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Original Article

Clinical Characteristics and Corticosteroid Responses of Acoustic Neuroma Treated as Idiopathic Sudden Sensorineural Hearing Loss

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BACKGROUND: Few investigations have been conducted on the clinical characteristics of the differential diagnosis of acoustic neuroma with acute sensorineural hearing loss and idiopathic sudden sensorineural hearing loss. The aim of the study was to investigate the clinical characteristics of the differential diagnoses between acoustic neuroma and idiopathic sudden sensorineural hearing loss.

METHODS: The medical records of patients with acute sensorineural hearing loss (142 ears), including acoustic neuroma (19 ears) and idiopathic sudden sensorineural hearing loss (123 ears), who underwent audiometric and hematologic examinations and received systemic corticosteroid treatment, were retrospectively reviewed.

RESULTS: Hematological examination revealed that the erythrocyte sedimentation rate and fibrinogen values were significantly higher in the idiopathic sudden sensorineural hearing loss group compared to the acoustic neuroma group. Although all patients received corticosteroid treatment, hearing thresholds at the initial examination and 3 months after corticosteroid treatment were significantly higher in the idiopathic sudden sensorineural hearing loss group compared to the acoustic neuroma group at all frequencies. However, hearing recovery was worse in the acoustic neuroma group compared to the idiopathic sudden sensorineural hearing loss group. Furthermore, speech discrimination and short increment sensitivity index tests were not significantly different between the acoustic neuroma and idiopathic sudden sensorineural hearing loss groups.

CONCLUSION: This is the first study to reveal that speech discrimination and short increment sensitivity index tests are not useful for the differential diagnoses between acoustic neuroma and idiopathic sudden sensorineural hearing loss, whereas erythrocyte sedimentation rate and fibrinogen, blood biomarkers of inflammation and blood viscosity, would be considered valuable. Furthermore, acoustic neuroma should be considered in cases where acute sensorineural hearing loss did not recover after corticosteroid treatment, although the initial hearing loss was mild.

KEYWORDS: Acoustic tumors, biomarkers, differential diagnosis, hearing loss

INTRODUCTION

Acoustic neuroma (AN) arises from Schwann cells of the vestibular nerve and is the most common benign tumor of the cerebellopontine angle.[1] Moreover, 95% of the patients with AN have sensorineural hearing loss. Although idiopathic sudden sensorineural hearing loss (ISSHL) is the most common among patients with acute sensorineural hearing loss (ASHL), 1.9%-4.9% of patients with ASHL are diagnosed with AN.[2] Idiopathic sudden sensorineural hearing loss and acoustic neuroma with ASHL are believed to have different pathogeneses. The causes of ISSHL include cochlear inflammation, viral infection, and microcirculation disorders,[3] whereas AN causes ASHL due to the compression of the auditory nerve and secretion of potentially ototoxic substances to the cochlea or cochlear nerve.[4,5] However, the detailed mechanisms of ASHL in patients with AN are unclear.

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Magnetic resonance imaging (MRI) is the gold standard for imaging diagnosis.[6] However, an MRI examination cannot necessarily be performed immediately after symptom onset in all patients with ASHL. Therefore, patients with AN are often misdiagnosed with ISSHL and treated with corticosteroids according to the ISSHL treatment protocol[7]; AN is finally detected by MRI examination after corticosteroid treatment. This indicates that it is important in clinics to help in the differential diagnoses of AN and ISSHL using primary clinical data without MRI examination. However, there is little information on the clinical characteristics that help with the differential diagnoses of AN and ISSHL. Therefore, identifying biomarkers or performing useful auditory examinations to detect AN is essential.

Inflammation and microcirculation disorders can cause ISSHL.[8] Therefore, biomarkers associated with inflammation and blood viscosity may be useful to detect AN in patients with ISSHL. Furthermore, the pathology involved in ISSHL is mainly cochlear, whereas the pathology involved in AN is retrocochlear.[9] Therefore, a detailed auditory evaluation of cochlear and retrocochlear functions may be useful for the differential diagnosis of AN and ISSHL. Taken together, this study aimed to investigate the clinical characteristics, including peripheral blood markers associated with inflammation, blood viscosity, and detailed auditory examination, of patients with AN and ISSHL and the treatment outcomes of AN compared to ISSHL.

METHODS

Patients

This study retrospectively reviewed the medical records of patients with ASHL and AN who were treated with ISSHL between 2015 and 2018 at Kitasato University Hospital (AN group) and those without AN between 2012 and 2019 (ISSHL group). Patients who have (1) sudden sensorineural hearing loss $\geq$ 30 dB in at least 3 consecutive frequencies; (2) aged $>$ 18 years; and (3) systemic corticosteroid treatment initiated within 2 weeks after onset were included in the study. Patients with a history of fluctuating hearing loss or otologic surgery were excluded. All patients underwent MRI after initial systemic corticosteroid treatment. The protocol for this study (B19-141) was approved by the Institutional Review Board of the Kitasato University Hospital. Informed consent was waived owing to the retrospective nature of the study.

Hematological Evaluation

At the first visit, all patients underwent blood examination to obtain baseline hematological parameters, including white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen levels.

Treatment

All patients were treated with systemic corticosteroids for 10 days (betamethasone 8 mg on day 1 and then tapered to 4 mg on days 2-4, to 2 mg on days 5-7, and to 1 mg on days 8-10).

Hearing Function

Pure-tone hearing thresholds were measured using a conventional audiometer (AA-78; Rion Co., Ltd., Tokyo, Japan). Air conduction (AC) thresholds were obtained from the frequencies of 0.5-4 kHz and the arithmetic means AC thresholds were calculated. Hearing thresholds were evaluated at the initial examination and 3 months after treatment.

Speech Audiometry Test

We examined speech audiometry using an AA-78 audiometer. The maximum speech discrimination score (SDSmax) was calculated using a recorded Japanese monosyllabic word list (67-S). Briefly, the test stimuli were initially started at a sound intensity of 40 dB above the average pure-tone threshold. Subsequently, the sound intensity was increased in 10 dB increments until a maximum score was obtained. The order of the test stimuli was randomized for each patient. The maximum score obtained was defined as SDSmax. SDSmax was examined 3 months after treatment.

Short Increment Sensitivity Index Test

We performed a short increment sensitivity index (SISI) test to evaluate the ability to detect 1 dB increases in sound intensity in 20 dB suprathreshold tone.[10] The identification rate of 20 increments was calculated and a score $\geq$ 70% was defined as positive, indicating the presence of a cochlear lesion.[11] The SISI test was performed 3 months after treatment.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism 8.2.1 (GraphPad Software Inc., La Jolla, Calif, USA) and JMP 14.2 (SAS Institute Japan Inc., Tokyo, Japan). The chi-square test, *t*-test, or nonparametric Mann–Whitney *U* test was performed to evaluate clinical characteristics and prognostic factors. Two-way analysis of variance (ANOVA) followed by Šidák's multiple comparison test was used to analyze differences in hearing thresholds. The correlation between SDSmax and the hearing threshold was calculated using linear regression and Pearson's correlation. Statistical significance was set at $P < .05$.

RESULTS

Clinical Characteristics and Hematological Examination

The clinical characteristics of 142 patients (142 ears) in the AN (19 ears) and ISSHL (123 ears) groups are presented in Table 1. No significant differences were observed between the 2 groups regarding age or sex. The initiation of treatment after symptom onset was significantly longer in the AN group than in the ISSHL group ($P < .0001$). The ISSHL group exhibited a higher prevalence of

Table 1. Clinical Characteristics of Patients with AN and ISSHL

Parameters	AN (n = 19)	ISSHL (n = 123)	*P*
Age (mean ± standard deviation, years)	51.8 ± 3.4	58.3 ± 1.5	.11
Sex (male/female; n)	13/6	71/52	.38
Initiation of treatment after symptom onset (mean ± standard deviation, days)	9.7 ± 2.5	4.3 ± 0.4	<.0001****
Accompanying symptoms			
Diabetes (with/without, n)	0/19	31/91	.013*
Vertigo (with/without, n)	3/16	56/67	.014*

****$P < .0001$; *$P < .05$.

AN, acoustic neuroma; ISSHL, idiopathic sudden sensorineural hearing loss.

Table 2. Blood Examination of Patients with AN and ISSHL

Parameters	AN (n = 19)	ISSHL (n = 123)	*P*
White blood cell count (WBC) (mean ± standard deviation, 10^4/μL)	8211 ± 3596	7423 ± 2378	.23
C-reactive protein (CRP) (mean ± standard deviation, mg/dL)	0.10 ± 0.24	0.17 ± 0.37	.48
Erythrocyte sedimentation rate (ESR) (mean ± standard deviation, mm/h)	4.5 ± 4.6	13.5 ± 14.2	.02*
Fibrinogen (mean ± standard deviation, mg/dL)	249.0 ± 47.2	320.2 ± 70.6	<.0001****

****$P < .0001$; *$P < .05$.
AN, acoustic neuroma; ISSHL, idiopathic sudden sensorineural hearing loss.

diabetes and vertigo than the AN group (diabetes: $P = .013$; vertigo: $P = .014$). Next, we investigated the hematological parameters related to inflammation, including WBC, CRP, ESR, and fibrinogen, at the initial examination. Although the WBC count and CRP level were comparable between the 2 groups, the ESR and fibrinogen values were significantly higher in the ISSHL group compared to the AN group ($P < .05$, Table 2), indicating that inflammation could be one of the causes of ISSHL.

Hearing Prognosis

To investigate the differences in treatment outcomes between AN and ISSHL, we compared hearing results measured using pure-tone audiometry (Figure 1). Hearing thresholds at initial examination and at 3 months of treatment were significantly higher in the ISSHL group compared to the AN group at all frequencies (2-way ANOVA, initial examination; $P < .0001$ and 3 months after treatment; $P = .0001$; Figure 1A and B). However, the threshold recovery was significantly better in the ISSHL group compared to the AN group at all frequencies (2-way ANOVA, $P < .0001$; Figure 1C). Next, to exclude the effects of age-related hearing loss, the hearing status in the unaffected ear was investigated. Hearing thresholds in the unaffected ear were comparable between the 2 groups (2-way ANOVA, $P = .66$; Figure 1D).

Speech Discrimination Ability

Different types of auditory pathology exhibit different results of speech discrimination ability; for example, central auditory damage, including AN, exhibits a lower speech discrimination score than peripheral cochlear damage, such as ISSHL.[12] However, recently, patients with AN have been shown to exhibit central and peripheral cochlear damage.[5] Therefore, to investigate the effect of AN on speech discrimination ability, the SDSmax was compared between the AN and ISSHL groups at 3 months after treatment (Figure 2). Although the hearing thresholds of the affected ears in the ISSHL group were higher compared to the AN group, the correlation between SDSmax and hearing thresholds was not significantly different between the

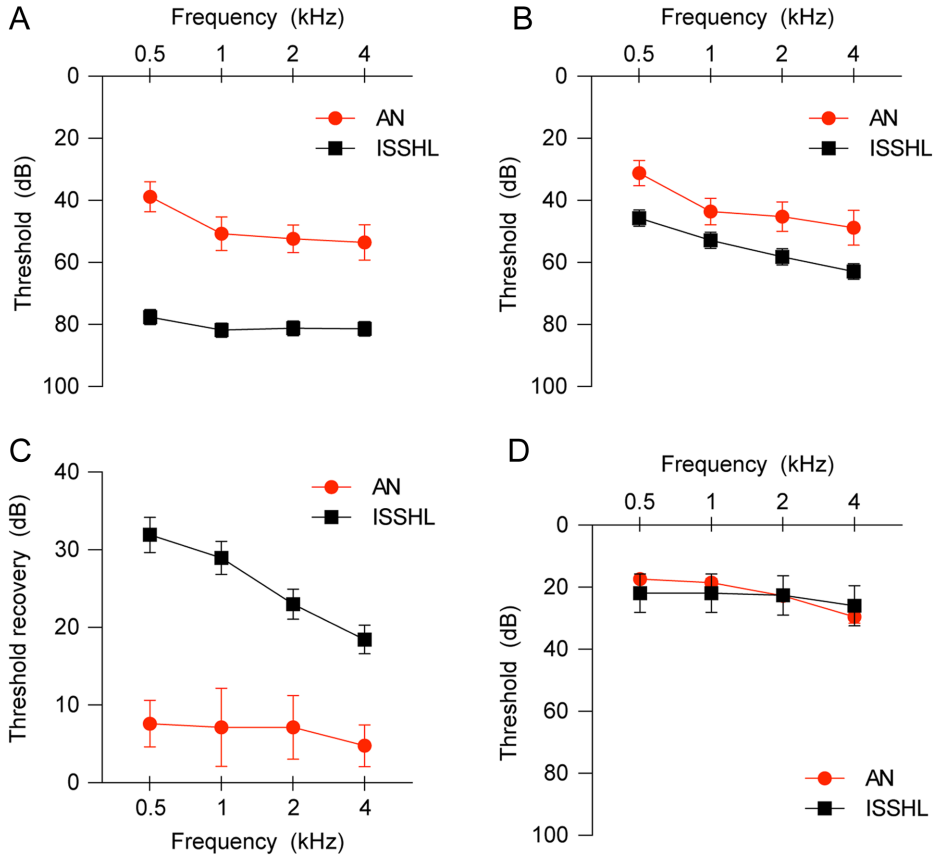

Figure 1. A-D. Outcomes of hearing status in the AN and ISSHL groups. (A) Pretreatment hearing thresholds are significantly better in the AN group compared to the ISSHL group at all frequencies. (B) The post-treatment hearing thresholds in the AN group are significantly better compared to the ISSHL group. (C) Threshold recovery is significantly better in the ISSHL group compared to the AN group at all frequencies. (D) Hearing thresholds for unaffected ears are comparable between the AN and ISSHL groups. AN, acoustic neuroma; ISSHL, idiopathic sudden sensorineural hearing loss.

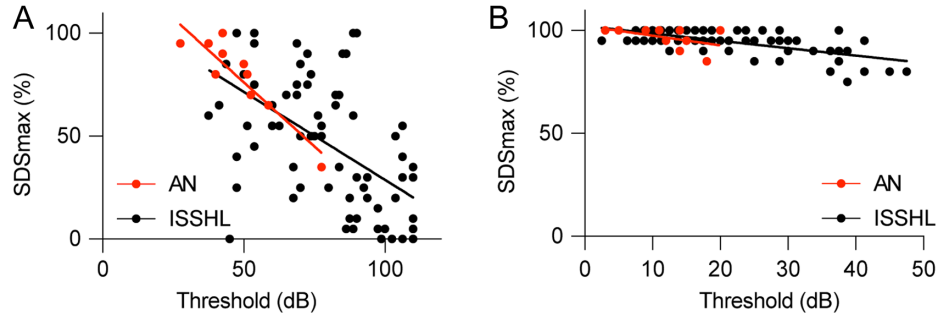

Figure 2. SDSmax of the AN (red) and ISSHL (black) groups. SDSmax exhibited a negative correlation with hearing thresholds in both groups. No statistically significant differences are observed in the SDSmax of affected ears (A) and unaffected ears (B) between the groups (B). AN, acoustic neuroma; ISSHL, idiopathic sudden sensorineural hearing loss; SDSmax, maximum speech discrimination score.

AN and ISSHL groups ($P = .53$, Figure 2A), indicating that AN, despite retrocochlear pathology, does not show a worse speech discrimination ability than the ISSHL group. In the unaffected ears, SDSmax in the AN group was comparable to that in the ISSHL group ($P = .46$, Figure 2B).

Short Increment Sensitivity Index Test

The SISI test is also frequently used to distinguish the cause of HL from cochlear or retrocochlear lesions. To investigate the differences in SISI results between AN and ISSHL groups, we compared the SISI results between AN and ISSHL groups 3 months after treatment (Table 3). The SISI test revealed that >50% of the ears in both groups were SISI-positive, and no statistically significant differences were observed between the 2 groups (Kruskal–Wallis test, 1 kHz, $P = .46$; 4 kHz, $P = .25$), indicating that patients with AN had a comparable extent of peripheral cochlear lesions to patients with ISSHL. Moreover, in unaffected ears, <50% of the ears in both groups were SISI-positive, and there was no statistically significant difference between the 2 groups in the SISI test (Kruskal–Wallis test, 1 kHz, $P = .26$; 4 kHz, $P = .17$).

DISCUSSION

In summary, we found that threshold recovery was significantly worse in the AN group compared to the ISSHL group, whereas hearing thresholds were significantly better in the AN group compared to the ISSHL group. Audiometric examinations, including the SDSmax and SISI tests, were not significantly different between AN and ISSHL, suggesting that these tests are not useful to distinguish AN from ISSHL. However, fibrinogen and ESR, biomarkers of inflammation and blood viscosity, were significantly different between the groups, indicating that these biomarkers may be useful for the differential diagnosis of AN in patients with ISSHL.

Table 3. SISI Results of Patients with AN and ISSHL

Parameters	AN (n = 11)	ISSHL (n = 61)	*P*
Affected ear			
1 kHz SISI (positive %)	52	52	.46
4 kHz SISI (positive %)	80	61	.25
Unaffected ear			
1 kHz SISI (positive %)	0	11	.26
4 kHz SISI (positive %)	17	43	.17

AN, acoustic neuroma; ISSHL, idiopathic sudden sensorineural hearing loss; SISI, short increment sensitivity index.

Acoustic neuroma has been considered to show retrocochlear pathology through mechanical compression of the cochlear nerve,[9] and supporting evidence includes histopathology, such as cochlear nerve atrophy and retrocochlear dysfunction, detected by auditory brainstem response examination.[13] However, the hearing threshold did not increase until the loss of >80%-90% of the cochlear nerve fibers.[14] This finding suggests that neural compression of the cochlear nerve is not the only mechanism underlying the progression of hearing loss in patients with AN. Interestingly, a previous study demonstrated that the histopathology of significant loss of cochlear neurons and inner and outer hair cells was observed in human temporal bone in patients with AN.[15] Furthermore, cytokines, such as tumor necrosis factor-alpha and extracellular vesicles secreted by AN, can cause degenerative changes in the cochlea.[5,16] Although the detailed mechanisms of cochlear damage in AN have not been completely elucidated, these results indicate that hearing loss in patients with AN may be caused by retrocochlear dysfunction and pathology.

Different types of auditory pathology exhibit different audiometric results; for example, central auditory damage exhibits a lower speech discrimination score than peripheral cochlear damage.[12] Therefore, a detailed evaluation of cochlear and retrocochlear functions might be useful for the differential diagnosis of AN and ISSHL. In this study, we also investigated the SISI test, which is frequently used to distinguish the cause of HL as cochlear or retrocochlear lesions. A negative SISI test indicated retrocochlear pathology.[17] Our results showed that the SISI-positivity rate was not significantly different between the AN and ISSHL groups. Moreover, the speech discrimination ability of AN was comparable to that of ISSHL. Our results also suggest that AN shows not only retrocochlear pathology but also cochlear pathology similar to ISSHL. Therefore, the SISI and speech discrimination ability tests are not useful to differentiate between AN and ISSHL. More studies are needed to determine the functional and pathological changes in auditory pathways after ASHL development.

We found that fibrinogen levels and ESR were significantly higher in the ISSHL group compared to the AN group. Consistent with this, a previous study demonstrated that elevated fibrinogen and ESR values were correlated with a poorer prognosis of hearing recovery in ISSHL.[18] Since fibrinogen and ESR were observed in response to inflammation, tissue damage, and ischemic changes in the acute phase,[19] it was unlikely that high values would be observed in AN caused by direct neural compression or cytokines and extracellular vesicles of AN. Our results suggest that performing a blood sampling test may be a reference for the differential diagnosis between AN and ISSHL.

According to previous studies, steroid therapy could be effective in treating ASHL with AN.[20,21] Similarly, in our study, 15.8% of patients with AN showed partial recovery from ASHL after corticosteroid treatment. Considering the mechanisms of action of corticosteroids, corticosteroid treatment would act on cochlear pathology rather than retrocochlear pathology associated with inflammation.

Finally, our findings have important clinical implications for the differential diagnoses of AN and ISSHL. However, this study had some limitations. First, the hearing thresholds at the initial examination were significantly different between ISSHL and AN groups. Therefore, this difference in hearing levels could influence speech discrimination scores and hematological results. Furthermore, this was a single-hospital retrospective study with a relatively small sample size, and therefore, additional studies are needed with larger populations.

CONCLUSION

Patients with AN, considered to have retrocochlear pathology, exhibited similar SDSmax and SISI test results compared to patients with ISSHL, who showed mainly cochlear pathology. This indicates that patients with AN had a comparable extent of peripheral cochlear lesions to those with ISSHL. In the peripheral blood test, ESR and fibrinogen values were significantly higher in the ISSHL group compared to the AN group, indicating that ESR and fibrinogen, as blood biomarkers of inflammation and blood viscosity, would be useful in identifying AN in patients with ISSHL.

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