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Original Article

Electrophysiological Changes Associated with the Progression of Noise-Induced Hearing Loss

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BACKGROUND: The aim of this study is to evaluate the clinical characteristics and electrophysiological changes in patients with different degrees of noise-induced hearing loss compared with those of normal controls to elucidate the progression of auditory neural damage attributed to noise exposure.

METHODS: A retrospective cohort study was conducted through a review of the medical records for the patients who presented to a tertiary referral center. Sixty-nine participants were included in the study: 29 had noise-induced hearing loss, and 40 were healthy controls. All the participants underwent electrophysiological tests and pure-tone audiometry.

RESULTS: Nine patients showed mild hearing loss (mild hearing loss group), while the others showed worse than moderate hearing loss on pure-tone audiometry (severe hearing loss group). Significantly reduced wave I and V amplitudes of auditory brainstem response were present in both mild and severe hearing loss groups compared to the control group ($P < .001$ and $P = .002$, respectively), without significant differences between the mild and severe hearing loss groups. In the multivariate analysis, auditory brainstem response wave V amplitude was negatively associated with auditory brainstem response wave I-V inter-peak latency delay ($B = -0.48$, $P = .02$).

CONCLUSION: The results of the present study confirm the similarity in the electrophysiological characteristics between the mild and severe hearing loss groups. Thus, widespread disruption in the auditory neural conduction could have been established in the early period when the patient developed mild hearing loss following noise exposure.

KEYWORDS: Noise-induced hearing loss, audiometry, auditory brainstem response, hearing loss, progressive hearing loss

INTRODUCTION

Noise-induced hearing loss (NIHL) is unique since it causes widespread damage to the auditory neural microstructures. Previous studies have mainly focused on the disruption of outer hair cells as a principal indicator of noise-induced changes in the auditory system. Changes in the microstructure of the cochlea, including the supporting cells, hair cell stereocilia, and strial edema, have also been reported.[1]

Recent evidence has demonstrated that NIHL results in a more extensive and direct damage beyond the cochlea to the auditory nerve and synapses between the inner hair cells and neurons of the spiral ganglion, even in the early stages.[2-7] These changes in the auditory system induced by noise can also alter the neural sound-evoked output of the auditory pathway or causes hearing loss in the early stage following noise exposure.[7]

Electrophysiological techniques, such as auditory brainstem response (ABR), help understand the pathophysiology of hearing loss (HL). In addition, electrophysiological tests can allow objective assessment of the integrity of the auditory neural system and identify the specific location of the lesion in the auditory pathway.

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Typically, decreased amplitudes of ABR wave I with consistent preservation of the amplitude of wave V have been reported as the evidences for hidden hearing loss (HHL).[3,8,9] This finding has also been regarded as a potential electrophysiological evidence for tinnitus generation.[10,11] Thus, the selective decrease in wave I amplitude has been frequently suggested as a sensitive marker for cochlear synaptopathy based on the evidences from animal studies which demonstrated a significant correlation with the number of viable synaptic ribbons of inner hair cells and spiral ganglion cell bodies.[11,12] Similarly, electrophysiological evidence has been actively investigated for HHL or cochlear synaptopathy, which is frequently considered to be the earliest stage of NIHL. However, few data have been reported about the electrophysiological characteristics of progressed NIHL with an evident decrease in the hearing threshold. This evidence could help understand the progression of damage to the auditory neural pathway attributed to prolonged noise exposure. Herein, we analyzed the clinical characteristics and electrophysiological changes in patients with different degrees of NIHL compared with those of normal controls to elucidate the progression of auditory damage attributed to noise exposure.

MATERIAL AND METHODS

Evaluation of the Electrophysiological Changes in Patients with Noise Exposure

This study was approved by the Ethics Committee of the Korea University Ansan Hospital (IRB No. 2022AS0188). Informed consent was waved in the confirmation of the IRB because this study was a retrospective study on medical records and was analyzed anonymously.

Among the 99 patients in our registry of NIHL, 29 were selected based on the following inclusion criteria: (1) existence of validated results of ABR and pure tone audiometry, (2) the results of pure tone audiometry with less than 10 dB gap in air- and bone-conduction thresholds along with type A tympanometry (sensorineural HL), (3) presence of symmetric sensorineural HL with less than 10 dB difference in bone-conduction thresholds between both sides, and (4) confirmed history of noise exposure (occupational or explosive noise exposure). In the case of explosive noise exposure, the patients whose HL did not improve after at least 1 month of follow-up were included. All the patients visited our clinic and received appropriate audiometric assessments between January 2007 and December 2019. Patients with a previous history of ear surgery, otitis media, or inner ear disease were excluded.

Twenty-nine patients were eligible for evaluation of the electrophysiological changes in the auditory pathway. Patients were subdivided into 2 groups: mild HL group (pure-tone average (PTA) < 40 dB) and severe HL group (PTA ≥ 40 dB). Nine patients showed normal-to-mild HL (mild HL group), while the others showed worse than moderate HL upon pure-tone audiometry (severe HL group). In terms of the nature of noise exposure, 26 patients experienced continuous occupational noise exposure (8 and 18 in the mild and severe HL groups, respectively), and 3 patients experienced episodic explosive noise exposure (1 and 2 in the mild and severe HL groups, respectively).

Forty control groups were selected by matching the age of patients without a memorable event of noise exposure to compare the electrophysiological changes. Therefore, 69 patients were included in this study.

Audiometric Assessment

All the patients were evaluated using the standard pure-tone audiometric threshold method. The bone-conduction PTA was obtained at average thresholds of 0.5, 1, 2, and 3 kHz. The speech recognition threshold (SRT) and word recognition score (WRS) were simultaneously obtained. SRT was the lowest level at which the participant could identify 50% of the suggested disyllabic words. WRS was checked using 50 single syllable, single words at 30-40 dB above the SRT in each ear.[13] Even though all patients exhibited symmetric HL with less than 10 dB difference bilaterally, we chose the worse hearing thresholds between both sides as the dominant side of noise exposure.

The stimuli for ABR were generated with 50 μs clicks at a 90 dB sound pressure level using a navigator system (Bio-logic Systems Corp., Orlando, Florida, USA) and presented via an insert earphone (ER-3A). Signals were bandpass filtered (100-1500 Hz) and averaged at ≥8000 repetitions. The amplitudes and latencies of waves I and V were measured from the local peak to the following trough (between 1.0 and 3.0 ms for wave I and 5.0 and 7.0 ms for wave V). For the distortion product otoacoustic emission (DPOAE) recordings, acoustic stimuli of 0.5-8 kHz (f1/f2 = 1.22) were presented at 65/55 dB SPL using Titan DPOAE440 (Interacoustics, Middelfart, Denmark). The acoustic stimulus consisted of 2 simultaneous and continuous pure tones of different frequencies, f1 and f2 (f2/f1 = 1/22). The intensities were L1 and L2 for the tones at frequencies f1 and f2, respectively, with L1 − L2 = 10 dB SPL (L1 = 65 dB SPL and L2 = 55 dB SPL). Therefore, the DPOAEs were measured from 0.5 to 8.0 kHz. In the present study, we analyzed the 2.0 kHz response, and if the DPOAE response was greater than the 6 dB signal-to-noise ratio, we verified that the DPOAE was normal at 2.0 kHz.

Statistical Analyses

All data are expressed as the mean ± standard deviation (SD). A Kruskal–Wallis test was performed to compare the PTA, SRT, WRS, and ABR in the 3 groups. Mann–Whitney *U* tests were applied with a Bonferroni correction as post hoc test. A 2-sided *P*-value of less than .017 (.05/3) was considered statistically significant when the Mann–Whitney *U* test was performed. The correlation between the PTA threshold and SRT was assessed using the Pearson product correlation coefficients. We calculated and compared the wave I/V amplitude ratio to minimize individual variations in the wave I and V amplitudes. A multivariate linear regression test was used to determine independent variables for changes in the amplitudes and latencies of waves I and V of the ABR. The following variables were considered for the

MAIN POINTS

- Significantly reduced wave I and V amplitudes were present in patients with noise-induced hearing loss.
- Wave V amplitude was negatively associated with wave I–V interpeak latency delay.
- The electrophysiological characteristics were similar between the mild and severe noise-induced hearing loss groups.

Table 1. Demographic Characteristics of the Study Population

	Normal Hearing (n = 40)	Noise Exposure Group		eP
		Normal-to-Mild Hearing Loss (n = 9)	Moderate or Worse Hearing Loss (n = 20)	
Age (years)	42.45 ± 12.74	50.11 ± 11.16	65.15 ± 13.34	<.001
Sex male, n (%)	16 (40 %)	8 (88.89 %)	20 (100 %)	
PTA threshold (dB)	9.78 ± 4.41	18.89 ± 9.41	59.00 ± 14.89	<.001
500 Hz	9.25 ± 6.26	13.89 ± 7.82	50.00 ± 18.50	<.001
1 kHz	10.25 ± 5.99	15.00 ± 8.66	51.75 ± 17.94	<.001
2 kHz	9.50 ± 5.41	20.00 ± 11.99	64.00 ± 15.18	<.001
3 kHz	10.13 ± 6.15	26.67 ± 17.32	70.25 ± 13.23	<.001
SRT (dB)	16.91 ± 5.08	23.57 ± 4.76	53.53 ± 20.46	
WRS (%)	99.41 ± 2.05 (n = 34)	99.29 ± 1.89 (n = 7)	71.32 ± 27.58 (n = 19)	
Noise exposure				
Occupational		8 (88.89 %)	18 (90 %)	
Explosive		1 (11.11 %)	2 (10 %)	

PTA (pure-tone average) indicates the mean ± SD at 0.5, 1, 2, and 3 kHz.SRT, speech recognition threshold; WRS, word recognition score.

univariate analyses: age, study groups, amplitudes of ABR wave I and V, and ABR wave I latency, which were assumed to be possibly associated variables. Variables with a *P*-value ≤.20 were selected for the multivariate linear regression model. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Baseline Characteristics

A summary of the demographic data of the enrolled patients is shown in Table 1. The mean age ± SD of the study population was 50.03 ± 16.08 years. The age was significantly different among the three groups since recruiting elderly patients with normal-to-mild HL was challenging; however, there was no difference between the control and mild HL groups ($P = .07$, Mann–Whitney *U* test).

The PTAs among the three groups were significantly different (Figure 1, $P < .001$, Kruskal–Wallis test). In the frequency-specific comparison, the control and mild HL groups were not significantly different at 500 Hz and 1 kHz ($P = .126$ and .17, respectively, Mann–Whitney *U* test). However, the severe HL group demonstrated a significant difference at all the frequencies compared to the other groups.

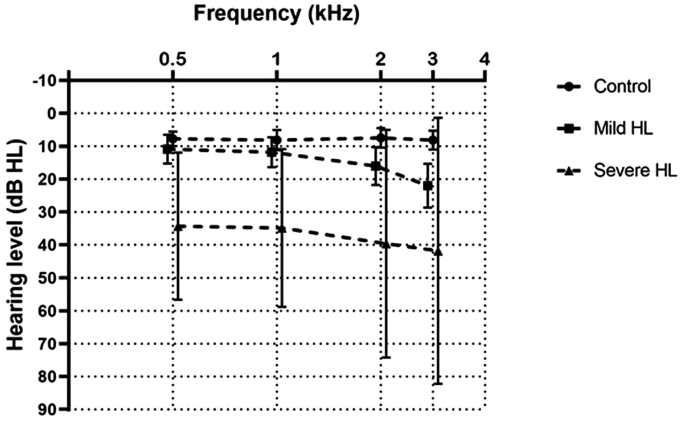

Figure 1. Averaged pure-tone audiogram in the control, mild hearing loss, and severe hearing loss groups.

The SRTs were positively associated with the PTA thresholds ($p = .89$, $P < .001$). The WRS of both control and mild HL groups showed good performance (99.41 ± 2.05% and 99.29 ± 1.89%, respectively); however, the severe HL group demonstrated a significantly lower WRS performance (71.32 ± 27.58, $P < .001$).

Auditory Brainstem Response Amplitude Analysis

Significantly reduced ABR wave I and V amplitudes were confirmed for both mild and severe HL groups compared to the control group (Figure 2A and B, $P < .001$ and $P = .002$, respectively). The ABR wave I amplitudes of each group were as follows: control, 0.28 ± 0.12 μV; mild HL, 0.14 ± 0.07 μV; severe HL, 0.16 ± 0.13 μV. The ABR wave V amplitudes of each group were as follows: control, 0.42 ± 0.16 μV; mild HL, 0.28 ± 0.13 μV; severe HL, 0.30 ± 0.12 μV. There was no difference in the ABR wave I and V amplitudes between the mild and severe HL groups (Figure 2C, $P = .13$). The I/V amplitude ratio was not different between the groups; however, the ratio was small for mild and severe HL groups.

Auditory Brainstem Response Latency Analysis

In the wave I latency analysis, the severe HL group showed a significant latency delay, whereas the mild HL group did not differ from the control group (Figure 3A, $P = .014$). The ABR wave I latency of each group were as follows: control, 1.41 ± 0.10 ms; mild HL, 1.60 ± 0.42 ms; severe HL, 1.54 ± 0.21 ms. The ABR wave V latency and I-V inter-peak latency were significantly delayed in both the mild and severe HL groups compared to the control group (Figure 3B and C, $P < .001$ and $P = .003$, respectively). The ABR wave V latency of each group were as follows: control, 5.48 ± 0.25 ms; mild HL, 5.85 ± 0.46 ms; severe HL, 5.83 ± 0.29 ms. There was no significant difference in the III-V inter-peak latency (Figure 3D, $P = .16$).

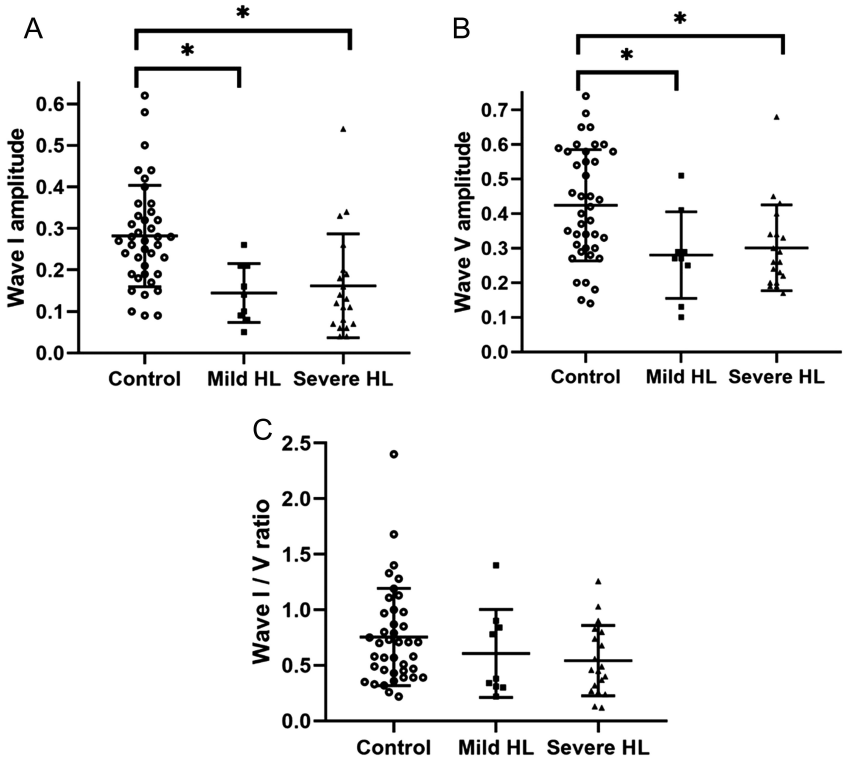

Figure 2. Auditory brainstem response wave I (A), V (B) amplitude and the ratio of wave I/V (C). The ABR wave I and V amplitudes were significantly reduced in both the mild and severe hearing loss groups compared to the control group.

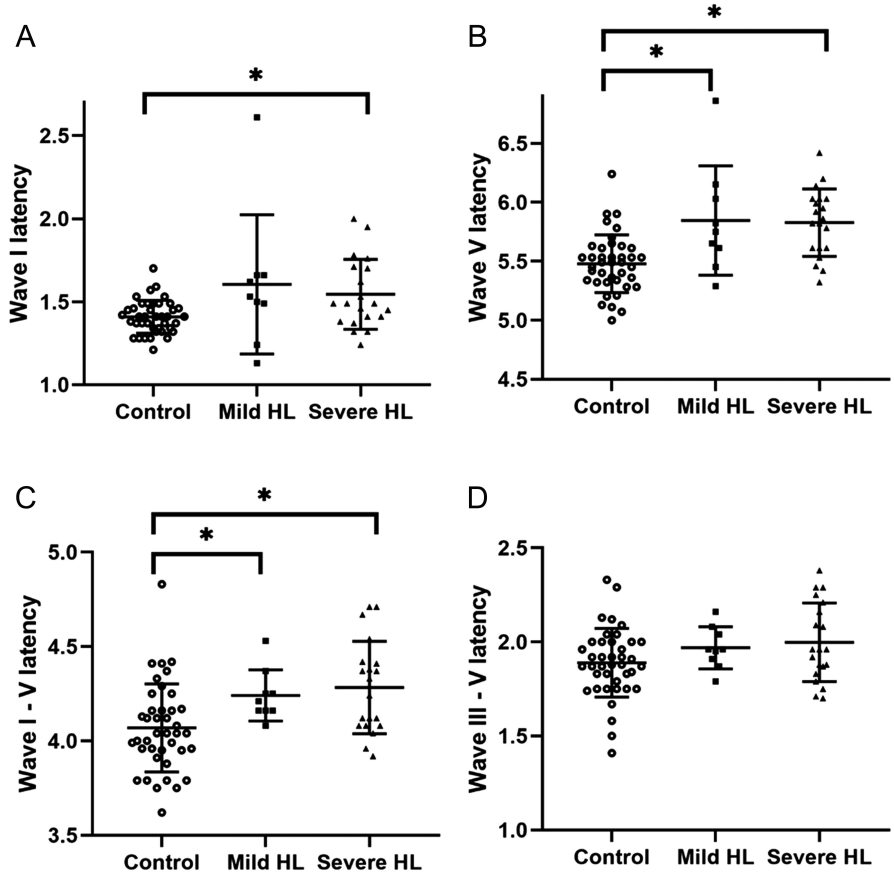

Figure 3. Latency of the auditory brainstem response. (A) Wave I latency was significantly delayed in the severe hearing loss (HL) group. (B) and (C) ABR wave V latency and I-V inter-peak latency were significantly delayed in both the mild and severe HL groups compared to the control group. (D) Wave III-V inter-peak latency were not significantly different.

Distortion Product Otoacoustic Emission Analysis

Twenty-five participants underwent DPOAE tests: 18, 6, and 1 in control, mild, and severe HL groups, respectively. Only the patient with severe HL showed an abnormal DPOAE response, whereas others showed normal responses at 2.0 kHz. This result shows that the function of the outer hair cells was preserved despite noise exposure in the mild HL group.

Multivariate Analysis of the Auditory Brainstem Response Parameters

A multivariate linear regression analysis was performed, considering ABR waves I-V inter-peak latency as a dependent, continuous variable (Table 2, adjusted $R^2 = 0.23$). ABR wave V amplitude was negatively associated with ABR waves I-V inter-peak latency delay ($B = -0.48$, $P = .02$).

A multivariate linear regression analysis was performed, considering ABR wave V latency as a dependent, continuous variable (Table 3, adjusted $R^2 = 0.59$). ABR wave V amplitude (negative) and I latency (positive) were significantly associated with the ABR wave V latency ($B = -0.51$, $P = .01$, and $B = 0.85$, $P < .001$, respectively). Although the result was not significant ($P = .06$), the "control group" demonstrated a negative association with the degree of ABR V latency delay ($B = -0.15$).

A multivariable linear regression analysis was performed, considering the ABR wave I amplitude as a dependent, continuous variable (Table 4, adjusted $R^2 = 0.34$). Age was significantly associated with the ABR wave I amplitude ($B = -0.003$, $P = .01$).

A multivariable linear regression analysis was performed, considering the ABR wave V amplitude as a dependent, continuous variable

Table 2. Analysis of the Factors Potentially Associated with Auditory Brainstem Response Waves I-V Inter-Peak Latency Delay

	Univariable				Multivariable			
	B	SE	*P*	95% CI	*B*	SE	*P*	95% CI
Age	0.005	0.002	.004	0.002 to 0.009	0.001	0.002	.60	−0.003 to 0.006
Group (reference: severe HL)								
Control	−0.21	0.06	.001	−0.34 to −0.09	−0.15	0.08	.07	−0.30 to 0.01
Mild HL	−0.04	0.09	.64	−0.23 to 0.14	−0.05	0.10	.57	−0.24 to 0.14
ABR wave I amplitude	−0.53	0.22	.02	−0.97 to −0.10	−0.03	0.25	.92	−0.53 to 0.47
ABR wave V amplitude	−0.69	0.17	<.001	−1.03 to −0.35	−0.48	0.19	.02	−0.86 to −0.09
ABR wave I latency	0.10	0.14	.49	−0.18 to 0.38				

ABR, auditory brainstem response; *B*, unstandardized regression coefficient; CI, confidence interval; HL, hearing loss; SE, standard error.

Table 3. Analysis of the Factors Potentially Associated with Delay in the Auditory Brainstem Response Wave V Latency

	Univariable				Multivariable			
	B	SE	*P*	95% CI	*B*	SE	*P*	95% CI
Age	0.01	0.002	<.001	0.004 to 0.01	0.001	0.002	.58	−0.003 to 0.01
Group (reference: severe HL)								
Control	−0.35	0.08	<.001	−0.51 to −0.19	−0.15	0.08	.06	−0.31 to 0.01
Mild HL	0.02	0.12	.88	−0.22 to 0.25	−0.04	0.10	.66	−0.23 to 0.15
ABR wave I amplitude	−1.19	0.28	<.001	−1.74 to −0.64	−0.08	0.26	.58	−0.59 to 0.43
ABR wave V amplitude	−1.17	0.22	<.001	−1.61 to −0.73	−0.51	0.20	.01	−0.91 to −0.12
ABR wave I latency	1.10	0.14	<.001	0.82 to 1.38	0.85	0.15	<.001	0.55 to 1.15

ABR, auditory brainstem response; *B*, unstandardized regression coefficient; CI, confidence interval; HL, hearing loss; SE, standard error.

Table 4. Analysis of the Factors Potentially Associated with the Auditory Brainstem Response Wave I Amplitude

	Univariable				Multivariable			
	B	SE	*P*	95% CI	*B*	SE	*P*	95% CI
Age	−0.004	0.001	<.001	−0.006 to −0.02	−0.003	0.07	.01	−0.005 to −0.001
Group (reference: sever HL)								
Control	0.12	0.03	<.001	0.06 to 0.19	0.02	0.04	.53	−0.05 to 0.1
Mild HL	−0.02	0.05	.72	−0.11 to 0.08	−0.05	0.05	.32	−0.14 to 0.05
ABR wave V amplitude	0.36	0.09	<.001	0.18 to 0.55	0.15	0.10	.10	−0.05 to 0.34
ABR wave I latency	−0.26	0.07	<.001	−0.40 to −0.12	−0.12	0.07	.13	−0.05 to 0.34

ABR, auditory brainstem response; *B*, unstandardized regression coefficient; CI, confidence interval; HL, hearing loss; SE, standard error.

Table 5. Analysis of the Factors Potentially Associated with the Auditory Brainstem Response Wave V Amplitude

	Univariable				Multivariable			
	B	SE	*P*	95% CI	*B*	SE	*P*	95% CI
Age	−0.004	0.001	.002	−0.01 to −0.001	−0.001	0.001	.32	−0.004 to 0.001
Group (reference: severe HL)								
Control	0.12	0.04	.004	0.04 to 0.21	0.04	0.05	.38	−0.06 to 0.14
Mild HL	−0.02	0.06	.73	−0.14 to 0.10	−0.03	0.06	.68	−0.15 to 0.10
ABR wave I amplitude	0.52	0.13	<.001	0.26 to 0.79	0.25	0.16	.13	−0.08 to 0.57
ABR wave I latency	−0.29	0.09	.002	−0.47 to −0.12	−0.15	0.09	.11	−0.34 to 0.04

ABR, auditory brainstem response; *B*, unstandardized regression coefficient; CI, confidence interval; HL, hearing loss; SE, standard error.

(Table 5, adjusted $R^2 = 0.34$). None of the factors were significantly associated with ABR wave V amplitude.

DISCUSSION

The most exclusive finding in our data was the decreased amplitudes of wave V similar to those of wave I, in the mild and severe HL groups. The delayed latencies of waves I and V in both the mild and severe HL groups was another distinct finding. The amplitudes and latencies of waves I and V were changed in the mild HL group, even though they had normal responses during DPOAE at 2 kHz. Considering that the electrophysiological characteristics of HHL are typically reported as decreased amplitudes of ABR wave I with consistent preservation of the amplitude of wave V,[3,8,9] our data suggest that the widespread disruption in auditory neural conduction could precede clinically apparent mild HL following noise exposure. The central compensatory mechanisms did not seem to be effectively activated in those cases where the central gain could be increased to keep the wave V amplitude unchanged against the decreased wave I amplitude.[3] The significant correlation between wave I amplitude and age is in accordance with a previous report.[14]

The latencies of waves I and V were also significantly delayed in noise-exposed groups, with an unaltered latency between waves III and V. Notably, these findings were observed regardless of the degree of HL. Along with the decreased amplitude of ABR waves I and V, potential supporting mechanisms can be speculated in several ways. First, the reduced peripheral inputs can delay the synaptic integration time due to noise-induced degeneration in the hair cells and synaptic ribbons. Based on previous evidence of disrupted functions in the ribbon synapses, these changes are more prominent in the synapses of the distal pathways, which are more directly affected by noise. This finding also supports the observed latency delay between wave I and III compared with the unaltered latency between wave III and V.[2,5] The significantly negative correlation between the wave V amplitude and the wave V latency or the wave I-V inter-peak latency could be another supporting evidence. Second, a conduction block or delay could be considered. Since a permanent decrease in the thickness of the myelin sheath could be observed upon exposure to high-intensity sound, the demyelination of the auditory nerve can directly delay the neural conduction time.[6] The noise could directly cause myelin sheath damage or induce interrupted myelin formation.[2,6,11] Suprathreshold noise-induced demyelination or the loss of cochlear Schwann cells was recently reported.[2,6,7] Noise exposure to the adult rodent directly resulted in a morphological deficit in myelin formation.[11] Molecular evidence has also suggested dysfunction of RNA splicing regulator Quaking (QKI) and numerous QKI target genes in the myelinating glia, which result in demyelination of the spiral ganglion neurons, disruption of the paranodal axo-glial junctions, and functional deficiencies of the auditory nerve.[2] The alteration in myelin formation could cause disruptions in the recruitment of the auditory nerve fibers and the synchronized firing of nerve fibers and also result in conduction block.[6] Resultant clinical complications include alteration of temporal precision.[6,7] In the hearing or electrophysiological tests, these changes can decrease speech discrimination and increase the latency of ABR.[6,7]

Despite the changes in ABR, speech discrimination decreased only in the severe HL group. This could be in agreement with the findings that demonstrated normal PTA or SRT, even in patients who were strongly suspicious of HHL. Thus, more delicate and sensitive measurement tools are warranted for speech recognition in noisy environments.

Our study has certain limitations. First, our data were obtained from a retrospective review of medical records, including the results of electrophysiological tests of auditory function. Thus, more delicate conditions could not be established for more sensitive discrimination of psychoacoustic or electrophysiological changes. Second, although the duration and intensity of noise exposure in our participants were fairly accurate since most of them had validated documents on occupational noise exposure, the patient groups were relatively small. This, in turn, could limit the construction of more comparable subgroups. Third, although none of the patients had a history of genetic HL, individual genetic factors related to NIHL susceptibility were not considered. The genetic basis of NIHL has been well demonstrated in animals with different susceptibilities to noise even in the inbred strains of mice.[15] Recent studies on genetic polymorphisms in humans have shown that some genetic polymorphisms, such as potassium ion channels (*KCNQ4* and *KCNE1*),[16] catalase (*CAT*),[17] protocadherin 15 (*PCDH15*),[18] myosin 14 (*MYH14*),[18] and heat shock protein (*HSP70*),[19] are associated with the susceptibility to noise. These genetic components may be associated with the disruption of different pathways and structures within the cochlea, thereby increasing the susceptibility of the inner ear to noise.

The electrophysiological characteristics of the auditory system in mild HL were similar to those in severe HL in terms of the amplitudes and latencies of waves I and V in ABR for patients with NIHL. These findings suggest that widespread disruption in auditory neural

conduction could have already been established in the early periods when the patient developed mild HL following noise exposure.

Ethics Committee Approval: This study was approved by Ethics Committee of Korea University Ansan Hospital (Approval No: 2022AS0188, Date: July 26, 2022).

Informed Consent: The Ethics Committee of our hospital waved individual informed consent because this study is based on a retrospective review of medical record.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.S.C., Y.C.R.; Design – Y.S.C., Y.C.R.; Supervision – Y.C.R.; Resources – I.S.S., J.H.H., J.C., Y.C.R.; Materials – I.S.S., J.C., Y.C.R.; Data Collection and/or Processing – I.S.S., J.C., Y.C.R.; Analysis and/or Interpretation – Y.S.C., Y.C.R.; Literature Search – Y.S.C., Y.C.R.; Writing – Y.S.C., Y.C.R.; Critical Review – J.H.H., Y.C.R.

Declaration of Interests: The authors have no conflicts of interest to disclose.

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