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Original Article

Analysis of Auditory Brainstem Response Change, according to Tinnitus Duration, in Patients with Tinnitus with Normal Hearing

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OBJECTIVES: The purpose of this study was to analyze auditory brainstem response (ABR) waveforms of patients with tinnitus with normal hearing, according to tinnitus duration, and demonstrate the possible pathophysiological mechanisms of tinnitus.

MATERIALS and METHODS: From January 2016 to December 2017, patients who presented to our hospital with tinnitus as their chief complaint were enrolled and reviewed retrospectively. Pure tone audiometry and ABR tests were performed. The patients were classified into three groups according to tinnitus duration: acute (<1 month), subacute (1-6 months), and chronic (>6 months). The amplitudes of waves I and V and the latencies of waves I, III, and V were evaluated. In this study, 177 ears of 128 patients with tinnitus with normal hearing were evaluated.

RESULTS: Wave V amplitude was significantly lower during the subacute phase than during the acute phase. The absolute latency value of wave V was greater during the subacute phase than during the acute phase. The interpeak latency I–V was significantly prolonged during the subacute phase compared with the acute and chronic phases. Wave V amplitude, wave V absolute latency, and interpeak latency I–V varied significantly between cases with a 1-month and 6-month tinnitus history.

CONCLUSION: The compensatory response to tinnitus decreased sharply after 1 month of symptoms. Early tinnitus identification and treatment initiation are recommended.

KEYWORDS: Tinnitus, auditory brainstem response, hearing

INTRODUCTION

Tinnitus is defined as a phantom noise perceived in the absence of any external sound [1]. Tinnitus is one of the most common otorhinolaryngological symptoms alongside hearing loss and vertigo. It is known that 10-30% of people have tinnitus, and 3-4% of patients present at a hospital during their lifetime for this reason [2]. As tinnitus is directly linked to the quality of life of patients, it is very important to better understand this issue [3].

The auditory brainstem response (ABR) test evaluates the auditory brainstem function in response to auditory stimuli. It has been widely used to evaluate patients with hearing loss since it was introduced by Jewett and Williston [4]. The ABR test is a useful method to identify retrocochlear lesions such as acoustic neuromas [5, 6]. Moreover, it can be used to identify the presence of auditory neuropathy [7].

The ABR is composed of various waves, of which waves I, III, and V are the most prominently observed and have clinical significance. Waves I, III, and V are generated in the distal portion of the cochlear nerve, in the cochlear nucleus, and the inferior colliculus, respectively [8-10]. However, there are relatively fewer studies on the ABR of patients with tinnitus, and the findings are controversial.

This study was presented at International Congress of ORL-HNS 2018 in conjunction with 92nd Annual Congress of Korean Society of Otorhinolaryngology-Head and Neck Surgery 2018 Spring Meeting of Korean Association of Otorhinolaryngologists, April 28, 2018, Seoul, Republic of Korea.

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Although there are many controversies, it is generally accepted that a reduced wave I amplitude could indicate cochlear synaptopathy, and a normal or elevated wave V amplitude could imply compensatory responses in central/cortical regions [1, 4, 11].

The authors hypothesized that there may be a change in ABR waveforms over tinnitus duration. Currently, there are no definite criteria for tinnitus classification by duration. However, in the literature, tinnitus with a duration shorter than 1 month has been classified as acute, whereas that lasting longer than 6 months has been classified as chronic [12-16]. Therefore, we defined tinnitus as acute tinnitus when it lasted less than 1 month, as subacute tinnitus when it lasted 1-6 months, and as chronic tinnitus when it lasted more than 6 months. The purpose of this study was to analyze ABR waveforms of patients with tinnitus with normal hearing, according to tinnitus duration.

MATERIALS and METHODS

Patients

From January 2016 to December 2017, the medical records of patients who visited our clinic with tinnitus were analyzed. All patients underwent pure tone audiometry and ABR tests. Normal hearing was defined as having a value lower than 25 dB at frequencies of 500 Hz, 1,000 Hz, 2,000 Hz, 4,000 Hz, and 8,000 Hz. Of 484 patients, 60, 95, and 78 patients were excluded owing to the absence of tinnitus direction, ambiguity of symptom duration, and missing ABR data, respectively. Of the remaining 249 patients (319 ears), 179 subjects presented unilateral tinnitus, and 70 had bilateral tinnitus. Of the 319 analyzed ears, 177 presented no hearing loss (Figure 1). Patients with tinnitus with hearing loss were excluded. The participants (patients with tinnitus with normal hearing) were classified into three groups: acute (within 1 month), subacute (1-6 months), and chronic (over 6 months), according to tinnitus duration. Institutional review board (IRB) approval was obtained from Korea University Ansan Hospital (IRB No: 2018AS0211).

Procedure and Analysis

Two electrodes were attached to the midline of the frontal bone and vertex after cleaning the scalp skin of the patients. The test was performed in the supine position for approximately 50–90 minutes using a 90 dB click sound with a Navigator pro (two channel, Bio-logic earphones, Natus Medical Inc., Pleasanton, California, USA).

Peak amplitudes were measured using the peak-to-peak difference between peak-to-peak amplitudes of waves I and V. The V/I ratio was recorded along with the value of the amplitudes for waves I and V.

MAIN POINTS

- Wave V amplitude was significantly lower during the subacute phase than during the acute phase.
- The absolute latency value of wave V was greater during the subacute phase than during the acute phase.
- Female patients maintain a shorter latency and larger amplitude, independent of the duration of tinnitus.

The absolute latencies of waves I, III, and V were measured, and the interpeak latencies (IPLs) of waves I–III, III–V, and I–V were investigated. We compared the ABR waveforms, including amplitude and latency, according to tinnitus duration. In addition, we analyzed the wave differences between male and female patients with different tinnitus duration because of known sex differences in wave amplitude and latency.

Statistical Analysis

Statistical comparisons of the amplitudes of waves I and V; V/I ratio; latencies of waves I, III, and V; and IPLs of waves I–III, III–V, and I–V between the acute, subacute, and chronic groups were performed using the Kruskal–Wallis test or Mann–Whitney U test with Bonferroni correction ($\alpha = 0.05/3 = 0.017$). We compared the same parameters of the ABR waves between male and female patients using an independent *t*-test or Mann–Whitney U test. Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) version 20.0 statistical software (IBM Corp.; Armonk, NY, USA). A $p \leq 0.05$ was considered to be statistically significant.

RESULTS

The mean age of patients with tinnitus with normal hearing was 47.916.4 years. The acute group included 20 ears with less than 1 month of tinnitus. The subacute group included 83 ears with 1 to 6 months of tinnitus. The chronic group included 74 ears with more than 6 months of tinnitus (Table 1). The mean duration of tinnitus was 20.58.0 days in the acute group, 2.71.2 months in the subacute group, and 37.336.1 months in the chronic group.

Comparison of Waves I and V Amplitudes and V/I Ratio, According to Tinnitus Duration

First, the amplitude changes according to tinnitus duration was evaluated. The absolute value of wave I amplitude was found to be 0.2820.117 μV in the acute group, 0.2730.130 μV in the subacute group, and 0.2670.141 μV in the chronic group. There was no significant difference between the three groups (Kruskal–Wallis test, p=0.888; Figure 2). The absolute value of wave V amplitude was 0.5010.199 μV in the acute group, 0.3660.130 μV in the subacute

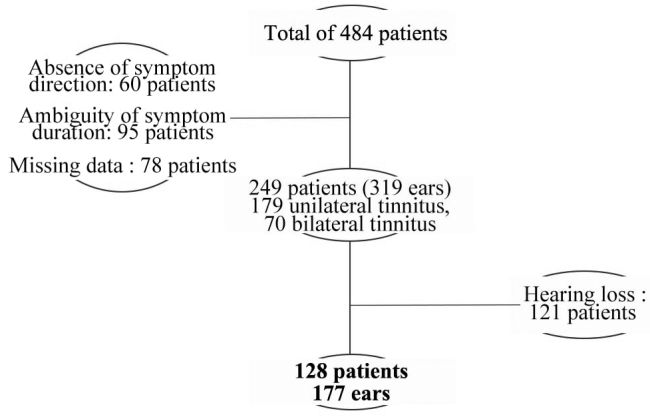

Figure 1. Flow chart detailing patient inclusion and exclusion in the study. We excluded 235 patients owing to uncertainty in the direction or duration of tinnitus or for a lack of ABR data. Of the remaining 249 patients, 177 ears of 128 patients with normal hearing were included in the study. ABR: auditory brainstem response.

group, and 0.4080.159 μV in the chronic group. The amplitude of wave V in the subacute group was significantly smaller than that in the acute group (Mann–Whitney U test with Bonferroni correction, p=0.003; α = 0.05/3; Figure 2). There was no significant difference between the subacute and the chronic groups or between the acute and the chronic groups (independent t-test and Mann–Whitney U test with Bonferroni correction, p=0.031 and p=0.072, respectively; α = 0.05/3; Figure 2). The V/I ratio was 2.0651.199 in the acute group, 1.6701.224 in the subacute group, and 2.7564.287 in the chronic group. There was no significant difference in the V/I ratio between the three groups (Kruskal–Wallis test, p=0.158; Figure 3).

Comparison of Absolute Latencies of Waves I, III, and V and IPLs of Waves I–III, III–V, and I–V, According to Tinnitus Duration

The absolute latency value for wave I was 1.4090.167 ms in the acute group, 1.4200.200 ms in the subacute group, and 1.4420.159 ms in the chronic group. There was no significant difference between the three groups (Kruskal–Wallis test, p=0.303). The absolute latency value for wave III was 3.5720.156 ms in the acute group, 3.6470.169 ms in the subacute group, and 3.6500.211 ms in the chronic group. There was no significant difference in absolute latency for wave III between the three groups (Kruskal–Wallis test, p=0.285). The absolute latency value for wave V was 5.3920.195 ms in the acute group, 5.5270.222 ms in the subacute group, and 5.4780.249 ms in the chronic group. There was a significant difference in the latency of wave V between the acute and the subacute groups (Mann–Whitney U test with Bonferroni correction, p=0.014; α = 0.05/3; Table 2).

Regarding the IPLs, there was a significant difference between groups only for the IPL I–V. The IPL I–V was 3.980.20 ms in the acute group, 4.110.27 ms in the subacute group, and 4.040.24 ms in the chronic group. The value of the subacute group was significantly higher than that of the acute and chronic groups (acute vs subacute, Mann–Whitney U test with Bonferroni correction, p=0.017; α = 0.05/3; subacute vs chronic, Mann–Whitney U test with Bonferroni correction, p=0.016; α = 0.05/3; Table 3).

Comparison of Amplitude and Latency of ABR Waves between Male and Female Patients, According to Tinnitus Duration

An additional subgroup analysis was conducted to compare the ABR results according to sex. No significant difference for variables related to ABR was found between male and female patients of the acute group (Figures 4 and 5). However, in the subacute group, there was a significant difference between male and female patients in the absolute latency of wave III, absolute latency of wave V, IPL I–III, and IPL I–V. The absolute latencies of waves III and V, IPL I–III, and IPL I–V of male patients were 3.7360.163 ms, 5.6350.210 ms, 2.2920.269 ms, and 4.1920.310 ms, respectively. All four variables were significantly higher in female patients (independent t-test or Mann–Whitney U test, p<0.001, p<0.001, p<0.001, and p=0.001, respectively; Figures 6 and 7). There was no significant difference in the ABR variables, except for wave V amplitude and absolute latency between male and female patients during the chronic phase (independent t-test, p=0.015). The amplitude of wave V was 0.355±0.148 μV for males and 0.445±0.157 μV for females in this group (Mann–Whitney test, p=0.003), whereas the absolute latency of wave V was 5.5640.220 ms for males and 5.4190.252 ms for females (Mann–Whitney U test, p=0.003; Figures 8 and 9).

Table 1. Classification of groups according to tinnitus duration

	Acute (<1 month), n = 20		Subacute (1–6 months), n = 83		Chronic (>6 months), n = 74	
	Male	Female	Male	Female	Male	Female
Ears	5	15	34	49	30	44

Table 2. Absolute latency values according to tinnitus duration

	Acute	Subacute	Chronic	p
Wave I latency	1.409±0.167	1.420±0.200	1.442±0.159	0.303
Wave III latency	3.572±0.156	3.647±0.169	3.650±0.211	0.285
Wave V latency	5.392±0.195	5.527±0.222	5.478±0.249	0.023

The values of wave I absolute latency did not show significant difference between the three groups (Kruskal–Wallis test, p=0.303). The values of wave III absolute latency did not show significant difference between the three groups (Kruskal–Wallis test, p=0.285). There was a significant difference in the wave V latency between the acute and subacute groups (Mann–Whitney U test with Bonferroni correction, p=0.014; α=0.05/3).

Table 3. IPL according to tinnitus duration

	Acute	Subacute	Chronic	p
IPL I–III (ms)	2.16±0.12	2.23±0.21	2.21±0.20	0.171
IPL III–V (ms)	1.82±0.13	1.88±0.19	1.83±0.17	0.159
IPL I–V (ms)	3.98±0.20	4.11±0.27	4.04±0.24	0.013

IPL: interpeak latency

The IPL value of the subacute group was significantly higher than that of the acute and chronic groups (acute vs subacute, Mann–Whitney U test with Bonferroni correction, p=0.017; α=0.05/3; subacute vs chronic, Mann–Whitney U test with Bonferroni correction, p=0.016; α=0.05/3).

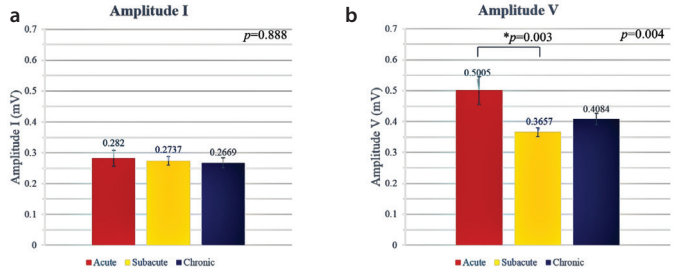

Figure 2. a, b. Amplitudes of waves I and V according to tinnitus duration. (a) There was no significant difference in wave I amplitude between the three tinnitus groups (Kruskal–Wallis test, p=0.888). (b) The amplitude of wave V in the subacute group was significantly smaller than that of the acute group (Mann–Whitney U test with Bonferroni correction, p=0.003).

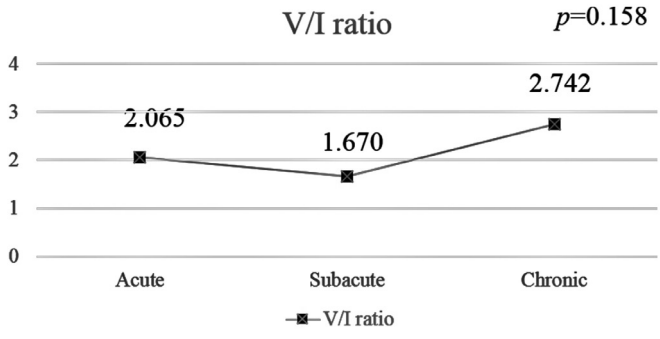

Figure 3. V/I ratio according to tinnitus duration. No significant difference in the V/I ratio was found between the three groups.

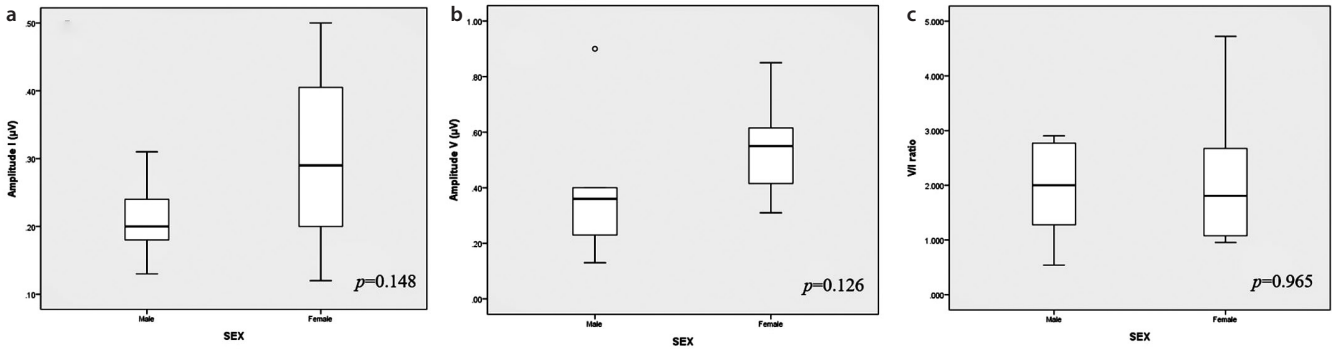

Figure 4. a-c. Comparison of waves I and V amplitudes and V/I ratio between male and female patients during the acute phase. (a-c) There was no significant difference in wave I amplitude, wave V amplitude, and V/I ratio between male and female patients (Mann–Whitney U test, p=0.148, p=0.126, p=0.965, respectively).

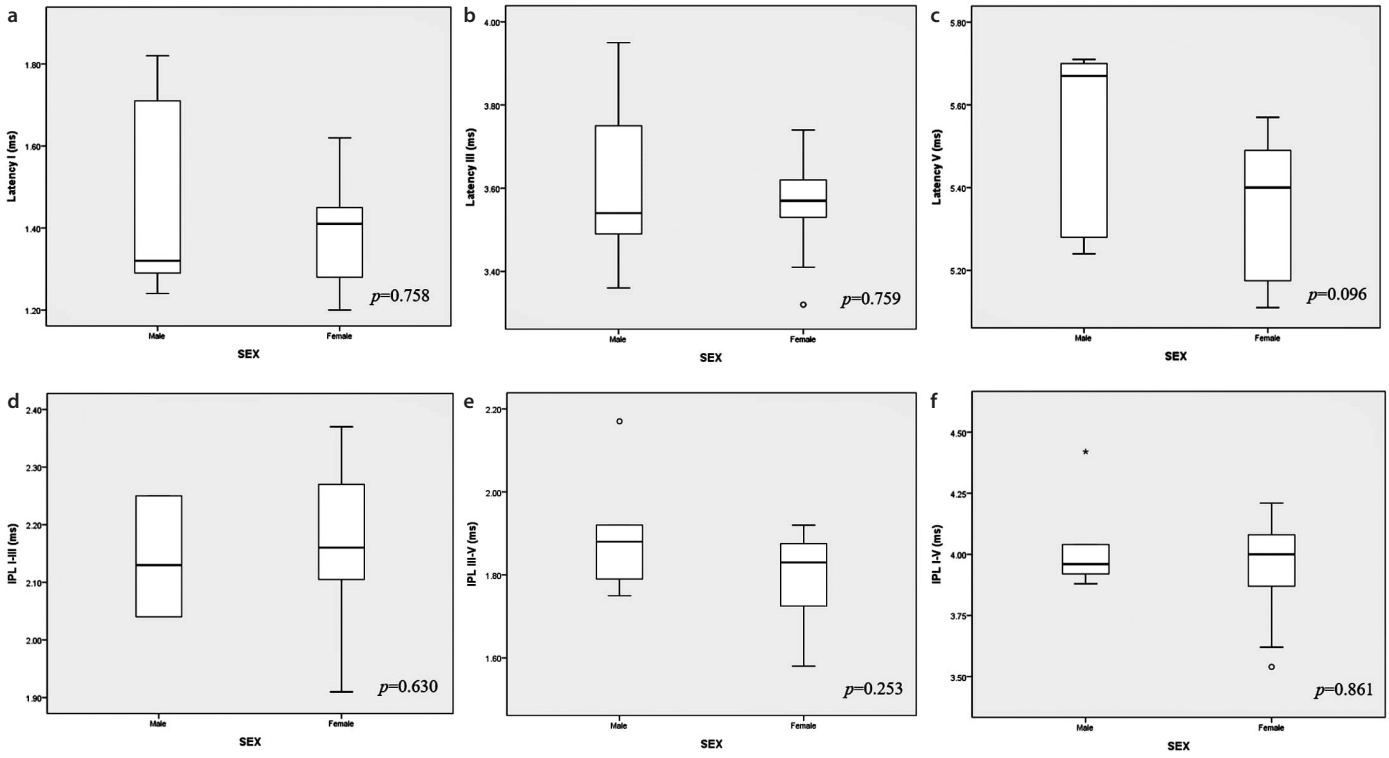

Figure 5. a-f. Comparison of absolute values of waves I, III, and V latencies and IPLs I–III, III–V, and I–V between male and female patients during the acute phase. (A–E) There was no significant difference in wave I latency, wave III latency, wave V latency, IPL I–III, IPL III–V, and IPL I–V between male and female patients (p=0.758, p=0.759, p=0.096, p=0.630, p=0.253, p=0.861, respectively). IPL: interpeak latency

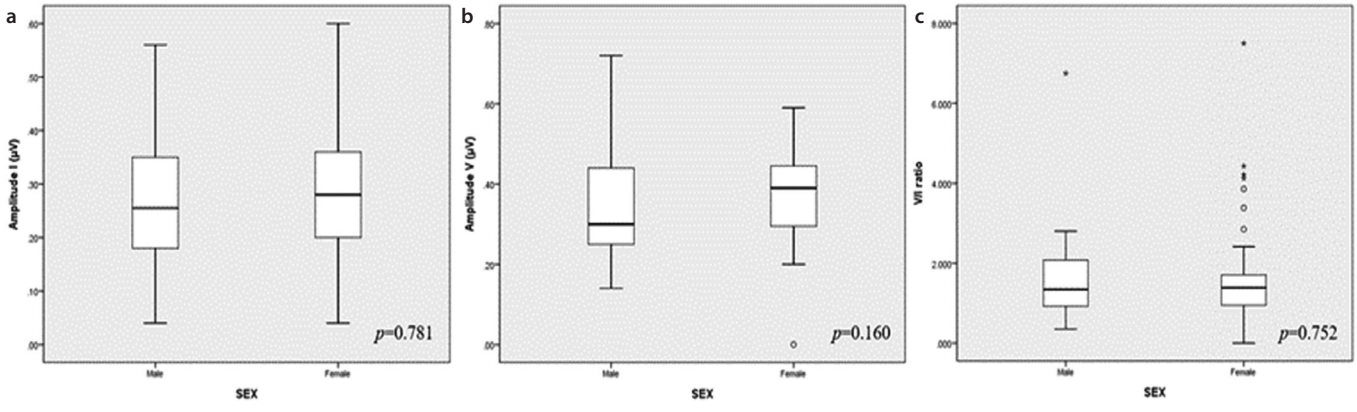

Figure 6. a-c. Comparison of waves I and V amplitudes and V/I ratio between male and female patients during the subacute phase. (a-c) There was no significant difference in wave I amplitude, wave V amplitude, and V/I ratio between male and female patients (p=0.781, p=0.160, p=0.752, respectively).

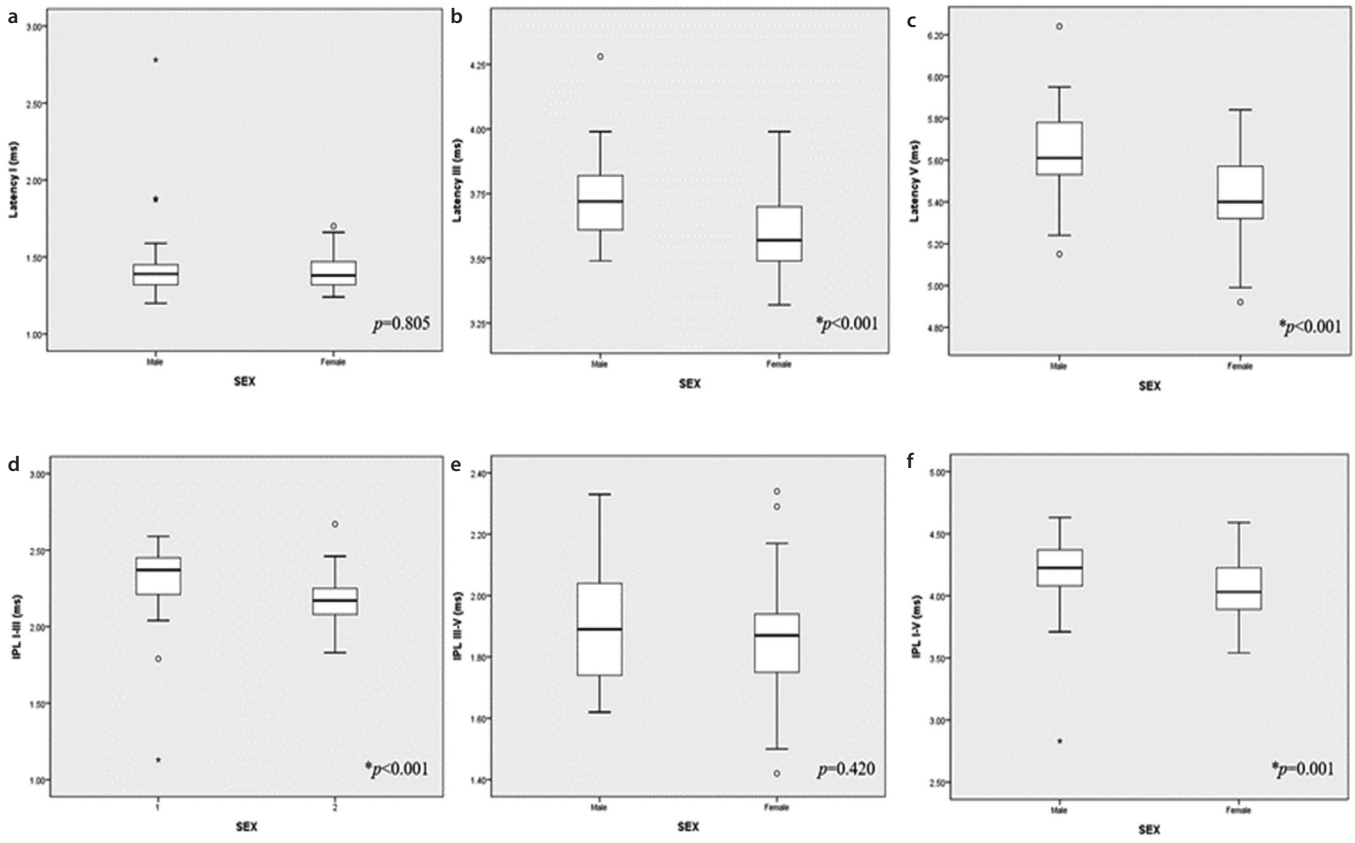

Figure 7. a-f. Comparison of absolute values of waves I, III, and V latencies and IPLs I–III, III–V, and I–V between male and female patients during the subacute phase. (a, e) There was no significant difference in wave I latency or IPL III–V (p=0.805 and p=0.420, respectively). (b-d, f) Wave III latency, wave V latency, IPL I–III, and IPL I–V values were lower in female than in male patients (p<0.001, p<0.001, p<0.001, p=0.001, respectively). IPL: interpeak latency

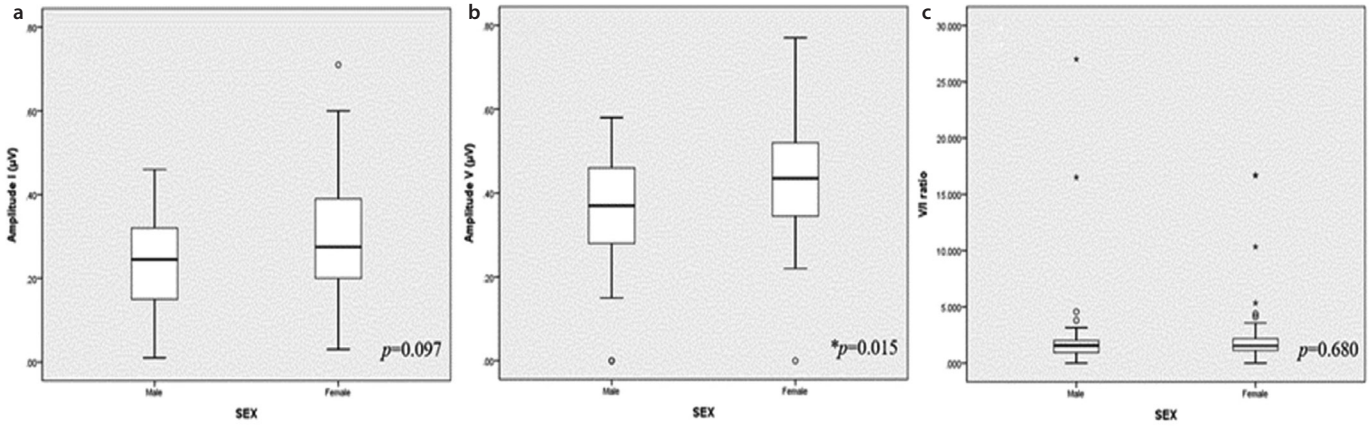

Figure 8. a-c. Comparison of waves I and V amplitudes and V/I ratio between male and female patients during the chronic phase. (a, c) There was no significant difference in wave I amplitude or V/I ratio between male and female patients (p=0.097 and p=0.680, respectively). (b) Wave V amplitude was higher in female than in male patients (p=0.015).

DISCUSSION

Tinnitus refers to a condition in which sound is perceived without any external auditory stimulation. Several studies have tried to elucidate the mechanisms underlying tinnitus, and various models such as the Jastreboff neurophysiological model, spontaneous auto-acoustic emissions, and biochemical models have been suggested [17].

To better understand tinnitus, ABR waves are often analyzed. Specifically, their amplitudes and latencies are investigated. Some authors have reported that the latencies of waves I, III, and V and the prognosis of wave III–V IPL were prolonged in patients with tinnitus [18]. In another study, wave I showed lower amplitude and significantly higher latency in tinnitus cases [19]. Absolute values of waves I, III, and V latencies in patients belonging to the tinnitus group were previously found to be higher than those in the control group [20]. In addition, a case control study showed that patients with tinnitus with normal hearing had reduced wave I amplitude, which was thought to reflect a decreased activity of low spontaneous rate auditory nerve fibers, and a normal or enhanced wave V amplitude, which was interpreted as a compensatory response to the diminished activity of the

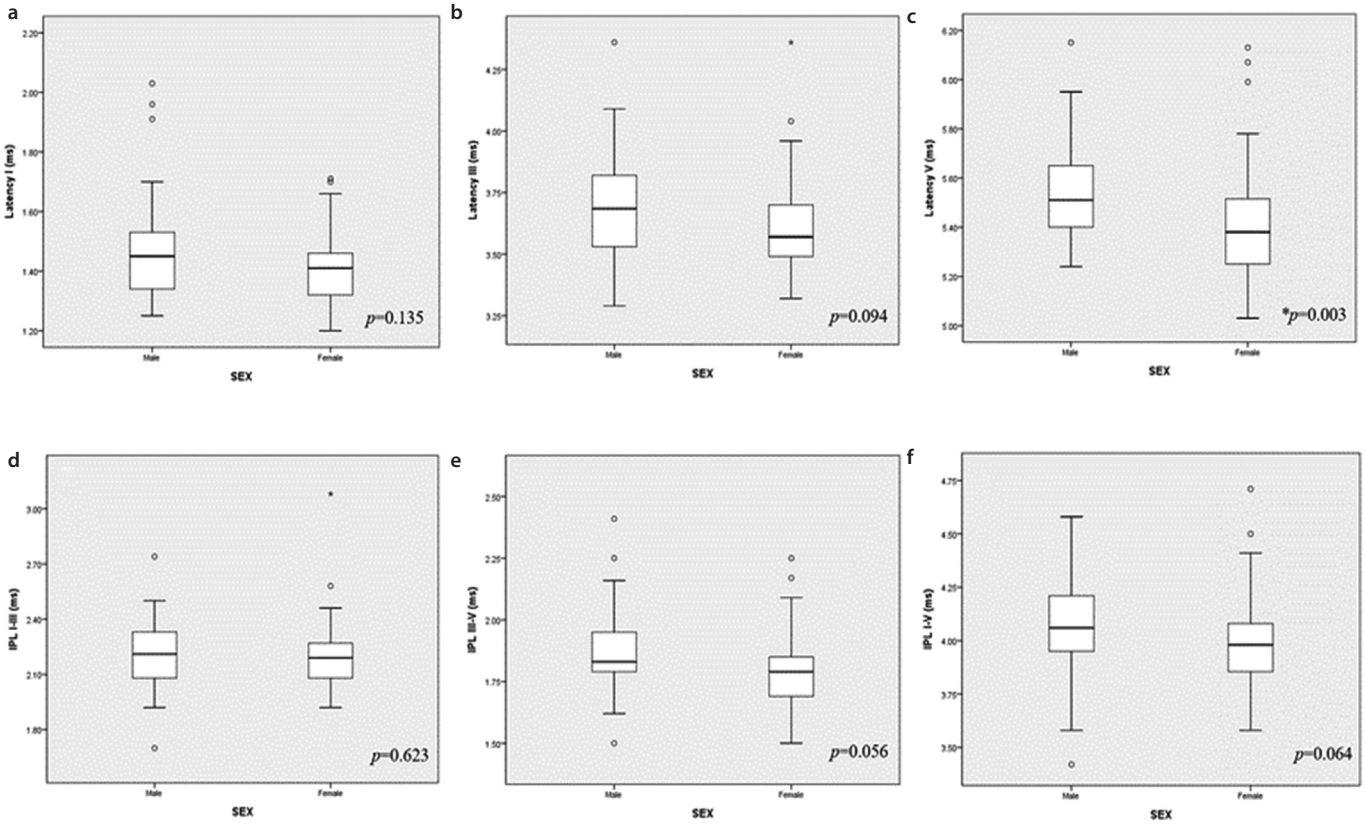

Figure 9. a-f. Comparison of absolute values of waves I, III, and V latencies and IPLs I–III, III–V, and I–V between male and female patients during the chronic phase. (a, b, d, f) There was no significant difference in wave I latency, wave III latency, IPL I–III, IPL III–V, and IPL I–V between male and female patients (p=0.135, p=0.094, p=0.623, p=0.056, and p=0.064, respectively). (c) Wave V latency was lower in female than in male patients (p=0.003). IPL: interpeak latency

auditory nerve [11, 21]. Conversely, no difference was reported in the amplitudes of waves I and V or in the V/I ratio between a unilateral tinnitus group and a group without tinnitus in both male and female subjects with normal audiogram [22, 23].

Hickox and Liberman [24] attempted to link synaptopathy to the development of tinnitus in noise-exposed mice. The mice exposed to loud noise displayed typical auditory nerve degeneration (based on ribbon counts), reduced wave I amplitude/enhanced wave V ABR, and subtle changes in tinnitus behavioral response that did not reach significance.

In contrast, another study suggested that patients with bilateral tinnitus exhibited a shortening of wave III latency on the right ear and of wave V latency on the left ear [25].

Although various ABR test results have been reported in patients with tinnitus, it is generally accepted that wave I latency increases and amplitude decreases in the tinnitus group, in comparison with healthy controls [11, 21, 26].

In this study, we analyzed ABR waveforms of patients with tinnitus. To our knowledge, this is the first investigation of ABR waveforms in a large number of patients with tinnitus, considering the tinnitus duration. Wave V amplitude of patients with tinnitus without hearing loss was significantly lower during the subacute phase than during the acute phase. Regarding latency, the values of wave V latency and IPL I–V were significantly higher during the subacute phase than during the acute phase. In addition, although there was no statistical significance, wave V amplitude and latency decreased and increased, respectively, in the chronic phase compared with the variation seen in amplitude and latency in acute phase. The reduction in wave V amplitude and prolongation of wave V latency after the acute phase might be due to the remarkable decrease of compensatory nerve firing observed after 1 month of tinnitus.

Furthermore, sex is one of the factors affecting ABR. As previously shown, females present shorter latency and larger amplitude than males [27, 28]. This is primarily due to the smaller head size and hormonal effects in females [29]. In our study, most amplitude parameters showed higher values in the female subjects of each group, although there were significant differences in the absolute latencies of waves I and III, IPL I–III, and IPL I–V during the subacute phase. These findings indicate that the difference in ABR between males and females seems to be maintained, regardless of the duration of tinnitus.

This study has several limitations. First, there were no comparable age- and sex-matched control groups, and the cases were not observed serially because of the retrospective nature of the study. Moreover, we did not thoroughly analyze factors that may be associated with ABR, noise exposure, age, and the condition of the middle ear. It is noteworthy that tinnitus itself has a definite pitch. Therefore, tinnitus pitch–matched (frequency-specific) ABR could be useful to identify auditory neuropathy in patients with tinnitus with normal hearing. However, this is difficult to assess in clinical practice. Hence, we evaluated click sound–evoked ABR in this study. Furthermore,

although electrocochleography (ECochG) is nowadays widely used to evaluate the distal cochlear nerve, ECochG results were not presented in this work [22, 24]. Finally, based on the definition of hearing loss adopted in this study, a hearing ability over 8,000 Hz was not considered, and hearing impairments at higher frequencies were not confirmed.

The mechanisms of tinnitus development are still unclear, and the effectiveness of available treatments is ambiguous. More case control studies are needed to better understand the underlying processes of tinnitus. This will ultimately result in more effective treatment options for the future.

CONCLUSION

Our study analyzed ABR waveforms in a relatively large number of patients with tinnitus with normal hearing, according to the duration of tinnitus. After 1 month of tinnitus, wave V amplitude, wave V latency, and IPL I–V values were significantly changed, suggesting a compensatory response. Therefore, it is important to implement early diagnosis and treatment. Moreover, female patients maintain a shorter latency and larger amplitude, independent of the duration of tinnitus. Further studies are required to analyze tinnitus mechanisms and better understand its natural progression.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Korea University Ansan Hospital (IRB No: 2018AS0211).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Authors Contributions: Conception: J.W.J., J.C.; Design: J.W.J., Y.J.Y., M.S.H.; Supervision: J.W.J., Y.S.C., J.C.; Resources: J.W.J., Y.C.R., J.C.; Materials: J.W.J., J.C.; Data Collection and/or Processing: J.W.J., Y.J.Y., M.S.H.; Data analysis and/or Interpretation: J.W.J., Y.J.J., M.S.H., Y.S.C., Y.C.R., J.C.; Literature Search: J.W.J., Y.J.J., M.S.H.; Drafting of the Manuscript: J.W.J., J.C.; Critical Revision: J.W.J., J.C.

Conflict of Interest: The authors have no conflict of interest to declare.

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