Prediction of hearing outcomes by auditory steady-state response in patients with unilateral sudden sensorineural hearing loss

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Abstract

Objectives: This study aimed to investigate whether auditory steady-state response (ASSR) can be a prognostic indicator of hearing outcome in patients with sudden sensorineural hearing loss (SSNHL). Design: Prospective clinical study. Setting: Tertiary-care hospital center. Participants: Fifty-three patients with unilateral SSNHL of [?] 90 dB HL were included. Patients with a worse ASSR threshold of [?] 15 dB HL compared to pure-tone threshold were included in the worse ASSR (WASSR) group. Patients without a worse ASSR thresholds were included in the similar or better ASSR (SBASSR) group. Main outcome measures: Pure-tone audiometry (PTA) was gathered before and after steroid treatment. The hearing recovery was defined as a $<$ 25 dB HL of final hearing level or a $>$ 15 dB HL of hearing gain. Hearing outcome of SSNHL according to the ASSR grouping was evaluated. Results: Twenty-one patients were included in the WASSR group, whereas the remaining of 32 patients were included in the SBASSR group. Although WASSR and SBASSR groups had similar initial pure-tone thresholds, WASSR group had significantly worse last pure-tone thresholds compared to SBASSR group ($p = 0.021$). The ASSR grouping was significantly associated with the hearing recovery in univariate and multivariate logistic regression model (all p-values < 0.05) Conclusions: This study suggests that ASSR measurements can be used to predict the hearing prognosis of SSNHL.

Keyword

Sudden sensorineural hearing loss, Auditory steady-state response, Hearing outcome, Prognosis

Key points

- Several studies have reported on the clinical application of electrophysiologic hearing tests to predict the hearing outcome in SSNHL, but no study has been reported on the predictive value of ASSR in SSNHL.
- Among patients with SSNHL of [?] 90 dB HL, 40% of patients had a worse ASSR threshold of [?] 15 dB HL compared to pure-tone threshold at least one of the 0.5, 1, 2, and 4 kHz frequencies.
- Although WASSR and SBASSR groups had similar initial pure-tone thresholds, WASSR group had significantly worse last pure-tone thresholds compared to SBASSR group.
- The ASSR grouping was significantly associated with the hearing recovery in univariate and multivariate logistic regression model.
- Our finding suggested that having a worse ASSR can be considered as a one of the poor prognostic factors in SSNHL and ASSR measurements can be used to predict the hearing prognosis of SSNHL.

1 | INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is defined as a sensorineural hearing loss greater than or equal to 30 dB HL over at least three consecutive frequencies, occurring within 3 days.[1]Although the exact etiology is not well clarified, viral infection, vascular compromise, autoimmune processes, and labyrinthine membrane ruptures have been proposed as possible etiologies.[1,2]Given the ambiguity of the etiology of SSNHL, a number of different regiments have been used as therapy, including vasodilators, anticoagulants, corticosteroids, vitamins, plasma expanders, antiviral agents, diuretics, and hyperbaric oxygen.[3-5] None of the treatment options have superiority on the others in randomized clinical trials,[6] but systemic high dose steroid is currently the most widely accepted treatment for SSNHL.[3-5]

The natural history of SSNHL is still obscure. SSNHL may recover spontaneously in up to 65% of the patients.[7,8]However, nearly 40% of steroid-treated cases did not recover at all, or the hearing worsened over the treatment period.[9] Thus, identification of prognostic factors is needed to predict the spontaneous recovery and risk for permanent or progressive hearing loss requiring maximal treatment. Many prognostic factors have been reported for SSNHL. Advanced age, presence of vertigo at onset, more severe initial hearing loss, descending type of audiogram, cardiovascular risk factors such as diabetes were shown to be negatively correlated with recovery.[10] In recent years, several authors have reported on the clinical application of electrophysiologic hearing tests such as otoacoustic emissions (OAEs) or auditory brainstem response (ABR) in patients with SSNHL.[11-14] However, there has been no report on the predictive value of auditory steady-state response (ASSR) in the hearing prognosis of SSNHL. The purpose of the present study was to investigate whether ASSR can be a prognostic indicator of hearing outcome in patients with SSNHL.

2 | MATERIALS AND METHODS

2.1 | Ethical Considerations

Removed for blind peer review

2.2 | Study design and patients

We retrospectively reviewed the medical records of patients who admitted to [Blinded for review] University Hospital for SSNHL between August 2013 and December 2018. Inclusion criteria for the study included 1) unilateral SSNHL with a minimum 30 dB HL in three continuous octaves that had occurred within a course of 3 days; 2) patients who performed ASSR test withing 2 days after initial audiogram; 3) patients who received systemic high dose steroid therapy within one month after onset; 4) patients who had initial and follow-up audiogram. Exclusion criteria included 1) a history of previous SSNHL; 2) any recognized cause of SSNHL such as Meniere's disease, active viral infection, vestibular schwannoma, or congenital anomalies; 3) a history of chronic otitis media or otologic surgery.

Age, sex, side of affected ear, the presence of dizziness, ear fullness, and dizziness, and comorbid diabetes mellitus (DM) were also collected. All enrolled patients received systemic steroid therapy and/or intratympanic dexamethasone (ITD) injection within one month after onset. Systemic steroid therapy was considered the first-line treatment and comprised a single morning dose of oral steroid each day for 2 weeks (48 mg of methylprednisolone for 4 days, followed by a taper of 8 mg every 2 days). ITD injection was administered as a salvage therapy for patients who did not exhibit recovery after an initial one week of systemic steroid treatment. ITD injections were performed 3–5 times with dexamethasone (4 mg/ml) within 2 weeks of diagnosis. No additional treatment, including antiviral agents, prostaglandin, vitamins, or hyperbaric oxygen therapy were used as second line treatments.

Patients were divided into two groups according to the difference of hearing thresholds between pure-tone audiometry (PTA) and ASSR ([ASSR threshold – pure-tone threshold] at 0.5, 1, 2, and 4 kHz). Because the ASSR mostly could not measure the hearing thresholds in profound hearing loss,[15] subjects who had more than 90 dB HL hearing thresholds were excluded in grouping. If the patients had a [?] 15 dB HL ASSR predicted thresholds compared to pure-tone threshold ([ASSR predicted threshold – pure-tone threshold] [?] 15 dB HL) at least one frequency, it defined as a worse ASSR (WASSR) group. If the patients had a $<$ 15dB of ASSR predicted thresholds compared to pure-tone threshold thresholds ([ASSR predicted threshold – pure-tone threshold] $<$ 15 dB HL) at all frequencies, it defined as a similar or better ASSR (SBASSR) group.

2.3 | ASSR measurement

ASSRs were recorded using a Bio-Logic MASTER II (Navigator Pro, Bio-Logic, San Carlos, CA) system. All participants were at rest, in the supine position. They were asked to relax and to close their eyes. The two active electrodes were placed at the vertex (active), and at the ipsilateral mastoid (reference), whereas the ground electrode is placed on the forehead. All electrode impedances were less than 5 kΩ. Air-conducted stimuli were presented to both ears through ER-3A earphones (Etymotic Research Inc., Elk Grove Village, IL). Four carrier frequencies were tested (0.5 k, 1 k, 2 k, and 4 kHz). These frequencies were 100% amplitude-modulated and 20% frequency modulated at modulation frequencies of 82, 87, 91, and 96 Hz (left side) and 84, 89, 94, and 99 Hz (right side), respectively, at intensities of [?] 80 dB HL. And in the intensity of [?] 90 dB HL, it was modulated at modulation frequency of 67 Hz (left side) and 69 Hz (right side). The stimulus intensity was started from 60 dB HL to the maximum presentation level (115 dB HL). The thresholds were determined at 5-dB precision. During the recording, 16–32 sweeps were made in each block, and data were averaged in the time domain and then subjected to a fast Fourier transform analysis. An F-ratio with a p value smaller than 0.05 was assumed meaningful for ASSR data analysis.

2.4 | Outcome evaluations

The pure-tone average of four frequencies (0.5, 1, 2, and 4 kHz) was calculated to compare the hearing outcome between two ASSR groups (WASSR and SBASSR groups). The initial PTA was performed within a month of onset of sudden hearing loss and before receiving steroid treatment. Hearing recovery was evaluated based on the result of the latest PTA. The hearing improved group was defined as patients whose final hearing level was better than 25 dB HL or whose hearing gain was more than 15 dB HL. Hearing gain was defined as the pure-tone average of four frequencies between the result of initial and last pure-tone thresholds.

2.5 | Statistical Analysis

Statistical comparisons of clinical characteristics between SBASSR group and WASSR group were based on independent t -test, Mann-Whitney U test, Chi-square test, and Fisher's exact test. Hearing outcome was compared between SBASSR group and WASSR group at baseline, one-week follow-up assessment, and last follow-up assessment. A two-way analysis of variance (ANOVA) was conducted that examined the effects of group and follow-up assessment on hearing outcome. Post hoc testing using the Sidak's multiple comparisons test was used to compare the hearing outcome between two groups. Multivariate logistic regression models were performed with backward selection to assess the independent association of ASSR group and hearing recovery. Clinical factors found to have possible association in univariate analysis ($p < 0.20$) were entered into the multivariate logistic regression analysis model. All statistical analyses were performed using SPSS software (ver. 18.0, SPSS Inc., Chicago, IL, USA) and p -values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Demographics

Eighty-eight patients with unilateral SSNHL performed ASSR testing. Of these, 35 patients with ASSR thresholds above 90 dB HL were excluded (Fig. 1). A total of 53 patients (23 men and 30 women) with a mean age of 48.9 ± 16.1 (range 8-78) years were finally included in the study. Twenty-one patients were included in the WASSR group and 32 patients were included in the SBASSR group.

Table 1 shows the clinical information between WASSR and SBASSR groups. Both groups had similar pure-tone thresholds and WRSs in both ears. However, estimated ASSR threshold of the affected ear in the WASSR group was significantly worse than that in the SBASSR group (Z = -2.394, p = 0.017). Estimated ASSR threshold of the unaffected ear was a slightly worse in the WASSR group than SBASSR group, but which was not statistically significant (Z = -1.859, p = 0.063). There were no significant differences in age, sex, side of affected ear, medical history of DM, and associated symptoms such as dizziness, tinnitus, or ear fullness between two groups. All patients had high dose steroid therapy. The number of patients who received ITD injections were similar between two groups. The duration of follow-up was also similar between two groups.

3.2 | Hearing Outcome

Figure 2 shows hearing outcome between SBASSR and WASSR groups. A two-way ANOVA was conducted that examined the effects of ASSR grouping and follow-up assessment on hearing outcome. There was a statistically significant interaction between the effects of ASSR grouping and follow-up assessment on mean pure-tone threshold ($F_{(2,\ 153)} = 3.299$, $p = 0.040$) and WRS ($F_{(2,\ 100)} = 3.7$, $p = 0.028$). Post hoc testing using the Sidak's multiple comparisons test was conducted to compare the hearing outcome between two ASSR groups. The last mean pure-tone thresholds was significantly better in the SBASSR group compared to the WASSR group (36.2 ± 21.1 dB HL vs 53.9 ± 21.4 dB HL, respectively, $t_{\ (153)} = 2.727$, $p = 0.021$). However, the SBASSR group elicited a slight better last WRS compared to the WASSR group (77.6 ± 31.8% vs 58.8 ± 34.6%, respectively), which was not statistically significant ($t_{\ (150)} = 2.053$, $p = 0.120$). The hearing outcome at one-week follow-up assessment was not significantly difference between two ASSR groups on mean pure-tone threshold ($t_{\ (153)} = 0.705$, $p = 0.861$) and WRS ($t_{\ (150)} = 0.554$, $p = 0.926$). The mean pure-tone thresholds at one-week follow-up assessment were 50.3 ± 19.9 dB HL for SBASSR group and 54.1 ± 23.4 dB HL for WASSR group. The WRS at one-week follow-up assessment were 60.1 ± 31.3% for SBASSR group and 60.4 ± 36.0% for WASSR group.

Table 2 shows the clinical factors related to hearing recovery. Twenty-eight patients in hearing improved group showed 40.6 ± 13.6 dB HL of hearing gain, but 25 patients in non-improved group showed 1.6 ± 9.1 dB HL of hearing gain. The proportion of patients from the SBASSR group who had hearing improvement was 68.8% whereas the proportion from the WASSR group who had hearing improvement was only 28.6%. The difference in proportions is significant ($\chi^2_{(1,\ N\ =\ 53)} = 8.214, p = 0.004$). The side of affected ear and method of steroid treatment were also significantly associated with hearing recovery (all$p < 0.05$). A logistic regression was performed to ascertain the effects of ASSR grouping on the likelihood of hearing recovery. Variables (ASSR group, age, side, tinnitus, and steroid treatment) found to have possible association in univariate analysis ($p < 0.20$) were entered into the multivariate analysis model. However, age was removed in multivariate linear regression model with backward selection. The final logistic regression model with backward selection was statistically significant, $\chi^2(4) = 21.782$, $p< 0.001$. The model explained 45% (Nagelkerke R^2) of the variance in hearing recovery and correctly classified 69.8% of cases. Patients in SBASSR group were 5.718 times more likely to have hearing recovery than patients in WASSR group. Patients without tinnitus were 17.631 times more likely to have hearing recovery than patients with tinnitus.

4 | DISCUSSION

This study was designed to retrospectively investigate whether ASSR can be a prognostic indicator of hearing outcome in patients with SSNHL. Previous studies reported that mean threshold differences between ASSR testing and PTA results at different frequencies did not exceed 15 dB.[16-19] Thus, if the patients had a [?] 15 dB HL of worse ASSR predicted threshold at least one of 0.5, 1, 2, and 4 kHz frequencies compared to pure-tone threshold, they included in the WASSR group. Also, for a reliable measure of ASSR thresholds, the ASSR measurements cannot be made for stimulus levels (on average) at and above 100 dB HL.[15,20] For this reason, subjects with a [?] 90 dB HL of pure-tone averages were excluded in grouping.

The main finding of the present study is that the worse ASSRs on the completion of high dose steroid treatment for SSNHL might predict unfavorable hearing outcome. Although the WASSR group and SBASSR group had similar initial pure-tone thresholds (Table 1), WASSR group had significantly worse last pure-tone thresholds compared to SBASSR group (Fig. 2-A). The proportion of patients with a worse ASSR in the hearing improved group was only 21%, whereas the proportion in non-improved group was 60% (Table 2). In univariate and multivariate logistic regression, patients in the WASSR group were significantly less likely to have more than 15 dB HL of hearing gain or better than 25 dB HL of final hearing thresholds than patients in SBASSR group (Table 2).

ASSR represents the synchronous discharge of auditory neurons in the brainstem, phase locked to the modulation frequency of the stimulus. The energy in the resultant response is at the modulation frequency and its harmonics, allowing response detection using automatic and objective analysis protocols.[21-23] Clinically, ASSR can be used to objectively estimate the frequency-specific hearing thresholds in individuals with normal hearing sensitivity and with various degrees and configurations of sensorineural hearing loss.[17,19]Although ASSR has good predictive value for behavioral hearing thresholds, there were no significant correlations between the behavioral thresholds and ASSR derived thresholds at the majority of the frequencies (1000, 2000, and 4000 Hz) in patients with auditory neuropathy.[24,25] ASSR derived thresholds were substantially worse than behavioral thresholds in such patients, and these findings seem to support the notion that poor synchronization is the cause of poor neural responses. While it is unknown whether neural damage is worse than hair cell damage in relation to recovery, previous study reported that wave I latency of auditory brainstem response (ABR), which is the recording waveform of the auditory nerve, was significantly correlated with hearing outcomes in patients with SSNHL.[14] Taken together, a worse ASSR might reflect neural damage of auditory nerve and a worse ASSR than PTA result can be considered as a one of the poor prognostic factors in SSNHL.

A limitation of this study is that patients with profound hearing loss were excluded from the analysis. The second limitation is that the last follow-up timing was inconsistent. Although the duration of follow-up was similar between WASSR group and SBASSR group, 19 patients had last audiogram within one month (5 patients in the WASSR group and 14 patients in the SBASSR group).

5 | CONCLUSION

Among patients with SSNHL of [?] 90 dB HL, 40% of patients had one or more worse ASSR predicted thresholds compared to pure-tone thresholds. Patients with a worse ASSR had greater last pure-tone thresholds than patients without a worse ASSR. The ASSR grouping was significantly associated with hearing recovery in SSNHL. Therefore, ASSR measurements can be used to predict the hearing prognosis of SSNHL.

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Table 1 Clinical information between SBASSR and WASSR groups

Variables	**SBASSR**	**WASSR**	***p*-value**
Number	32	21	
Age (years)	47.4 ± 16.6	51.1 ± 15.8	0.420^{*}
Sex (Male/Female)	14/18	9/12	0.949^{++}
Side (Right/Left)	18/14	9/12	0.340^{++}
Diabetes mellitus (No/Yes)	25/7	14/7	0.355^{++}
Dizziness (No/Yes)	19/13	15/6	0.371^{++}

Variables	SBASSR	WASSR	p-value
Tinnitus (No/Yes)	6/26	2/19	0.455§
Ear fullness (No/Yes)	14/18	12/9	0.340^{++}
Unaffected ear			
Initial PTA (4FA, dB HL)	14.7 ± 8.0	16.3 ± 8.5	0.495*
Initial WRS (%)	99.8 ± 1.4	99.0 ± 2.2	0.053^{+}
ASSR (4FA, dB HL)	25.5 ± 9.2	31.4 ± 11.1	0.063^{+}
Affected ear			
Initial PTA (4FA, dB HL)	66.6 ± 13.3	61.7 ± 14.6	0.216*
Initial WRS (%)	32.8 ± 31.2	40.4 ± 31.8	0.326^{+}
ASSR (4FA, dB HL)	62.2 ± 15.2	73.2 ± 15.2	**0.017^{+}**
Steroid treatment (with ITD/ without ITD)	15/17	7/14	0.328^{++}
Duration of follow-up (days)	137 ± 195	122 ± 177	0.730^{+}

*Independent t-test; $^{+}$Mann-Whitney test; $^{++}$Chi-square test; §Fisher's exact test, Results that are significantly different (with p < 0.05) are given in bold face.

SBASSR: similar or better ASSR; WASSR: worse ASSR; PTA: pure tone audiometry; 4FA: four frequencies (0.5, 1, 2, and 4 kHz); WRS: word recognition score; ASSR: auditory steady-state response; ITD: intratympanic dexamethasone

Table 2 Clinical factors related to hearing recovery

Variables	Improved (n = 28)	Non-improved (n = 25)	Univariate	Multivar
			p-value	B
ASSR group (SBASSR/ WASSR)	22/ 6	10/ 15	**0.006**	1.744
Age (years)	45.5 ± 17.4	52.8 ± 14.1	0.970	
Sex (Male/ Female)	11/ 17	12/ 13	0.523	
Side (Right/ Left)	18/ 10	9/ 16	**0.043**	1.317
Diabetes mellitus (No/ Yes)	22/ 6	17/ 8	0.386	
Dizziness (No/ Yes)	20/ 8	14/ 11	0.245	
Tinnitus (No/ Yes)	7/ 21	1/ 24	0.061	2.87
Ear fullness (No/ Yes)	14/ 14	12/ 13	0.884	
Steroid treatment (without ITD/ with ITD)	16 /12	6/ 19	**0.017**	1.396
Duration of follow-up (days)	117 ± 169	148 ± 207	0.554	

Variables (ASSR group, age, side, tinnitus, and steroid treatment) found to have possible association in univariate analysis (p< 0.20) were entered into the multivariate logistic regression analysis model. Results that are significantly different (with p < 0.05) are given in bold face.

Figure Legends

Figure 1 Relation between PTA and ASSR thresholds . X-axis represents mean pure-tone thresholds and Y-axis represents mean ASSR thresholds. Mean hearing thresholds defines averaged thresholds for four frequencies (0.5k Hz, 1 kHz, 2 kHz, and 4 kHz). Results of scatter plots for unaffected ear is shown in black diamond (*). Hearing thresholds of affected ear for SBASSR group, WASSR group, and exclusion are shown in blue circle (*), red squared (), and black triangle ([?]), respectively. PTA: pure tone audiometry; ASSR: auditory steady-state response; 4FA: four frequencies (0.5, 1, 2, and 4 kHz); SBASSR: similar or better ASSR: WASSR: worse ASSR

Figure 2 Hearing outcome between SBASSR and WASSR groups . Mean pure-tone thresholds defines averaged thresholds for four frequencies (0.5, 1, 2, and 4 kHz). Error bar means standard deviation. The asterisk (*) indicate statistically significant difference in multiple comparison test. PTA: pure-tone audiometry; WRS: word recognition scores; *ns* : not significant