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Limitation of Conventional Audiometry in Identifying Hidden Hearing Loss in Acute Noise Exposure

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Purpose: The concept of hidden hearing loss can explain the discrepancy between a listener's perception of hearing ability and hearing evaluation using pure tone audiograms. This study investigated the utility of the suprathreshold auditory brainstem response (ABR) for the evaluation of hidden hearing loss in noise-exposed ear with normal audiograms.

Materials and Methods: A total of 15 patients (24 ears) with normal auditory thresholds and normal distortion product otoacoustic emissions were included in a retrospective analysis of medical records of 80 patients presenting with histories of acute noise exposure. The control group included 12 subjects (24 ears) with normal audiograms and no history of noise exposure. Pure tone audiometry and suprathreshold ABR testing at 90 dB peSPL were performed. The amplitudes and latencies of ABR waves I and V were compared between the noise-exposed and control groups.

Results: We found no significant difference in the wave I or V amplitude, or the wave I/V ratio, between the two groups. The latencies of ABR wave I, V, and I–V interpeak interval were compared, and no significant intergroup difference was observed.

Conclusion: The results suggest that either hidden hearing loss may not be significant in this cohort of patients with acute noise exposure history, or the possible damage by noise exposure is not reflected in the ABRs. Further studies are needed to inquire about the role of ABR in identification of hidden hearing loss.

Key Words: Auditory brainstem response, hearing loss, noise-induced hearing loss

INTRODUCTION

Noise-induced hearing loss (NIHL) is a common and significant cause of acquired sensorineural hearing loss in adults. Hearing threshold changes following acute noise injury are described as either temporary threshold shifts (TTSs) or permanent threshold shifts (PTSs) in terms of the extent of recovery. It has been generally accepted that hearing sensitivity is usually restored, without any anatomical change within 24 hours in the case of TTSs.[1] Traditionally, cellular damage after noise exposure has been explained by the death of cochlear hair cells and spiral ganglion (SGNs), but the relationship between noise exposure and inner ear damage varies.[2,3] However, recent animal studies have highlighted the fact that synaptic loss between inner hair cells (IHCs) and the auditory nerve (AN) is the principal pathology even in those experiencing only TTSs after noise exposure, and such synaptic loss is independent of the loss of either or both IHCs and SGNs.[4,5] When synapses are damaged, the nerve fibers subsequently degenerate, and this process has been termed the cochlear synaptopathy, or "hidden hearing loss."[4,6] The name "hidden hearing loss" primarily refers to the fact that cochlear damage can occur without affecting the hearing thresholds.

In experimental animal models, cochlear synaptopathy has been demonstrated using direct histopathological methods and electrophysiological approaches.[5,7-9] Damage to synapses between IHCs and AN fibers after noise injury, and a reduction

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in the wave I amplitude of the auditory brainstem response (ABR) (without a significant threshold shift), substantiate the concept of hidden hearing loss, explained by the finding that synaptopathy loss appears to selectively affect low-spontaneous rate (SR) fibers (which have high thresholds).[10] These low-SR fibers do not contribute to sensitivity to quiet sounds, and are thought to be responsible for encoding of sound intensity at moderate-to-high levels.[10] On the other hand, selective loss of low-SR fibers by pharmacologic treatment did not affect the hearing threshold or the compound action potentials (APs).[11] Such discrepancies suggest that not only the loss of low-SR fibers but also other factors, such as neural synchrony, might be involved in suprathreshold auditory processing.

Correlates of cochlear synaptopathy in human ears have been sought using non-invasive electrophysiological techniques. While it is difficult to examine AN fibers directly in humans, animal studies have shown that the ABR wave I amplitude reflects the proportion of intact synapses.[5,12] In humans, the ABR wave I amplitude was decreased as a function of the extent of noise exposure in subjects with normal hearing.[13] Also, suprathreshold ABR responses to tone bursts of 1, 3, 4, and 6 kHz were compared for young veterans and non-veterans with normal pure tone thresholds.[14] The ABR wave I amplitudes were smaller in veterans reporting high levels of noise exposure and non-veterans reporting history of firearm use, compared to veterans and non-veterans with lower levels of noise exposure, after controlling for gender and distortion product otoacoustic emissions (DPOAEs) measures/amplitude. Other human studies have reported conflicting results. Among young adults with a history of recreational noise exposure, tinnitus symptoms did not correlate with pure tone thresholds or otoacoustic emissions (OAE) or ABR measurements, but those with tinnitus exhibited decreased speech reception in noise.[15] Another study recruited young college students at varying risk of noise injury based on self-reported noise exposure and the use/non-use of hearing protection.[16] Audiologic tests were performed including pure tone audiometry and word recognition test, and electrocochleogram (ECoG) was used to measure the AP, which, in essence, corresponds to ABR wave I, and the summating potential (SP). Since the neural damage in animal models of cochlear synaptopathy was shown by decreased AP while the SP remained unaffected, the SP/AP ratio was calculated, and the SP/AP ratio was increased in the high-risk group.[16] Notably, although the SP/AP ratio was increased, the AP did not differ between the low- and high- risk groups. In contrast, a recent study showed that there was no relation between noise exposure and mean ABR amplitude in young adults with normal hearing. When the ABR responses to suprathreshold high pass filtered clicks were measured, the wave I amplitudes were not affected, and only wave V latency was increased as a function of the history of noise exposure.[17] Such discrepancies may suggest that noise-induced changes in the ABR waves have little effect in young humans, or that the ABR measurement are not sensitive to reflect subtle changes in cochlear synaptopathy.

In clinical settings, it would be helpful if ABR measurements could be used to identify hidden hearing loss in patients after noise exposure, but the evidence to date remains equivocal. Previous studies have assessed a subject's noise exposure status based on the cumulative history of exposure to loud noise. The study subjects included musicians, veterans, and those enjoying leisure music long-term. Since it would not be ethical to expose humans to excessive noise deliberately, we designed a retrospective study on patients who complained of ear discomfort without overt hearing loss after acute noise injury. We hypothesized that if cochlear synaptopathy developed in human ears after acute noise exposure, as is the case in experimental animal models, this would be reflected by changes in ABR wave I. Therefore, we measured suprathreshold ABR waveforms in patients presenting with subjective discomfort after acute noise exposure, but with normal audiograms and OAEs, and compared their data with those of normal hearing subjects without a history of acute noise exposure.

MATERIALS AND METHODS

Ethical consideration

The Review Board of the authors' institution approved this study (approval no. IRB3-2017-0124). All of the procedures performed in the studies involving human participants were conducted in accordance with the ethical standards of our institutional and/or national research committees and those of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Selection of subjects

The medical records of 42 patients who visited our outpatient clinic after acute noise exposure from 2014 to 2017 were retrospectively reviewed. The inclusion criteria were: 1) no known history of neuro-otological disease; 2) normal otoscopic findings; 3) clinically normal audiograms (defined as ≤25 dB HL for all frequencies of 250, 500,1000, 2000, 3000, 4000, 6000, and 8000 Hz); 4) normal tympanograms (type A, defined as peak pressure±50 daPa for a 226 Hz tone, and compliance between 0.3–1.3 mL); 5) intact DPOAE at 1–8 kHz; and 6) identifiable waves I, III, and V in ABR recordings. Of 84 ears from 42 patients, 41 ears with pure tone thresholds ≥25 dB HL, 16 ears with no or undiscernible ABR waveforms, and three ears with abnormal DPOAEs were excluded from the study. As a result, 24 ears of 15 patients (male:female=10:5) were included as the noise-exposed group. The control group included 24 ears of 12 young subjects (male:female=7:5) with no known history of neuro-otological disease or noise exposure, who yielded normal audiograms (pure tone thresholds ≤25dB HL for all frequencies of 250, 500,1000, 2000, 3000, 4000, 6000, and 8000 Hz).

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Equipment and procedures

All tests were performed in a double-walled soundproof booth in accordance with the ANSI standard S3.1-1999 (R 2008). Pure tone audiometry was performed with the aid of a Madsen ORBITER 922 diagnostic audiometer (GN Otometrics, Taastrup, Denmark) and supra-aural headphones (TDH-39P; Telephonics, New York, NY, USA). Measurements were made at the frequencies of 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz using the modified Hughson-Westlake procedure,[18] also described in ANSI S3.21-1978 (R-1992), and were considered clinically normal when the threshold within ≤25 dB HL at all frequencies as in previous studies.[19,20] Tympanometry was performed using a Grason Stradler GSI TympStar Middle Ear Analyzer v.2 (Viasys NeuroCare, Madison, WI, USA) with 226 Hz probe tones. The DPOAE measurements were performed with a GSI Audera® DPOAE system and dedicated software (Grason-Stadler, Eden Prairie, MN, USA). DPgrams were measured at two primary tones of f1 and f2 (f2/f1=1.22; f1=65 dB SPL and f2=55 dB SPL). The primary frequencies were swept from f2= 500 Hz to 12 kHz, using four logarithmically spaced steps per octave. The DPOAEs at 2f1-f2 were extracted. ABRs were evaluated using the GSI Audera® AEP system dedicated software (Grason-Stadler). Disposable electrodes (Nicolet Biomedical, Madison, WI, USA) were placed on the high forehead and on the ipsilateral and contralateral mastoids. All electrodes had impedances <2 kΩ. Stimuli [100-μs clicks at 90 dB peak equivalent sound pressure level (peSPL)] were presented via the Telephonics TDH 39P headphones at a rate of 11 clicks/s, with alternating polarity. The signals were bandpass-filtered (100–1500 Hz) and averaged over at least 8000 repetitions. GSI generic default calibrations were used. The signals were calibrated to conform to the ANSI S3.6 1196 standard for audiometers. Two independent audiologists separately identified positive peaks and the following negative troughs for waves I, III, and V using visual overlay cursors on a computer screen. Wave amplitudes for waves I and V were defined as the difference between the voltage at the positive peak and the following negative trough (Fig. 1). Both observers were blinded to the subject information during ABR waveform analyses. Any interscorer disagreements between the two observers were resolved by reviewing the data together.

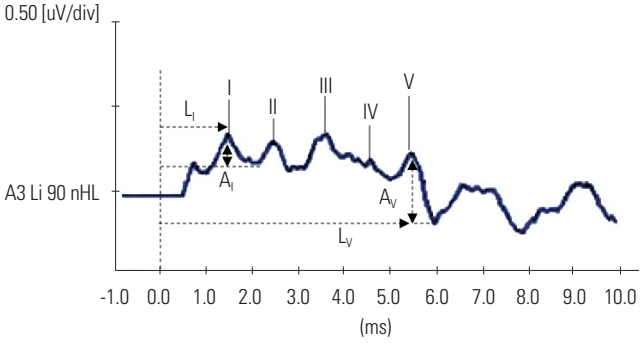

Fig. 1. A representative tracking of suprathreshold auditory brainstem response tracing for the measurement of amplitudes and latencies of waves I and V.

Data analyses

All statistical analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). Differences in age, gender, pure tone thresholds, and ABR parameters between the control group and patient group were analyzed using the independent two samples t-test when the data was normally distributed, and by Mann-Whitney test otherwise. All data are presented as means±standard deviations. A p-value<0.05 was considered statistically significant.

RESULTS

Audiological data from 24 ears of 15 patients with noise-exposure history were compared to those of 24 ears of 12 subjects from the control group. The mean duration between the reported noise exposure to evaluation was 6.79±1.58 days. In the noise-exposed group, the mean age was 36.67±15.45 years, and the male:female ratio was 10:5. In the control group, the mean age was 25.92±2.78 years, and the male:female ratio was 7:5. This showed that the control group was younger (p=0.014). We found no statistical between-group difference in pure tone thresholds, as shown in Table 1 and Fig. 2. In the noise-exposed group, the mean pure tone thresholds for 0.5, 1, and 2 kHz was 6.25±4.99 dB HL, and the mean hearing threshold from 0.5 kHz to 8 kHz was 8.20±4.83 dB HL. In the control group, the figures were 4.58±2.92 and 6.33±3.16 dB HL, respectively (Table 1). The principal complaints of the noise-exposed group were tinnitus in seven cases (46.7%), a subjective feeling of hearing impairment in six (40.0%), and aural fullness in two (13.3%). The patients' noise exposure history, as retrieved from their medical records, is detailed in Supplementary Table 1 (only online). Patients reported exposure to various types of noise prior to symp-

Table 1. Clinical Characteristics of Noise-Exposed Group and Control Group (n, Number of Ears)

	Control (n=24)	Noise-exposed (n=24)	p value
Age (yr)	25.92±2.78	36.67±15.45	0.014
Mean PTA in dB HL (0.5, 1, and 2 kHz)	4.58±2.92	6.25±4.99	0.165
Mean PTA in dB HL (0.5 to 8 kHz)	6.33±3.16	8.20±4.83	0.119
Presenting symptoms (%)			
Tinnitus	-	7 (46.7)	
Subjective hearing impairment	-	6 (40.0)	
Aural fullness	-	2 (13.3)	
Types of noise exposure (%)			
Attendance at musical events	-	6 (40.3)	
Explosive machinery noise	-	5 (33.3)	
Use of firearms	-	4 (26.7)	

PTA, pure tone average.

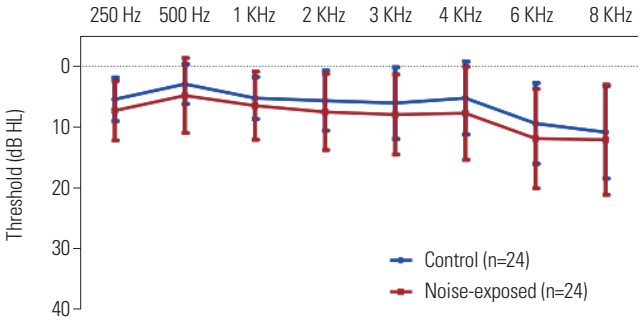

Fig. 2. Pure tone thresholds in the range of 0.25 to 8 kHz in noise-exposed group and control group. There was no significant difference in the thresholds between the control and noise-exposed groups at all frequencies from 0.25 to 8 kHz. Error bar represents mean value±standard deviation.

Table 2. Suprathreshold Auditory Brainstem Response Measurements in Noise-Exposed and Control Groups

	Noise-exposed (n=24)	Control (n=24)	*p* value
Wave I amplitude (μV)	0.30±0.13	0.33±0.10	0.373
Wave V amplitude (μV)	0.35±0.14	0.41±0.10	0.094
Wave I/Wave V amplitude ratio	0.90±0.34	0.86±0.36	0.693
Wave I latency (ms)	1.34±0.12	1.29±0.07	0.131
Wave V latency (ms)	5.48±0.23	5.42±0.19	0.322
Interpeak interval I–V (ms)	4.14±0.25	4.13±0.20	0.805

tom development, including attendance at concerts (6 ears, 40%), exposure to machine noise (5 ears, 33.3%), and the use of firearms (4 ears, 26.7%).

Table 2 lists the ABR measurements obtained when click stimuli were delivered at 90 dB peSPL. The ABR wave I amplitudes of the noise-exposed and control groups were 0.30±0.13 and 0.33±0.10 μV, respectively. The ABR wave V amplitudes were 0.35±0.14 and 0.41±0.10 μV. Neither the wave I nor V amplitude differed between the two groups. Also, the wave I/wave V amplitude ratio did not differ significantly (0.90±0.34 in the noise-exposed group and 0.86±0.36 in the control group, p=0.693). The wave I and V latencies were 1.34±0.12 and 5.48±0.23 ms, respectively, in the noise exposed group, and 1.29±0.07 and 5.42±0.19 ms, respectively, in the control group. The interpeak intervals between waves I and V were 4.14±0.25 ms in the noise-exposed group, and 4.13±0.20 ms in the control group. Neither the wave I nor V latencies, nor the wave I–V interpeak intervals, differed between the groups.

As gender is a potential confounder of ABR variability and the number of females were smaller in both groups, we analyzed the males-only data from both the noise-exposed (15 ears) and control (14 ears) groups (Table 3). Again, no significant difference was found in the amplitudes of wave I or V, the amplitude ratio, the wave latencies, or the interpeak intervals.

Table 3. Suprathreshold Auditory Brainstem Response Measurements for Males in Noise-Exposed and Control Groups

	Noise-exposed (n=15)	Control (n=14)	*p* value
Wave I amplitude (μV)	0.25±0.11	0.29±0.10	0.158
Wave V amplitude (μV)	0.34±0.17	0.40±0.10	0.077
Wave I/Wave V amplitude ratio	0.81±0.32	0.82±0.44	0.652
Wave I latency (ms)	1.35±0.15	1.29±0.07	0.290
Wave V latency (ms)	5.55±0.22	5.49±0.19	0.561
Interpeak interval I–V (ms)	4.20±0.26	4.20±0.20	0.988

DISCUSSION

For decades, it has been presumed that NIHL was attributable to damage to the outer hair cells and SGNs.[21] However, recent studies have suggested that the synapses between IHC and SGNs with low spontaneous firing rates and high thresholds are the most vulnerable to aging and noise exposure.[4] Such cochlear synaptopathy may be "hidden," as the synaptic loss can occur without permanent hearing threshold shifts.[6] Recently, the cochlear synaptopathy has been described as possible mechanisms of hidden hearing loss in several animal experimental studies.[10,22-24] A similar concept of cochlear synaptopathy has also been inferred in humans.[6,13,25] If such hidden hearing loss can be identified in humans, it would be helpful in the diagnosis and prevention of NIHL. Therefore, it is essential to establish reliable diagnostic methods to assess cochlear synaptopathy in humans. ABR analysis has been considered to be a likely option, such analysis is, and the ABR wave I is the most direct measure of AN function. Moreover, the ABR wave I has shown amplitudes that correlate with the extent of cochlear synaptopathy (as measured immunohistologically) in animal models. However, direct measurements of wave I are complicated by the well-known inter- and intra-subject variability in ABR recordings.[26,27] The ABR waves vary by gender, age, stimulus, and recording method. The ABR wave I amplitudes are smaller for males than for females, even when the hearing levels are similar.[28] A recent study re-analyzed the relationship between ABR wave I amplitude and noise exposure history in subjects with normal hearing, and found that the amplitudes were decreased with more extensive noise exposure history in females, but not in males, highlighting the significance of sex as a confounding factor.[13,29] Another study including normal hearing subjects found no significant correlation between the noise exposure history and the ABR wave I amplitudes in both males and females.[20] Since inter- and intra- subject variability may mask or exaggerate small differences in amplitude and the ratios of amplitudes of ABR wave I/wave V, the AP/SP values yielded by ECoG can be used instead.[14,16,17] To control for relevant factors, we analyzed the wave I amplitudes and the wave I/V amplitude ratio for all subjects, and for males only. We found no significant difference between the noise-exposed and control groups. As our study population was predominantly male, we

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could not subject only females to further analysis. Another factor affecting the ABR is the presence of hearing loss at higher frequencies. Previous studies have confirmed that noise-exposed subjects had normal pure tone thresholds for frequencies of up to 6 kHz[14] or 8 kHz.[13] A more comprehensive evaluation of hearing thresholds in the range of 10–16 kHz may be required.[16,17] A recent study suggested that the effect of masking noise on the ABR wave V latency might more sensitively reflect the underlying synaptic damage.[30]

For obvious ethical reasons, human subjects cannot be deliberately exposed to controlled noise. Therefore, we alternatively reviewed patients who presented with a history of acute noise exposure. We hypothesized that patients who experience ear symptoms after acute noise injury but retain normal hearing thresholds would correlate to the experimental animal models of cochlear synaptopathy using controlled noise exposure, although it cannot be confirmed histologically. Unlike what was found in animal experiments and several earlier human studies, we found no reduction in ABR wave I amplitude in the noise-exposed subjects. Grinn, et al.[19] performed a prospective study where participants were exposed to recreational noise to investigate the possibility of hidden hearing loss. The participants did not show any evidence of auditory deficit prior to noise exposure. After exposure to conventional recreational noise exposure, there were no permanent changes in the participants' audiometric, electrophysiologic, or functional measures. Their data were in accordance with our results that acute exposure to recreational noise, such as attending concerts or festivals, did not cause changes in ABR measurements. However, our study is unique in that our patients presented with ear symptoms after acute noise exposure. Since TTS is quite variable among individuals, the patients included in our study might represent a subset of those who are possibly more vulnerable to noise injury.

We evaluated only patients presenting after acute noise injury caused by firearm discharge, concert attendance, or exposure to explosive machinery, without any hearing protection. It is possible that any synaptic damage that might be present in our patient group who reported subjective discomfort after acute noise exposure might be less severe than that associated with long-term exposures to noise, as assessed in other studies.[13,14,16,17] We lacked data on lifetime noise exposure; and such data would have allowed useful comparisons with data from other studies. For example, we cannot rule out the possibility that our patients did not differ from the controls, since the patients had been exposed to less noise than the controls until their recent episodes of noise exposure. Previous studies have utilized several methods, including self-report questionnaires, to estimate the patient's noise exposure history. Liberman, et al.[16] used different questionnaires, such as the 1) Hearing Health and Personal Characteristics, 2) Experiences and Abilities in Different Listening Situations, and 3) Loudness/Annoyance of Sounds and Hyperacusis. Bramhall, et al.[14] used the Lifetime Exposure of Noise and Solvents Questionnaire (LENS-Q). As the concept of hidden hearing loss gains more attention and clinical experiences accumulate, self assessment tools such as questionnaires are likely to be valuable. It should be noted that the noise-exposed group was significantly older than the control group. However, we believe that this would not significantly affect our conclusions. Aging was shown to be associated with significant reduction in the amplitudes of all principal ABR waves after controlling for the confounding effects of hearing loss.[31] Nevertheless, future studies should consider that aging affects both the amplitudes and latencies of ABR waveforms. More selective methods are required to distinguish synaptic damage caused by aging and noise exposure.

The principal limitation of our study was its retrospective design. The types of noise varied, and presumably, the noise levels and duration of exposure also differed among patients. Due to the small number of patients in our study, we were not able to compare the ABR measurements according to the types of noise exposure. Also, it is possible that the noise-induced injuries may not have been severe enough to cause synaptic loss in some patients, although they experienced aural fullness and other ear symptoms. Also, we recorded suprathreshold ABRs using click stimuli delivered at only 90 dB peSPL, which was the usual setting of ABR testing. Additional information supporting (or not) cochlear synaptopathy would have been useful, but we lacked data that may contribute to this possibility, such as speech perception in noise.[16,32,33] It has been suggested that poorer word recognition in noisy and difficult listening conditions might be related to cochlear synaptopathy.[16] Studies have suggested that a test battery including electrophysiological and behavioral evaluations would be more reliable than a single test to identify the hidden hearing loss caused by cochlear synaptopathy in subjects with normal hearing in conventional audiograms. A person with noise-induced synaptopathy might experience hearing difficulties in suprathreshold levels, even with normal audiograms.[6,16,30] In addition to routine audiograms, it would be helpful to check the hearing thresholds and speech recognition performance in noise conditions. Changes in the ratio of SPs and AP from the click-evoked and word recognition in noise were noted in the high-risk group for noise exposure.[16] Also, the ratio of amplitudes of wave I to wave V was shown to be increased in the normal hearing patients with tinnitus and previous noise exposure history,[6] and a shift of wave V latency in ABR recorded in noise condition has been suggested as a measure of cochlear synaptopathy.[30] Another study investigated the frequency-following responses (FFRs) to suprathreshold pure tones in noise-exposed ears, but showed no significant difference.[17] To build on from our current results, a longitudinal prospective study of ABR responses, with objective quantification of accumulated amount of noise exposure, would be ideal to validate the role of ABR analysis in detecting hidden hearing loss.

In summary, the waveforms in the ABR measurements us-

ing suprathreshold click stimuli did not show significant difference between the patient group with acute noise exposure history and the control group in our study. Future investigations should include more comprehensive assessment of noise exposure history and additional electrophysiological tests, such as ECoG and FFR, to derive reliable and sensitive methods for detecting hidden hearing loss related to noise exposure.

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AUTHOR CONTRIBUTIONS

Conceptualization: Ju Young Kim and Eun Jin Son. Data curation: Ju Young Kim and Eun Jin Son. Formal analysis: Gi-Sung Nam, Ju Young Kim, and Eun Jin Son. Funding acquisition: Eun Jin Son. Investigation: Gi-Sung Nam, Ju Young Kim, and Eun Jin Son. Methodology: Seong Ah Hong, Seon Geum Kim, and Eun Jin Son. Project administration: all authors. Resources: Eun Jin Son. Software: Eun Jin Son. Supervision: Eun Jin Son. Validation: Seong Ah Hong, Seon Geum Kim, and Eun Jin Son. Visualization: Gi-Sung Nam and Eun Jin Son. Writing—original draft: Gi-Sung Nam, Ju Young Kim, and Eun Jin Son. Writing—review & editing: Eun Jin Son. Approval of final manuscript: all authors.

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