

Original Article

Clinical Significance of White Matter Lesions in Idiopathic Sudden Sensorineural Hearing Loss

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BACKGROUND: We aimed to analyze the patient characteristics in accordance with white matter lesions and confirm whether white matter lesions affect final treatment outcomes in idiopathic sudden sensorineural hearing loss.

METHODS: Medical records of 126 patients treated for unilateral idiopathic sudden sensorineural hearing loss and who underwent magnetic resonance imaging of the brain at an otology clinic in a university hospital from 2013 to June 2019 were reviewed. The Fazekas scale was used to evaluate the severity of white matter lesions. Complete recovery was defined if final hearing at 3 months did not exceed 25 dB.

RESULTS: Overall, 107 patients were enrolled in this study. A score of 0 on the Fazekas scale was most frequent (n = 78, 72.9%), followed by 1 (n = 17, 15.9%), and 2 (n = 12, 11.2%). Prevalence of diabetes ($P = .032$) and/or hypertension ($P = .006$) and distribution of age ($P < .001$) were different according to Fazekas scale scores. Hearing level in the affected side was significantly different between those with scores of 1 and 2 ($P = .009$). Contralateral hearing thresholds were not different according to Fazekas scale scores, but hearing on the contralateral side was significantly poorer in patients with hypertension than those without hypertension ($P < .001$). Regression analysis revealed that Fazekas scale score and initial hearing thresholds of the affected side were significant prognostic factors for complete recovery.

CONCLUSION: Although the prevalence of white matter lesions in idiopathic sudden sensorineural hearing loss was not high, severe white matter lesions and accompanying cardiovascular risk factors may increase the possibility of initially worse hearing and decrease response to treatment in idiopathic sudden sensorineural hearing loss. Therefore, it might be important to control cardiovascular abnormalities in idiopathic sudden sensorineural hearing loss to achieve a better prognosis.

KEYWORDS: Leukoaraiosis, prognosis, sudden hearing loss, treatment

INTRODUCTION

Hyperintense signal of white matter (WMH) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) is a common finding in the elderly.¹ Previously, this was regarded as a consequence of aging because the prevalence of WMH increased exponentially with age. However, it is currently thought to reflect small vessel disease and is a common risk factor for various cardiovascular diseases including diabetes, hypertension, aging, ischemic stroke, intracranial hemorrhage, and Alzheimer's disease.^{1,2}

The Fazekas scale is a commonly used, simple method to rate WMH; a higher Fazekas scale score predicts cognitive function in Alzheimer's disease.³ Patients with ischemic stroke and a Fazekas score of 3 had a higher risk of stroke and major vascular events compared with those with a Fazekas score of 0-1, indicating that the severity of WMH might indicate recurrent vascular events.⁴

For idiopathic sudden sensorineural hearing loss (ISSNHL), MRI is used to diagnose retrocochlear pathologies. In general, the clinician performs MRI for ISSNHL to rule out brain lesions including vestibular schwannoma or infarct. In a retrospective study based on data from 291 patients with ISSNHL, vestibular schwannoma was the most common MRI abnormality.⁵ Other common pathologic

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findings include intralabyrinthine hemorrhage (ILH).⁶ In a study on the clinical implications of MRI targeting unilateral ISSNHL, labyrinthine abnormalities were seen in 27% of enrolled patients and their recovery rates were lower than those of patients with normal MRI.⁷

Traditionally, common etiologies that cause ISSNHL include viral infection, vascular compromise, autoimmune disease of primary origin; however, other conditions such as stroke, neoplasm, and irradiation can also result in ISSNHL.⁸ Recently, 3 Italian consecutive studies on the association between white matter lesions (WML) and ISSNHL were published.⁹⁻¹¹ However, controversies regarding recovery rate or relatively short-term follow-up period in previous studies remain for ISSNHL and WML.

In this study, we analyzed the patient characteristics in accordance with WML to confirm whether WML affects the final treatment outcomes in ISSNHL.

MATERIALS AND METHODS

Initially, the medical records of 129 patients who visited an ear clinic at a university hospital and were admitted to the hospital for the treatment of ISSNHL were screened in this study. All patients were initially treated with 4 mg/kg of oral methylprednisolone for 4 days, which was tapered to 8 mg every 2 days. For intratympanic dexamethasone (IT-DEX) injection, patients who did not show improvement after initial oral steroid treatment were treated 4 times with concomitant IT-DEX from the second day of admission. Intratympanic dexamethasone IT-DEX was finally administered to 85% of these patients (n = 91).

The inclusion criteria were as follows: (1) aged 18 years or more, (2) sensorineural hearing loss in the affected side, (3) acute onset of symptoms to treatment ≤ 7 days, and (4) mean pure-tone threshold at 500, 1000, 2000, and 3000 Hz in the affected side of at least 30 dB. The exclusion criteria were as follows: (1) MRI not obtained during hospitalization, (2) intracranial malignancies including vestibular schwannoma and meningioma, and (3) suspicious of brain infarct or multiple sclerosis.

Ethical committee approval was received for this study from the Ewha Mokdong Hospital (2020-12-040). The board granted a waiver for written informed consent because of the retrospective nature of the study.

Complete recovery (CR) was defined if the pure-tone average at 500 Hz, 1 kHz, 2 kHz, and 3 kHz were equal to 25 dB or less following Siegel's criteria.

An MRI was performed on either a 3T system (MAGNETOM Skyra, SIEMENS[®], Erlangen, Germany) or a 1.5T system (SONATA, SIEMENS[®], Erlangen, Germany) with a standard head coil. Magnetic resonance imaging (MRI) included an axial T1-weighted, axial T2-weighted, sagittal T1 and T2-weighted sequences, FLAIR images, diffusion-weighted images (DWI), and with or without subsequent contrast enhancement spin-echo T1 W images. Magnetic resonance imaging parameters were as follows: 250-486/3.2-7.7 ms/70-75°/512-259 or 256 × 168 (TR/TE/FA/matrix) for T1-weighted images; 4500-4770/108-125 ms/132-150°/384 × 384 or 256 × 179 (TR/TE/FA/matrix) for T2-weighted images; 6240-9000/95-122 ms/150°/256 × 224 or 512 × 259 (TR/TE/FA/

matrix) for FLAIR images; and 4500-8200/98-99 ms/90°/128 × 127 or 192 × 154 (TR/TE/FA/matrix) at $b = 0$ or 1000 sec/mm² for DWI. Other parameters were the same for both scanners: section thickness, 5 mm with a 1-mm gap and field of view of 175 × 200 mm. One neuroradiologist with more than 25 years of clinical experience reviewed the brain MRIs and graded the Fazekas scale scores (Figure 1).

A repeated-measures analysis of variance (ANOVA) was performed to confirm the changes in hearing thresholds over time. If sphericity was violated, a multivariate analysis was selected. One-way ANOVA was conducted to confirm the difference of initial hearing thresholds of the affected side and the contralateral side according to the Fazekas scale scores. A trend test with a linear-by-linear association was conducted to search for any trends by chi-square analysis between Fazekas scale scores and nominal variables. Bivariate analysis including one-way ANOVA and chi-square analysis was performed to analyze the relationship between Fazekas scale scores and documented variables. Binary logistic regression analysis with backward elimination was then performed with chosen factors including diabetes mellitus (DM), hypertension (HTN), initial hearing, age, and Fazekas scale score to confirm the prognostic factors for CR. All analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Macintosh ver. 27.0 (IBM Corp., Armonk, NY, USA). *P* values < .05 were considered statistically significant.

RESULTS

Overall, 107 patients were enrolled in this retrospective cohort study. These consisted of 61 males and 43 females with a mean age of 54.64 years (standard deviation (SD): 13.354, range: 21-84 years), with right side hearing loss in 47 and left side hearing loss in 60. Mean days to treatment was 3.05 days (SD: 2.107, range: 0-7). The pure-tone average of the affected side and the healthy side at 500 Hz, 1 kHz, 2 kHz, and 3 kHz were 63.514 dB (SD: 19.9507, range: 30-103.0) and 14.98 dB (SD: 11.515, range: 0-61 dB), respectively. Regarding accompanying symptoms, tinnitus was the most frequent (81.3%, n = 87), followed by aural fullness (75.7%, n = 81) and dizziness (31.8%, n = 34); 12.1% of patients had DM (n = 13) and 21.5% had HTN (n = 23).

Hearing thresholds improved significantly over time (Pillai's trace, $P < .001$). Pairwise comparisons showed that hearing improved significantly until week 4 ($P < .001$). However, no significant

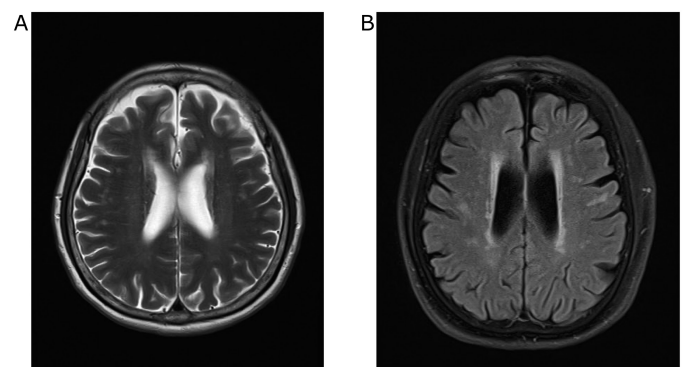


Figure 1. a,b. Example of Fazekas scale scores. (a) Fazekas score of 1: image from a 56-year-old male patient. Multiple small unidentified bright objects are present in the frontoparietal white matter area. (b) Fazekas score of 2: an image of an 82-year-old female patient. A hyperintense signal is observed in the periventricular and deep white matter areas.

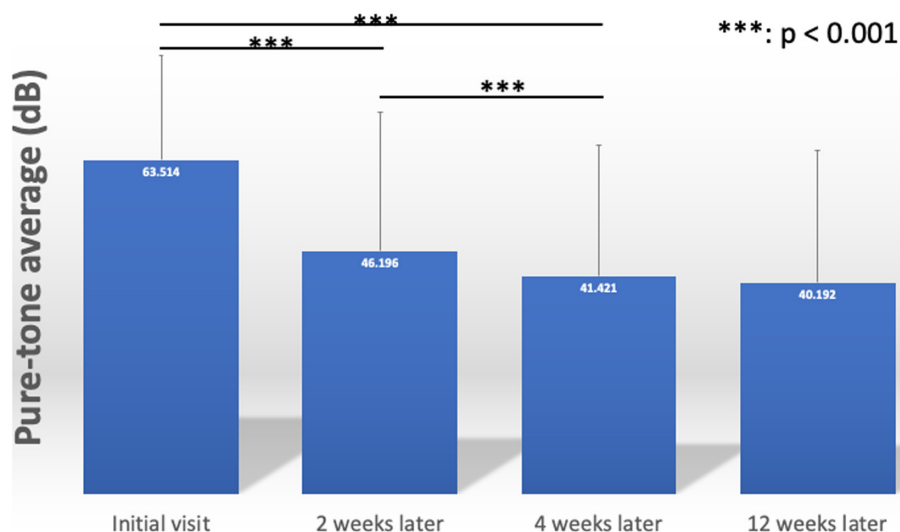


Figure 2. Change of pure-tone average over time.

difference in hearing threshold was seen between week 4 and week 12 ($P = .082$) (Figure 2).

Regarding Fazekas scale scores, a score of 0 was most frequent ($n = 78$, 72.9%), followed by 1 ($n = 17$, 15.9%), and 2 ($n = 12$, 11.2%). Of the document variables, DM ($P = .032$), HTN ($P = .006$), and age ($P < .001$) were significantly different according to Fazekas scale scores; the prevalence of DM and HTN tended to increase as the Fazekas scale score approached 2. Post hoc test with Dunnett's T3 analysis revealed that age was significantly different between those with scores of 0 and 1, and 0 and 2 (Figure 3). However, no difference was seen between those with scores of 1 and 2 ($P > .05$). Sex and laterality did not differ according to Fazekas scale scores ($P > .05$).

Regarding hearing level, the hearing thresholds in the affected side were different according to Fazekas scale scores ($P = .012$). Post hoc tests revealed a statistically significant difference between those with a score of 1 and 2 ($P = .009$, Tukey's honestly significant difference test) but not between those with a score of 0 and 1

(Figure 4). Regarding the contralateral side, hearing thresholds were not different according to Fazekas scale scores, and no correlation was observed ($P > .05$, one-way ANOVA and Pearson's correlation). However, the pure-tone average of the contralateral side in patients with HTN was 22.52 dB (SD: 14.292) and this was significantly higher than those without HTN (12.92 dB, SD: 9.754, $P < .001$). However, no significant difference was seen for DM ($P > .05$).

Complete recovery was achieved in 33.6% of patients ($n = 36$) based on Siegel's criteria. Regression analysis with backward elimination revealed that Fazekas scale scores and initial hearing thresholds of the affected side were significant prognostic factors for CR (Table 1). Other factors were not included in our regression model.

DISCUSSION

In this study, we found that higher Fazekas scale scores were observed in ISSHL patients with DM and/or HTN. Better initial hearing thresholds in the affected side and a lower Fazekas scale score were associated with CR.

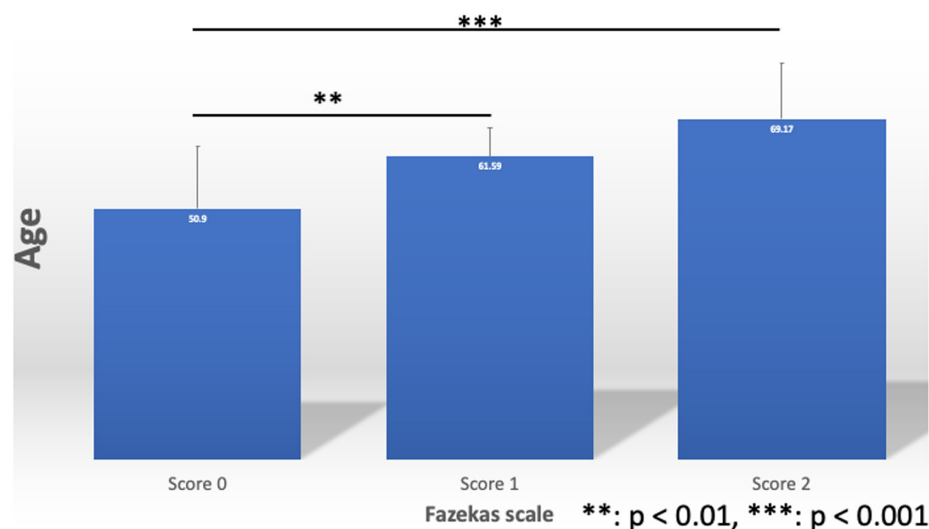


Figure 3. Age distribution according to Fazekas scale scores.

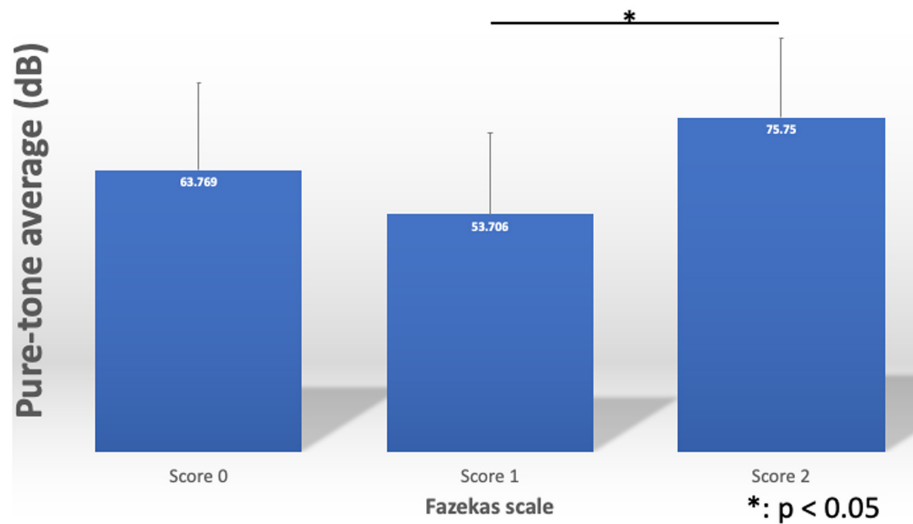


Figure 4. Initial pure-tone average in the affected side according to Fazekas scale scores. A significant difference was observed between Fazekas scale scores 1 and 2; no difference was seen between scores 0 and 1 or scores 0 and 2 ($P > .05$).

In terms of possible ISSNHL etiologies, the viral infection theory and vascular insufficiency hypothesis are the most plausible.⁸ Other potential causes include autoimmune disorders, irradiation, radio-surgery, and neoplasm. Here, we focused on vascular insufficiency. Our findings support the vascular insufficiency theory because both the WML and cardiovascular risk factors may influence the vascular system. Such patients exhibited poorer initial hearing than the others and were less responsive to treatment.

White matter consists of myelinated axons that are mainly involved in nerve signal transduction. Thus, abnormalities of the white matter such as myelin damage may slow down signal transmission leading to delayed nerve development, cognitive impairment, and learning difficulties.^{12,13} In addition, cerebral glucose metabolism was decreased in the frontal, temporal, and limbic regions of patients with higher Fazekas scale scores.¹⁴ Cognitive impairment was reported to begin to appear in patients with Fazekas scale scores of 3 or higher.¹⁵ For stroke, poorer collateral blood flow was seen in patients with more severe WML.² Interestingly, the deterioration of function differed according to lesions of the WMH; frontal WMH for the executive function, parieto-temporal WMH for memory, and deep white matter for motor speed performance were declined in healthy elderly subjects.¹⁶ In our previous study on vestibular neuritis (VN), the distribution of WML differed according to the subtype of VN.¹ Taken together, severe WML may be associated with various neurologic findings and might be a potential marker to evaluate cerebrovascular function indirectly.

Also, metabolic syndrome is closely linked to vascular disease.¹⁷ Such patients exhibited poorer prognoses after ISSNHL

treatment; accompanying diabetes or hyperlipidemia negatively affected treatment outcomes.¹⁷ Considering these previous studies, WML may reflect the vascular status. However, the sensitivity of WML is not high because the incidence of DM and/or HTN did not increase significantly until Fazekas scale scores approached 2 in this study, and none of our ISSNHL patients had a high Fazekas scale score of 3 or more.

Regarding age, we observed that increased age was associated with an increase in Fazekas scale scores. An Italian group previously reported that ISSNHL patients aged between 48 and 60 years tended to have a 26% higher possibility of a Fazekas scale score of 1 than a control group.¹⁰ In addition, a higher Fazekas scale score was associated with a lower chance of hearing recovery from 71% (score 0) to 15% (scores 3 and 4).⁹ This tendency was similar to our findings and those of another Italian study that compared the incidence of WML between ISSNHL and pituitary adenoma, which showed that patients with WML tended to have a poor recovery at 1 month.⁹

In contrast, another Italian group reported that WML was more frequent in patients with ISSNHL than controls who did not have ISSNHL but did have headache and dizziness. They showed that Fazekas scale scores correlated with age, female sex, body mass index, cholesterol, and recovery rate.¹¹ Their findings were different from those of previous studies, including our study, in that higher Fazekas scale scores were associated with poorer treatment outcomes and that there was no sex difference. We think that the patients' demographic characteristics in the control group of that study might have resulted in these differences; they enrolled patients with dizziness and headache to the control group. In fact, vascular etiologies of headache and dizziness are common, and these include vascular headache, migraine, transient ischemic attack, vertebrobasilar insufficiency, and anterior inferior cerebellar artery infarction.¹⁸ In addition, another population-based imaging study reported a higher association between tension-type headache and WMH compared with normal controls.¹⁹

Our data also showed that Fazekas scale scores had no relationship to pure-tone thresholds in the healthy side. Instead, the contralateral hearing level was poorer in patients with HTN than without HTN.

Table 1. Result of Binary Regression Analysis for Complete Recovery

| Variables | B | Sig. | EXP(B) | 95% CI | |
|---------------------------|--------|-------|--------|--------|-------|
| | | | | Lower | Upper |
| Fazekas scale | -1.002 | 0.031 | 0.367 | 0.148 | 0.912 |
| Initial pure-tone average | -0.039 | 0.001 | 0.962 | 0.939 | 0.985 |

Contralateral hearing is usually regarded as the baseline hearing level in ISSNHL; better contralateral hearing thresholds are not only associated with the occurrence of acute-onset tinnitus in unilateral ISSNHL but are also considered a good prognostic factor for recovery.^{20,21} In general, noise exposure, aging, drugs, and infection are the most representative nongenetic causes for sensorineural hearing loss.²² Therefore, our results indicate that cardiovascular risk factors contribute to the worsening of hearing. In addition, we assumed that patients with possible vascular etiologies and accompanied by higher Fazekas scale scores may have both poorer baseline hearing and a higher risk of ISSNHL.^{9,23} That is, the clinical significance of Fazekas scale scores seems to be secondary to underlying cardiovascular risk factors rather than an independent risk factor for hearing loss.

Magnetic resonance imaging for ISSNHL provides more information than the use of audio-vestibular testing. In addition to WML, signal changes in the labyrinth is another major issue. In our previous study, we observed that an absence of high-intensity signal on 3D FLAIR MRI was associated with a good prognosis and its clinical significance was associated with accompanying dizziness.²⁴ Similar to our observations, others also reported that the possibility of a positive finding in ISSNHL was higher if patients had accompanying vertigo in addition to ISSNHL.²⁵ Patients with ILH tend to have irreversible initial profound hearing loss accompanied by vestibular dysfunction; thus, this finding on MRI is associated with poorer treatment outcomes in ISSNHL.²⁶

This study had several limitations. First, the last follow-up period was made at 3 months, and this might be too short to evaluate final hearing after ISSNHL. However, we confirmed that the hearing level did not differ between 1 and 3 months and this might confirm our observation period was not too short. Second, we did not include the results of audio-vestibular tests in this study except for pure-tone audiometry (PTA); speech audiometry data were largely unavailable. Analysis of such data in combination with the PTA results might have yielded valuable information on whether WML affect audibility. Further studies will be performed to analyze these test results in accordance with Fazekas scale scores. Third, no control group was used. If appropriate, a healthy age- and sex-matched control group should be used to evaluate the clinical significance of WML more strictly. However, MRI scans are expensive, therefore it is more cost-effective to enroll a control group from subjects with no specific symptoms who had undergone MRI previously.

In conclusion, nearly one-third of ISSNHL patients had WML. A high Fazekas scale score was observed in patients with DM and/or HTN in this study. Regarding accompanying diseases, patients with HTN had worse contralateral hearing. Better initial hearing thresholds in the affected side and lower Fazekas scale scores were associated with CR. Although the prevalence of WML in ISSNHL is not high, more severe WML and accompanying cardiovascular risk factors may increase the possibility of initially worse hearing and decrease responses to treatment of ISSNHL. Therefore, it is important to control cardiovascular abnormalities in ISSNHL to achieve a better prognosis.

Ethics Committee Approval: Ethical committee approval was received for this study from the Ewha Mokdong Hospital (2020-12-040).

Informed Consent: N/A.

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Declaration of Interests: The authors have no conflict of interest to declare.

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