 Step by Step. Routledge; 2019.
16. Abramovich S, Prasher DK. Electrocochleography and Brain-Stem Potentials in Ramsay Hunt Syndrome. Arch Otolaryngol Head Neck Surg. 1986;112(9):925–8.
17. Cohen BE, Durstenfeld A, Roehm PC. Viral Causes of Hearing Loss: A Review for Hearing Health Professionals. Trends Hear. 2014 Oct;18:233121651454136.
18. Lamounier P, Gonçalves VF, Ramos HVL, Gobbo DA, Teixeira RP, Dos Reis PC, et al. A 67-year-old woman with sudden hearing loss associated with SARS-CoV-2 infection. American Journal of Case Reports. 2020;21:1–6.
19. Brzycki M, Richard R, Burwick N, Graf S, O'Brien C, Wu D, et al. Autologous hematopoietic transplantation following COVID-19 infection. Clin Case Rep. 2021;9(3):1167–70.
20. Sağlam S. Audiological Evaluation of Healed Covid-19 Patients. Gelisim University, Istanbul.; 2021.
21. Groiss SJ, Balloff C, Elben S, Brandenburger T, Müttel T, Kindgen-Milles D, et al. Prolonged Neuropsychological Deficits, Central Nervous System Involvement, and Brain Stem Affection After COVID-19—A Case Series. Front Neurol. 2020;11.
22. Gedik O, Hüsam H, Başöz M, Tas N, Aksoy F. The effect of coronavirus disease 2019 on the hearing system. Journal of Laryngology and Otology. 2021;135(9):810–4.
23. Mustafa MWM. Audiological profile of asymptomatic Covid-19 PCR-positive cases. American Journal of Otolaryngology - Head and Neck Medicine and Surgery. 2020;41(3).
24. Dorobisz, K., Pazdro-Zastawny, K., Misiak, P., Kruk-Krzemień, A., & Zatoński, T. Sensorineural Hearing Loss in Patients with Long-COVID-19: Objective and Behavioral Audiometric Findings. Infection and Drug Resistance. 2023; 16:1931–1939. https://doi.org/10.2147/IDR.S398126
25. Celesia GG. Hearing disorders in brainstem lesions. In: Handbook of Clinical Neurology. 2015. p. 509–36.