Patogenesis of tinnitus in patients with post-COVID syndrome – preliminary report

Paweł Rozbicki1ABCDEF, Sandra Krzywdzińska1BEF, Michał Kaczmarchyz1BEF, Jacek Usowski1ABDE, Arkadiusz Lubas2ACDE, Dariusz Jurkiewicz1ABDE

1Clinic of Otolaryngology and Oncological Otolaryngology with Clinical Department of Cranio-Maxillofacial Surgery, Military Institute of Medicine – National Research Institute, Warsaw, Poland
2Clinic of Internal Medicine, Nephrology and Dialysis, Military Institute of Medicine – National Research Institute, Warsaw, Poland

ABSTRACT:
Introduction: Similarly to hearing loss and dizziness, tinnitus is a frequently reported complication of COVID-19 and remains the subject of numerous scientific reports. However, the exact impact of SARS-CoV-2 on the pathophysiology of tinnitus observed in post-COVID syndrome remains unclear. One suspected cause behind the development of vestibulocochlear symptoms is the inflammation of neural tissue triggered by SARS-CoV-2 infection.

Aim: The aim of this study was to analyze the results of Brainstem Auditory Evoked Potentials (BAEP) in the context of tinnitus development among patients diagnosed with post-COVID syndrome.

Material and methods: This retrospective study involved the analysis of BAEP test results of patients admitted to the Audiology Clinic of the Military Institute of Medicine at the National Research Institute and diagnosed with the post-COVID syndrome. The study compared the average latency values of waves I, II, III, IV, and intervals I–III, III–V, I–V. The statistical analysis of the obtained data was performed.

Results: Out of 18 patients (9 female, 9 male) with an average age of 54.22 years (±9.65) diagnosed with post-COVID syndrome, tinnitus was identified in 5 individuals (27.78%). A statistically significant increase in wave V latency (5.98 vs. 5.63 [ms]; P < 0.05) and interval III–V (1.99 vs. 1.71 [ms]; P<0.05) was observed between the groups of patients with and without tinnitus.

Discussion: Study results analyzing BAEP changes in patients with post-COVID syndrome in the context of tinnitus are insufficient in current literature. The only available report linking post-COVID syndrome with sensorineural hearing loss demonstrated a statistically significant increase in latency values of waves III, V, and an increase in intervals I–III, III–V.

Conclusions: Tinnitus in patients suffering from post-COVID syndrome may be related to prolonged conduction of nerve impulses within the brainstem auditory pathway. Detailed pathophysiology of these changes requires further research.

KEYWORDS: ABR, audiology, COVID-19, post-COVID, tinnitus

ABBREVIATIONS
AT – tone audiometry
BAEP – Brainstem Auditory Evoked Potentials
COVID-19 – coronavirus disease 2019
IL-6 – interleukin-6
SARS-CoV-2 – systemic acute respiratory syndrome coronavirus 2
TNF-α – tumor necrosis factor α
VAERS – Vaccine Adverse Event Reporting System
WHO – World Health Organization
WIM-PIB – Military Institute of Medicine – National Research Institute

INTRODUCTION
Clinical implications of COVID-19 (coronavirus disease 2019) remain the main focus of numerous scientific studies since the World Health Organization (WHO) announced a global pandemic caused by SARS-CoV-2 (systemic acute respiratory syndrome coronavirus 2).

Initially, the world scientific community concentrated mainly on the symptomatology, pathophysiology, and treatment of acute respiratory failure caused by SARS-CoV-2. However, as symptoms of the acute phase of COVID-19 infection resolved, patients started to report symptoms of a more chronic character, such as shortness of breath, cognitive impairment, chronic fatigue, anxiety, and depression [1, 2]. This observation attracted the interest of research teams around the world. As more and more cases of persistent disease symptoms after COVID-19 infection were being documented, a time-based classification of syndromes was developed:

- acute COVID-19 (up to 4 weeks),
- persistent symptomatic COVID-19 (from 4 to 12 weeks),
- post-COVID syndrome (symptoms persisting for more than 12 weeks which may overlap or fluctuate, provided that other causes were excluded).

Otoneurological components of the post-COVID syndrome include dizziness, tinnitus, ear pain, and sensorineural hearing loss [3–5]. Meta-analysis conducted by Jafari et al. summarized the results...
of scientific research conducted among the entire population of COVID-19 survivors and estimated the frequency of persistent symptoms as follows: dizziness (12.2%), tinnitus (4.5%), hearing loss (3.1%) [5]. Considering the global scale of the COVID-19 pandemic which has resulted in 767,364,883 confirmed cases of SARS-CoV-2 [6] infections, tinnitus in the course of post-COVID syndrome should be regarded as a novel and valuable direction of research in the field of clinical audiology. The pathogenesis behind the development of tinnitus in the post-COVID syndrome remains unclear. One speculated mechanism suggests that tinnitus develops as a result of brainstem disorders of inflammatory character related to oxidative stress, which stimulates the synthesis of pro-inflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α ) [5, 7–10]. An audiological test which allows for evaluation of the auditory pathway is the brainstem auditory evoked potentials test (BAEP), which records bioelectrical potentials emitted by particular ear structures and presents them in the form of waves representing: I – proximal part of the cochlear nerve II – distal part of the cochlear nerve, III – cochlear nuclei, IV – superior olivary complex, V – lateral lemniscus. The latencies of waves I, III, and V and the intervals between them are of utmost clinical importance [11–15]. The I–III interval indicates the time an electrophysiological stimulus travels from the cochlea to the brainstem through the auditory nerve, while the III–V interval represents the time of sensory impulse conduction along the auditory pathway within the brainstem. The aim of the study was to compare BAEP test results between patients suffering from post-COVID syndrome with or without tinnitus.

**MATERIAL AND METHODS**

The study involved a retrospective analysis of medical records of patients admitted to the Audiology Outpatient Unit of the Clinic of Otolaryngology and Oncological Otolaryngology at the Military Institute of Medicine – National Research Institute (WIM-PIB). The inclusion criteria for the study were:

- pure Tone Audiometry (AT) results and BAEP results included in the analyzed medical records;
- age >18 and <80 years.

Exclusion criteria for the study were as follows:

- organic damage to the central nervous system;
- hereditary hearing disorders;
- inflammatory diseases of the ear at the time of examination;
- use of ototoxic drugs;
- diagnosis of Meniere’s disease.

The patients were divided into groups depending on the time the BAEP examination was performed – either before or after the first case of SARS-CoV-2 was confirmed in Poland (March 2020). The groups were then further divided into subgroups based on the presence of tinnitus. Differences in the latency of waves I–V, as well as intervals I–III, III–V, and I–V between subgroups were analyzed. The results are presented as mean values with standard deviations. Normality of data distribution was assessed using the Shapiro-Wilk test. For normal distribution of variables, the statistical significance of differences was evaluated with the Student’s t-test for independent variables. Otherwise, the Mann-Whitney U test was applied. Statistical analysis was performed using Tibco Statistica v. 13.3 software (TIBCO Software Inc., USA).

**RESULTS**

We carried out a retrospective analysis of BAEP test results of 45 patients (23 women, 22 men) with an average age of 58.2 ±13.8 years. In terms of the examination time, 27 patients underwent BAEP prior...
to the COVID-19 outbreak in Poland, while the remaining 18 patients were examined after this date. A total number of 18 respondents complained of tinnitus in the entire study group (12 reported this symptom before the pandemic and 6 started to experience tinnitus during the pandemic). Mean values of the PTA thresholds are presented in Tab. I.

After all data from the BAEP exams was collected, the Shapiro-Wilk test was applied to verify whether the distribution of variables between subgroups was normal. The obtained results are presented in Tab. II.

Statistical analysis confirmed normal distribution of all tested parameters and subgroups, apart from the latency of waves II and III in patients who developed tinnitus before the pandemic outbreak and the latency of wave II in patients without tinnitus who reported to the audiology unit during the pandemic.

Afterwards, the statistical significance of differences identified between particular variables was analyzed among patients from the pre-pandemic group. The results of this analysis are presented in Tab. III. According to Student’s t-test and Mann-Whitney U-test results, a statistically significant difference (P < 0.05) was identified for wave II latency. The remaining variables did not show statistically significant differences (P > 0.05).

The same statistical analysis was performed for a group of patients admitted during the pandemic. The results of these tests are presented in Tab. IV. Statistical assessment revealed a significant increase in the latency of wave V and the III–V interval in this group. Otherwise, the differences determined for the remaining variables were not statistically significant (P > 0.05).

**DISCUSSION**

Statistically significant differences demonstrated between the examined subgroups suggest that the development of tinnitus in patients with post-COVID syndrome originates in the central nervous system. The analyzed correlations are not observed in BAEP test results of patients who reported prior to the pandemic outbreak. The available databases do not contain any scientific reports comparing the results of brainstem auditory evoked potential tests in terms of tinnitus development in patients after SARS-CoV-2 infection. Therefore, the correlations demonstrated in the study serve as a turning point for clinical interpretation of tinnitus in post-COVID patients. A similar study analyzing the relationship between BAEP results of patients diagnosed with post-COVID syndrome and the occurrence of sensorineural hearing loss after SARS-CoV-2 infection, documented an increase in the latency of waves III and V, as well as an increase in intervals I–III and I–V [16]. The above-mentioned publication concluded that hearing disorders after SARS-CoV-2 infection may only be a symptom of chronic inflammatory changes within neural tissue. Apart from electrophysiological hearing and balance test results, the relationship between post-COVID syndrome and the occurrence of complications in the central nervous system seems to be confirmed by studies reporting cases of “COVID-19 brain fog” syndrome [17]. Verification of such hypotheses requires conducting further research on larger groups of patients, including prospective analysis of bioelectrical functioning of the central nervous system and the dynamics of cognitive disorder symptoms. These conclusions are somehow incoherent with current state of medical knowledge, according to which the majority of cases of tinnitus characterized by a fixed frequency result from damage to the inner ear which produces a pathologically exaggerated neuronal response to afferent stimuli [18].

The available literature also contains scientific reports describing tinnitus as a complication of vaccines against SARS-CoV-2. The total number of post-vaccination tinnitus cases reported until August 14, 2021 was 12,247, according to the Vaccine Adverse Event Reporting System (VAERS) [19, 20]. The role of COVID-19 in the emergence of tinnitus seems to be confirmed not only by an increased number of patients who reported with tinnitus to various clinical centers since the pandemic outbreak but also by a significantly higher trend search terms relating to tinnitus and tinnitus masking hearing aids [21].

It is clear that the retrospective character of our study is one of its limitations, making it impossible to precisely track the course of COVID-19 among analyzed patients. A potential way of verifying the hypothesis of tinnitus being related to oxidative stress in patients diagnosed with post-COVID syndrome could be an analysis of the “cytokine storm” course in the context of the severity of tinnitus symptoms. A small group of study participants included in the
statistical analysis may have influenced the lack of statistically significant differences between the remaining variables (potentials and intervals) within the examined subgroups. It is therefore crucial to continue research on the nature of hearing disorders among patients diagnosed with post-COVID syndrome.

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### Corresponding author:

Paweł Rozbicki; Clinic of Otolaryngology and Oncological Otolaryngology with Clinical Department of Cranio-Maxillofacial Surgery, Military Institute of Medicine – National Research Institute, Warsaw, Poland; Szaserów 128, 04-141 Warsaw, Poland;  
E-mail: prozbicki@wim.mil.pl

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