Criteria for acute low-tone hearing loss

[The Ministry of Health, Labor and Welfare, Acute Severe Hearing Loss Study Group (2000)]
[The Ministry of Health, Labor and Welfare, Acute Severe Hearing Loss Study Group (revised in 201)2]

Main symptoms

1. Acute or sudden onset of cochlear symptoms including ear fullness, tinnitus and hearing loss
2. Low-tone hearing loss
3. Without vertigo
4. Unknown etiology

For reference

1. Audiometric criteria of low-tone hearing loss.
   ① The sum of hearing levels at low frequencies of 0.125 kHz, 0.25 kHz and 0.5 kHz is 70dB or more.
   ② The sum of hearing levels at high frequencies of 2 kHz, 4 kHz and 8 kHz is 60dB or less.
2. Cochlear symptoms may be recurrent.
3. May progress to Meniere's disease.
4. May be accompanied with light dizzy sensation.
5. May be bilateral.

Definite: All of the main symptoms. Audiometric criteria ① and ②
Probable: All of the main symptoms. Audiometric criteria ① and the same hearing levels at high frequencies of 2 kHz, 4 kHz and 8 kHz as the contralateral ear.

ムンプス難聴：診断基準

（厚生省特定疾患急性高度難聴調査研究班、1987年改訂）
（厚生労働省特定疾患急性高度難聴調査研究班、2013年改訂）

1．　確実例

1）　耳下腺・顎下腺腫脹など臨床的に明らかなムンプス症例で、腫脹出現4日前より出現後18日以内に発症した急性高度難聴の症例

2）　臨床的にはムンプスが明らかでない症例で、急性高度難聴発症直後から2ヵ月以内にムンプスIgM抗体が検出された症例

2．　参考例

臨床的にムンプスによる難聴と考えられた症例

1）　家族・友人にムンプス罹患があった症例

2）　確実例1）における日数と差のあった症例

Criteria for diagnosis of mumps deafness

[The Ministry of Health and Welfare, Acute Severe Hearing Loss Study Group in 1987]
[The Ministry of Health, Labor and Welfare, Acute Severe Hearing Loss Study Group (revised in 2013)]

Definite

1) Patients with evident clinical signs of mumps, such as swelling of the parotid gland and submandibular gland, and acute severe hearing loss during the period from 4 days before to 18 days after the appearance of such swelling.
2) Patients without evident clinical signs of mumps, but IgM antibody to mumps virus is detected within 3 months after the onset of acute severe hearing loss.

Referent case

Patients in whom mumps deafness is suspected clinically.

1) Patients whose family members or friends have mumps infection
2) Patients who have different period in Difinite 1)

Ⅳ. 研究成果の刊行物・別刷

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Self-Reported Symptoms in Patients With Idiopathic Sudden Sensorineural Hearing Loss

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Objective: This study evaluated self-reported symptoms in patients with idiopathic sudden sensorineural hearing loss (ISSHL).
Study Design: Cross-sectional study.
Setting: Multicenter clinical investigation in 9 university hospitals.
Patients: In total, 140 patients with ISSHL and 24 patients with unilateral sensorineural hearing loss (USHL; control) were included.
Main Outcome Measures: A questionnaire on symptoms of ISSHL was distributed and the Short-Form Health Survey (Version 2) was used for assessing the quality of life.
Results: In response to questions on hearing difficulty, many of patients in both groups experienced symptoms. In response to questions on hearing-related discomfort, a significantly higher number of patients with ISSHL experienced symptoms compared with those with USHL. Compared with a high incidence of tinnitus in patients with ISSHL, very low incidence of tinnitus was observed in those with USHL.

In the multiple linear regression analysis, hearing-related discomfort was the sole significant factor on the Mental Component Summary scores of the Short-Form Health Survey (Version 2).
Conclusion: Many patients with ISSHL experience several symptoms such as hearing difficulty, hearing-related discomfort, tinnitus, and anxiety. Hearing-related discomfort strongly affected the quality of life in patients with ISSHL. **Key Words:** Hearing difficulty—Hearing-related discomfort—Spatial hearing—Tinnitus.
Otol Neurotol **34:**1405–1410, 2013.

Idiopathic sudden sensorineural hearing loss (ISSHL) is characterized by sudden onset of sensorineural hearing loss. The lesion is most often cochlear in origin and less frequently retrocochlear. Although cure of or improvement in ISSHL is possible, hearing problems persist in approximately 60% patients (1–4). The National Epidemiological Survey in Japan estimated that ISSHL occurred in approximately 35,000 patients in 2001. Approximately 20,000 patients are estimated to develop permanent hearing loss every year in Japan. Because ISSHL is unilateral in most patients, severe auditory communication problems are not usually observed. Symptoms and quality of life (QOL) in patients with ISSHL have rarely been investigated. In a previous study, we investigated QOL in patients with ISSHL. The study results showed deterioration in QOL ,mainly in terms of mental health (5). Social life and daily activities were particularly affected according to both mental and physical assessments. In this study, symptoms were evaluated in the same group of patients with ISSHL.

Unilateral hearing loss may be a very sudden change for patients who have never experienced hearing problems before the onset of ISSHL. Two main symptoms affect QOL in ISSHL patients with persistent hearing problems: difficulty in hearing and tinnitus (6,7). Other problems, such as hearing-related discomfort, vertigo, anxiety about recurrence, and psychosocial problems in social or family life, may also affect QOL. These symptoms may differ from those in the patients with congenital unilateral sensorineural hearing loss (USHL) or USHL developed in early childhood.

Information about symptoms in patients with ISSHL in the persistent phase is currently lacking. Our multicenter clinical study was conducted to investigate the symptoms in patients with ISSHL and the relationship of these symptoms to QOL.

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The authors declare no conflicts of interest.

PATIENTS AND METHODS

Nine university hospitals representing the Acute Profound Deafness Research Committee of the Ministry of Health, Labour and Welfare in Japan participated in this study conducted from December 2009 to December 2011. Patients with ISSHL and USHL (control group) were recruited. ISSHL was defined as sudden onset of hearing loss or hearing loss first noticed on awakening, hearing loss severe enough to be recognized by the patients themselves, and sensorineural hearing loss of unknown etiology.

Inclusion criteria for patients with ISSHL were as follows: age of 20 years or older, time interval from onset of 30 days or greater, unilateral involvement, and an average hearing level (measured at 500, 1,000, and 2,000 Hz) of 30 dBHL or lower in the unaffected ear. Inclusion criteria for patients with USHL patients were as follows: age 20 years or older, hearing loss diagnosed before 7 years of age, an average hearing level of 90 dBHL or greater in the affected ear, and 30 dBHL or lower in the unaffected ear.

In a previous investigation, information on symptoms was elicited from 104 patients with ISSHL using a free writing method (data not published). These symptoms were rewritten and organized to create a new questionnaire comprising 17 questions for use in this study (Table 1).

The Short-Form Health Survey Version 2 (SF-36v2) was used to assess the health-related QOL. This survey has been translated, adapted, and validated for use in Japan. (8,9) It measures 8 health-related QOL domains and 2 more comprehensive scores: the physical component summary (PCS) and the mental component summary (MCS). Scores for these 8 domains and the 2 component summaries were standardized (norm-based scoring, Japanese average = 50, standard deviations = 10) for comparison with the scores of people in the general population or those reported in other studies.

Patients who fulfilled the inclusion criteria were requested to complete the questionnaire on the symptoms and SF-36v2 before seeing a physician to avoid interviewer bias. The questionnaire was sent to the investigators at Kitasato University along with the information on sex, age, date of onset, hearing levels at the time of the investigation, and general complications.

Statistical analysis was performed as follows: For the scores of SF-36v2, the standardized scores of the 2 component summaries were investigated. Statistical evaluations were performed using SPSS (version 15.0; SPSS Inc., Chicago, IL, USA). The Spearman's rank correlation was used for evaluating relationships between among the 17 questions. Pearson's correlation was used for evaluating the relationship between responses to the questionnaire on symptoms and summary scores of the SF-36v2. The Mann-Whitney U test was used for comparing the scores between the ISSHL and USHL groups. Multiple linear regression analysis was used to analyze the effects of multiple factors on QOL; $p < 0.05$ was considered statistically significant.

The ethics committee of each participating institution approved the study protocol. All patients provided written informed consent. All steps of the study were planned and conducted according to the principles outlined in the Declaration of Helsinki (2008).

RESULTS

In total, 140 patients with ISSHL (64 male and 76 female subjects; mean age, 59.1 yr; range, 21–85 yr) and 24 patients with USHL (13 male and 11 female subjects; mean age, 30.5 yr; range, 20–77 yr) were included (Fig. 1). In the USHL group, patients aged 20 to 29 years constituted the majority (71%). Figure 2 shows the distribution of average hearing levels in the affected ear of patients with ISSHL.

Figure 3 shows the distribution of time intervals from the onset of hearing loss in patients with ISSHL. The intervals varied widely from 30 days to 62 years (average, 5.5 yr; median, 2.7 yr).

Chronic general complications were reported for 19 patients with ISSHL (13.5%) and 1 patient with USHL (4.1%).

Table 2 shows the results of the rank correlation analysis among the 17 questions in the symptoms questionnaire in the ISSHL group. Correlations among Questions 1, 2, and 3 were high. Therefore, these 3 questions were categorized into 1 group: "hearing difficulty." Correlations among Questions 4, 5, 6, and 7 were also relatively high;

TABLE 1. *Questionnaire on symptoms in patients with idiopathic sudden sensorineural hearing loss*

1. Do you face difficulty in hearing during conversation or difficulty in hearing in general?
   Always Frequently Sometimes Never
2. Do you face difficulty in hearing during conversations involving several people?
   Always Frequently Sometimes Never
3. Do you face difficulty in hearing conversations in noisy places?
   Always Frequently Sometimes Never
4. When you are in noisy places (e.g., a crowded restaurant, or a reception room), do you feel:
   Very uncomfortable Uncomfortable Slightly uncomfortable No discomfort
5. When you hear a loud sound, do you feel:
   Very uncomfortable Uncomfortable Slightly uncomfortable No discomfort
6. Are surrounding sounds distorted? If so, does it make you feel:
   Very uncomfortable Uncomfortable Slightly uncomfortable No discomfort / No
7. Do you experience ear fullness? If so, does it make you feel:
   Very uncomfortable Uncomfortable Slightly uncomfortable No discomfort / No
8. Do you face difficulty in locating an unseen sound source?
   Always Frequently Sometimes Never
9. Do you face difficulty in perceiving stereophony?
   Always Frequently Sometimes Never
10. Do you experience tinnitus? If so, does it make you feel:
    Very uncomfortable Uncomfortable Slightly uncomfortable No discomfort/No
11. Do you experience anxiety due to tinnitus?
    Always Frequently Sometimes Never
12. Do you hesitate to communicate with other people?
    Always Frequently Sometimes Never
13. Do you experience anxiety regarding communication with other people?
    Always Frequently Sometimes Never
14. Do you experience vertigo?
    Always Frequently Sometimes Never
15. Do you experience anxiety regarding the possibility of recurrence of vertigo?
    Always Frequently Sometimes Never
16. Do you experience anxiety regarding progression of hearing loss in your affected ear?
    Always Frequently Sometimes Never
17. Do you experience anxiety regarding development of hearing loss in your unaffected ear?
    Always Frequently Sometimes Never

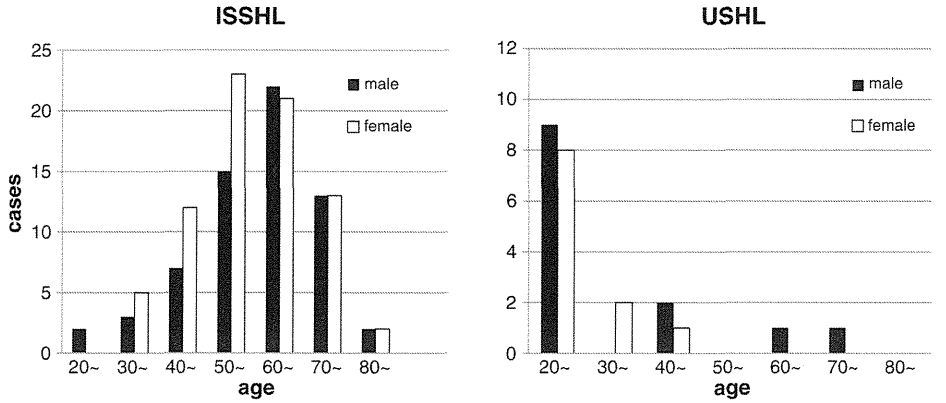

FIG. 1. Age distribution in the 2 groups.

these 4 questions were therefore categorized into 1 group: "hearing-related discomfort." Questions 8 and 9 were associated with binaural hearing. Correlations between these 2 questions were high, and they were also relatively highly correlated with questions in the hearing difficulty group (Questions 1–3). Therefore, these 2 questions were also categorized in the hearing difficulty group. Questions 10 and 11 were concerned with tinnitus. No strong correlation between these 2 questions and the other questions was observed. Questions 12 and 13 were concerned with attitude toward communication. A relatively strong correlation was observed between these 2 questions and Questions 1, 2, 3, and 8. Questions 14 and 15 were concerned with vertigo. No strong correlation was found between these 2 questions and the other questions. Questions 16 and 17 were concerned with anxiety, both for recurrence and further development of hearing loss. No strong correlation was found between these 2 questions and the other questions.

Figure 4 shows the results of the questionnaire on symptoms in patients with ISSHL and USHL. On the whole, a greater number of patients with ISSHL experienced symptoms compared with those with USHL. In response to the questions regarding hearing difficulty (Questions 1–3, 8, and 9), patients in both groups reported that they frequently experienced problems. With regard to Questions 2 and 3, significantly greater number of patients with ISSHL experienced difficulty in hearing than those with USHL. In the responses to Questions 8 and 9, although a greater number of patients with USHL reported difficulty in binaural hearing than those with ISSHL, the difference between both groups was not significant. In response to the questions regarding hearing-related discomfort (Questions 4–7), significantly greater number of patients with ISSHL experienced symptoms compared with those with USHL. Regarding tinnitus (Questions 10 and 11), a very low incidence was reported in the patients with USHL, whereas many patients with ISSHL reported experiencing tinnitus. For questions 12 and 13 regarding attitude toward communication, results were similar for patients in both groups: problems related to communication were fairly uncommon. The same was true for vertigo (Question 14). However, for anxiety regarding the possibility of recurrence of vertigo (Question 15), patients with ISSHL reported more anxiety than those with USHL. In response to Question 16 on anxiety regarding recurrence in the affected ear, patients with

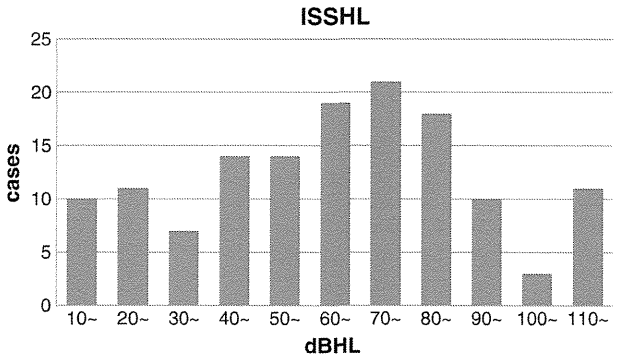

FIG. 2. Distribution of hearing levels in the ISSHL group. The 3 frequencies of average hearing levels in the affected ear of patients with ISSHL.

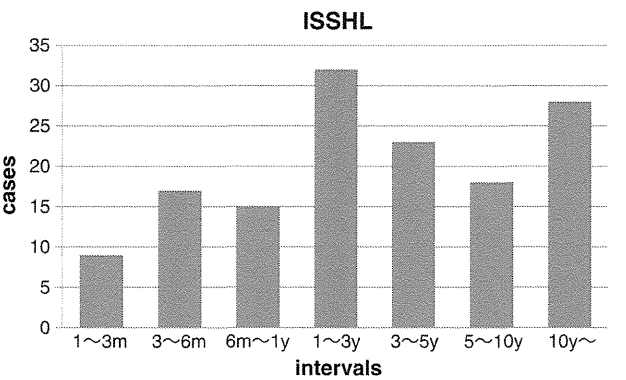

FIG. 3. Distribution of time intervals from the onset in the ISSHL group.

TABLE 2. *Spearman's rank correlation among the 17 questions in the questionnaire on symptom and the Pearson's correlation between the 17 questions and mental component summary scores of SF-36v2 in the idiopathic sudden sensorineural hearing loss group*

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Q1	—	0.81	0.7	0.53	0.42	0.43	0.44	0.62	0.58	0.39	0.40	0.57	0.57	0.33	0.33	0.33	0.45
Q2	0.81	—	0.84	0.62	0.45	0.45	0.44	0.67	0.60	0.43	0.39	0.60	0.62	0.26	0.33	0.28	0.52
Q3	0.72	0.84	—	.58	0.40	0.36	0.40	0.6	0.52	0.41	0.38	0.57	0.64	0.27	0.32	0.33	0.54
Q4	0.53	0.62	0.58	—	0.63	0.57	0.53	0.50	0.44	0.49	0.41	0.50	0.54	0.37	0.41	0.18	0.39
Q5	0.42	0.45	0.40	.63	—	0.74	0.43	0.35	0.31	0.39	0.41	0.41	0.40	0.27	0.29	0.11	0.30
Q6	0.43	0.45	0.36	.57	0.74	—	0.50	0.38	0.43	0.38	0.38	0.43	0.46	0.15	0.22	0.06	0.33
Q7	0.44	0.44	0.40	.53	0.43	0.50	—	0.37	0.42	0.40	0.43	0.41	0.42	0.25	0.29	0.28	0.28
Q8	0.62	0.67	0.60	.50	0.35	0.8	0.37	—	0.63	0.30	0.29	0.59	0.59	0.23	0.34	0.19	0.51
Q9	0.58	0.60	0.52	.44	0.31	0.43	0.42	0.63	—	0.36	0.39	0.47	0.59	0.19	0.28	0.13	0.30
Q10	0.39	0.43	0.41	.49	0.39	0.38	0.40	0.30	0.36	—	0.71	0.43	0.47	0.34	0.38	0.31	0.32
Q11	0.40	0.39	0.38	.41	0.41	0.38	0.43	0.29	0.39	0.71	—	0.49	0.48	0.27	0.42	0.44	0.35
Q12	0.57	0.60	0.5	.50	0.41	0.43	0.41	0.59	0.47	0.43	0.49	—	0.84	0.26	0.43	0.26	0.48
Q13	0.57	0.2	0.64	.54	0.40	0.46	0.42	0.59	0.59	0.47	0.48	0.84	—	0.29	0.43	0.25	0.49
Q14	0.33	0.26	0.27	.37	0.27	0.15	0.25	0.23	0.19	0.34	0.27	0.26	0.29	—	0.54	0.14	0.25
Q15	0.33	0.33	0.32	.41	0.29	0.22	0.29	0.34	0.28	0.38	0.42	0.43	0.43	0.54	—	0.33	0.33
Q16	0.33	0.28	0.33	.18	0.11	0.06	0.28	0.19	0.13	0.31	0.44	0.26	0.25	0.14	0.33	—	0.53
Q17	0.45	0.52	0.54	.39	0.30	0.33	0.28	0.51	0.30	0.32	0.35	0.48	0.49	0.25	0.33	0.53	—
MCS	0.42	0.28	0.27	.43	0.39	0.32	0.38	0.37	0.35	.31	0.40	0.46	0.48	0.34	0.41	0.21	0.32

MCS indicates mental component summary.

ISSHL reported more anxiety than those with USHL. Patients in both groups expressed anxiety about the possibility that the unaffected ear may get affected in future (Question 17): no significant difference was observed in response to this question between both groups.

Table 3 lists average scores for the 2 summary components of SF-36v2 in both groups with regard to age. The Japanese average PCS scores decrease with age; conversely, the MCS scores increase with age. No significant difference was observed between PCS scores for both ISSHL and USHL patients in all age groups and Japanese average scores for all age groups. However, MCS scores for ISSHL patients aged 40 to 49, 50 to 59, 60 to 69, and 70 years or older were significantly lower

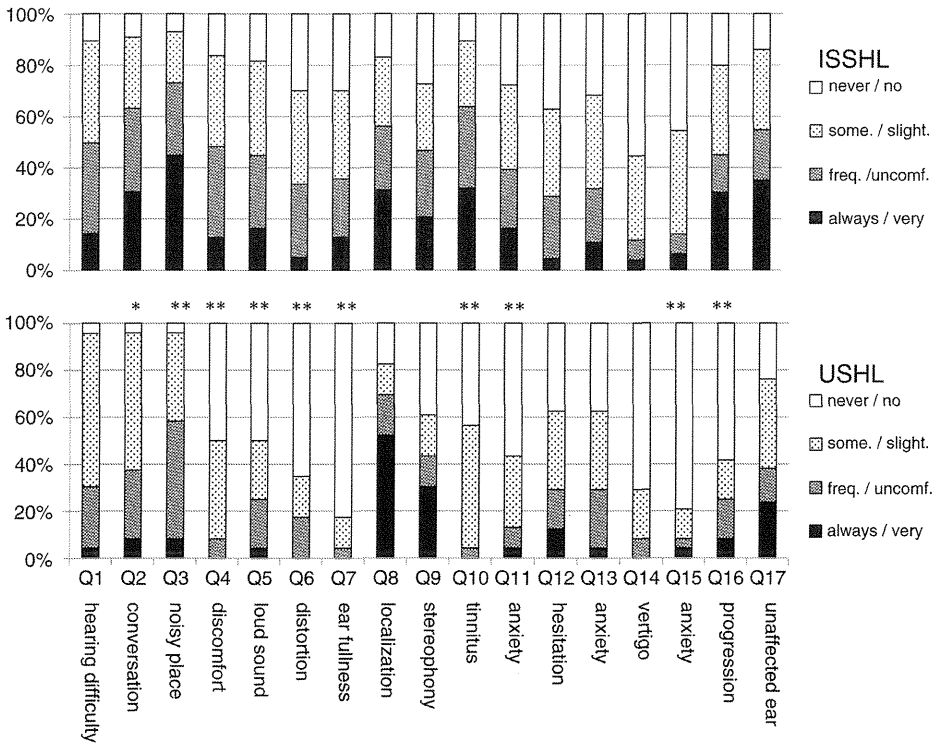

FIG. 4. Results of the questionnaire on symptoms in the 2 groups. $*p < 0.05$, $**p < 0.01$ values are presented as comparison between the ISSHL group and USHL groups using the Mann-Whitney *U* test.

TABLE 3. *Scores for the 2 component summaries of SF-36v2 in each age group*

	Idiopathic sudden sensorineural hearing loss	Unilateral sensorineural hearing loss	Japanese
PCS			
20s		55.7 ± 5.2 (16)	54.1
30s	54.5 ± 8.8 (7)		52.2
40s	48.7 ± 5.8 (15)		51.6
50s	48.7 ± 10.0 (35)		49.5
60s	47.7 ± 10.8 (42)		47.2
70s	40.1 ± 9.9 (24)		41.3
MCS			
20s		44.3 ± 10.3 (16)	48.4
30s	42.0 ± 18.4 (7)		48.8
40s	41.4 ± 5.8 (15)[a]		49.1
50s	45.0 ± 11.2 (35)[b]		50.8
60s	48.4 ± 9.8 (42)[a]		52.0
70s	46.2 ± 9.4 (24)[b]		51.7

PCS indicates Physical Component Summary; MCS, Mental Component Summary Parentheses indicates number of cases.
[a] $p < 0.05$.
[b] $p < 0.01$ (t test). Values are presented in comparison with Japanese average for each age group.

than the Japanese average. MCS scores for USHL patients aged 20 to 29 were lower than the Japanese average, although not significantly lower ($p = 0.13$).

Results of the investigation using SF-36v2 indicated that MCS scores in patients with ISSHL were significantly lower than the Japanese average in all age groups. Therefore, factors influencing MCS scores in patients with ISSHL were investigated. First, the correlations between MCS scores and the 17 questions in the questionnaire on symptoms were evaluated. (Table 1, last line) On the whole, weak-to-moderate correlations were indicated. For the questions on hearing difficulty (Questions 1–3, 8, and 9), the highest correlation was found between MCS scores and Question 1. For questions on hearing-related discomfort (Questions 4–7), the highest correlation was found between MCS scores and Question 4. Relatively high correlation was observed between MCS scores and the questions on attitude toward communication (Questions 12 and 13) and anxiety regarding the

TABLE 4. *Results of the multiple linear regression analysis*

Result of multiple regression analysis on mental component summary (idiopathic sudden sensorineural hearing loss)		
Independent variables	Beta coefficient	p
Age	0.137	0.088
Intervals	0.112	0.180
Hearing levels	-0.104	0.234
Question 1	-0.124	0.186
Question 4	-0.287	0.002
Question 10	-0.135	0.141

The intervals from the onset were divided into 6 ordinal variables and investigated as interval variables because a linear relationship with MCS scores was observed. The responses to Questions 1, 4, and 10 were divided into 2 categories: "Always" and "Frequently" = 1, "Sometimes" and "Never" = 0,/"Very uncomfortable" and "Uncomfortable" = 1, "Slightly uncomfortable" and " No discomfort/No" = 0.

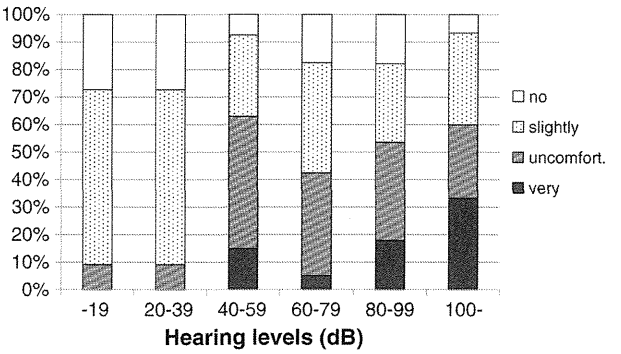

FIG. 5. Relationship between the response to question 4 and the hearing levels in ISSHL group.

recurrence of vertigo (Question 15). In the next stage of the investigation, confounders influencing MCS scores in patients with ISSHL were determined using multiple linear regression analysis. The associations between age, hearing level at the time of the investigation, time interval from the onset, and the responses to the questionnaire on symptoms and MCS scores were evaluated (Table 4). The answers to 3 questions were used for this part of the investigation. Responses to Question 1 were taken as representative of hearing difficulty, those to Question 4 as representative of hearing-related discomfort, and those to Question 10 as representative of tinnitus. Tinnitus was identified as a significant confounder in another report (7). The results showed that Question 4 regarding hearing-related discomfort was the sole significant confounder (Table 4).

We further investigated the relationship between the response to Question 4 and the hearing levels in the affected ear at the investigation in the patients with ISSHL (Figs. 5 and 6). The result shows that the response to Question 4 was not associated with the hearing levels in the range of moderate-to-profound hearing loss, and the

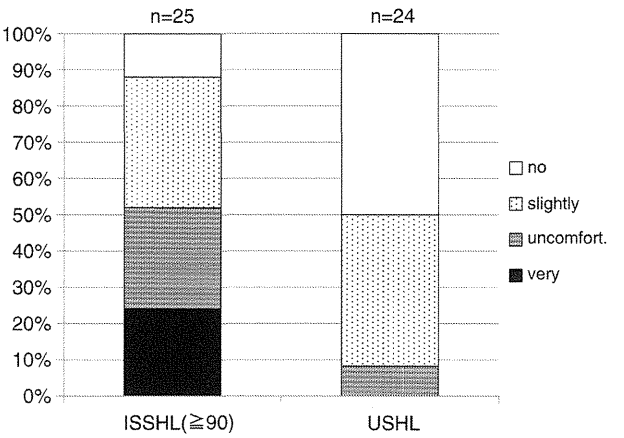

FIG. 6. Response to question 4 in ISSHL patients with a 90 dB or greater hearing loss in the affected ear and USHL patients. Mann-Whitney U test, $p < 0.01$.

high incidence of symptom was reported even in the patients with profound hearing loss.

DISCUSSION

Various difficulties have been identified in patients with unilateral hearing loss, including difficulty hearing sounds from the affected ear, difficulty localizing unseen sounds, and difficulty with speech perception in noisy places (10–14). When recovery is incomplete in patients with ISSHL, these problems may also be observed. In a previous study, tinnitus and vertigo were reported as significant factors influencing the QOL in patients with ISSHL (7). In our investigation, hearing difficulty, hearing-related discomfort, and tinnitus were the significant problems reported by patients with ISSHL. Anxiety about the possibility of recurrence and hearing loss in the unaffected ear were also frequently reported problems. However, vertigo was not a frequent problem for the patients included in this study in contrast to the results of a former report (7). Because the incidence of vertigo at the time of that investigation was quite high (34%), there is a possibility that patients with Ménière's disease were included in that report.

Of the 3 significant symptoms identified in this study, 2 (hearing-related discomfort and tinnitus) were experienced significantly less often in patients with USHL than in those with ISSHL. In most patients with USHL in our investigation, hearing loss was congenital or developed in early childhood. These 2 problems may therefore occur only in the patients with mature central auditory nervous systems, who suddenly lose their peripheral hearing ability in 1 ear.

In this study, the patients were basically recruited during their regular visiting. Because the patients with USHL tended to quit visiting after mature age, we could only recruit a small number and a relatively young age of patients. Therefore, the results comparing with USHL might be affected by the difference of age distribution in 2 groups. The difference of distribution of hearing levels in the 2 groups—all patients in the USHL group had profound hearing loss, whereas the patients in the ISSHL group varied from mild-to-profound hearing loss—could also affect the results especially in hearing difficulty.

Although hearing-related discomfort is a well-known symptom in patients with sensorineural hearing loss, its incidence and severity in patients with ISSHL has not been investigated. Therefore, the fact that hearing-related discomfort was the sole confounder influencing QOL (as evidenced by MCS scores) in this study was an unexpected result. This symptom may be caused by 2 mechanisms: hyperacusis due to the recruitment phenomenon and distortion due to disturbances in frequency selectivity. These 2 mechanisms could be involved in patients with mild-to-moderate hearing loss. However, no association was found between the response to Question 4 and the hearing levels of the affected ear in the range of moderate-to-profound hearing loss. Many of patients with profound hearing loss, who were unable to hear in the affected ear, also experienced this symptom. This result indicated that mechanisms other than hyperacusis or distortion must be considered. This symptom could be derived from deprivation of localization of sound because of unilateral hearing loss. In this study, some of these patients described their symptoms as "surrounding noises are exaggerated and fill my head." Because of the sudden loss of the ability to localize the sounds coming from various directions, spatial hearing perception may have been lost in these patients. This symptom can be termed *collapse of spatial hearing perception*. This mechanism may also be important for understanding the symptoms of ISSHL.

In conclusion, the frequently reported problems in patients with ISSHL in this study included hearing difficulty, hearing-related discomfort, tinnitus, and anxiety. Hearing-related discomfort strongly affected QOL regardless of hearing levels. Therapists often treat patients with ISSHL by fitting or inserting of hearing devices to improve hearing or tinnitus. The results of this study demonstrate that evaluation of hearing-related discomfort should be added. A new approach may be required to address the problem in the treating patients with ISSHL.

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Hearing Handicap in Adults With Unilateral Deafness and Bilateral Hearing Loss

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Objective: To assess the perception of hearing handicap in adult patients with unilateral sudden sensorineural hearing loss (SNHL) compared with those with bilateral SNHL or unilateral congenital SNHL.
Study Design: Retrospective chart review.
Setting: Multicenter department of otolaryngology referrals.
Patients: Seventy-one subjects in the unilateral severe-profound (>70 dB) sudden SNHL group (Group 1), 17 subjects in the unilateral prelingual or congenital SNHL group (Group 2), and 121 subjects in the bilateral SNHL group (Group 3).
Interventions: Questionnaire.
Main Outcome Measures: Hearing Handicap Inventory for Adults (HHIA) and visual analogue scale (VAS) measurements of hearing handicap.
Results: Average levels of hearing loss were 92 dB in Group 1, 109 dB in Group 2, and 67 dB in Group 3. The relative percentage scores of HHIA and VAS compared with Group 3 were 72.6% and 81.0% in Group 1 and 25.4% and 50.3% in Group 2, respectively. A mild correlation between the HHIA subscale or VAS scores and degree of hearing loss could be found in Group 3. No significant correlation was found between the HHIA subscale or VAS scores and duration of hearing loss in Group 1 or Group 3. Higher scores were obtained in male subjects than in female subjects. Patients in Group 1 who were troubled by tinnitus scored significantly higher in the HHIA. In multiple logistic regression analysis, presence of tinnitus, older age, higher average hearing loss level, and group (bilateral SNHL>unilateral sudden SNHL>unilateral precongenital SNHL) revealed a significant positive association with high score (>42) of HHIA (odds ratio, 3.171, 1.021, 1.031, and 6.690, respectively).
Conclusion: The results of HHIA and VAS suggest that not only patients with bilateral SNHL but also those with unilateral sudden SNHL, particularly those who have tinnitus, experience a hearing handicap. **Key Words:** Sudden hearing loss—Hearing handicap—Questionnaire—Unilateral deafness.
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Population studies of sudden sensorineural hearing loss (SNHL) show a wide age distribution with an average of 50 to 60 years. The hearing loss is unilateral in most cases, with bilateral involvement reported in less than 5% of patients (1). The incidence of sudden SNHL has been reported to be between 5 and 30 cases per 100,000 per year (2). However, a study from Japan has shown an incidence as high as 275 cases per 100,000 per year (3).

Patients with single-side deafness (SSD) have difficulty hearing sounds coming from the deaf side, localizing a sound source, and perceiving speech against background noise, all of which have been explained by the "head shadow effect" (4,5). However, whether SSD has a noteworthy impact on the patients' well-being and social life remains under discussion.

Conventionally, the audiologic treatment of patients with SSD is a contralateral routing (CROS) hearing aid, in which a microphone, placed on the deaf side, transmits sound to the hearing ear either by wire or wireless means. Recently, the Bone-Anchored Hearing Aid (BAHA), which is a semi-implantable hearing aid and bone-conducting device, has also been applied as a treatment for patients with SSD (6,7). Cochlear implants have also been used in some patients with unilateral severe-to-profound hearing loss and ipsilateral tinnitus and were found to be beneficial in some cases (8,9). Several studies using the Hearing Handicap Inventory for Adults (HHIA) have demonstrated that unilateral hearing loss may affect the emotional and social

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well-being of adults with this condition and adults with unilateral hearing loss perceive themselves as handicapped (10–12). However, there is less information regarding the effects of unilateral sudden deafness with or without tinnitus compared with unilateral congenital deafness or bilateral hearing loss. In this study, we aimed to assess the level of hearing handicap using the HHIA and visual analog scale (VAS) for patients with unilateral sudden SNHL compared with those having unilateral congenital SNHL or bilateral SNHL in a multicenter study.

MATERIALS AND METHODS

Study Design

All subjects were enrolled in this multicenter study at 7 university schools of medicine in Japan, in institutions that belonged to the Acute Profound Deafness Research Committee (Tokyo, Japan). Questionnaire charts of 209 patients, treated between December 2009 and January 2011 at the Department of Otolaryngology of each Medical University Hospital, were reviewed retrospectively. All patients provided written informed consent for review of their records for research purposes. Each university review board approved the conduct of this study.

Subjects

Subjects were classified into 3 groups as follows: 1) unilateral severe to profound (>70 dB) sudden SNHL (Group 1), 2) unilateral severe to profound prelingual or congenital SNHL (Group 2), and 3) bilateral SNHL (Group 3). All subjects fulfilled the following criteria: a) a questionnaire with self-rated scales was completed over 6 months after the onset of hearing loss, b) patients were older than 20 years when they completed the questionnaire, c) unilateral severe-to-profound hearing loss was defined as average level of hearing loss (500, 1,000, 2,000, and 4,000 Hz) of more than 70 dB and an average level of the opposite side of below 30 dB, d) bilateral hearing loss was defined as an average level of hearing loss in the better hearing ear of greater than 30 dB, e) sudden SNHL was defined as a decrease in hearing occurring within 3 days or fewer without any identifiable cause, and f) prelingual or congenital SNHL was defined as onset of hearing loss occurring before the age of 7 years.

Questionnaire

The Japanese version of the HHIA questionnaire (Table 1) was used to evaluate the handicap. The HHIA is a self-assessment questionnaire of hearing handicap comprising 25 items, of which, 13 deal with emotional aspects (E) and 12 deal with social and situational aspects (S). For each item or situation, subjects are asked to give one of the following responses: "yes" (4 points),

TABLE 1. *The hearing handicap inventory for adults*

		tTeet p value G1-G2	t Teet p value GI-G3
S-1	Does your hearing difficulty make you use the phone less often than you would like?	0.079	0.001
E-2	Does your hearing difficulty make you feel embarrassed or out of place when you are introduced to stranger?	0.733	0.000
S-3	Does your hearing difficulty make you avoid group of people?	0.261	0.083
E-4	Does your hearing difficulty make you touchy?	0.092	0.898
E-5	Does your hearing difficulty make you feel frustrated or unhappy when talking to people of your family?	0.038	0.080
S-6	Does your hearing impairment cause any other difficulties when you go to the party or social meeting?	0.024	0.297
E-7	Does your hearing difficulties make you frustrated when talking to work mates?	0.223	0.001
S-8	Does your hearing difficulties when you go to the movies or theaters?	0.017	0.169
E-9	Does your feel harmed or down because of your hearing difficulty?	0.073	0.098
S-10	Does your hearing impairment cause difficulties when you visit friends, relatives and neighbors?	0.344	0.031
S-11	Does your hearing difficulty cause you problem to hear/understand work mates?	0.409	0.999
E-12	Does your hearing difficulty cause you nervous?	0.181	0.959
S-13	Does your hearing difficulty make you visit friends, relatives and neighbors less often than you would like to?	0.048	0.519
E-14	Does your hearing difficulty make you argue or fight with your family?	0.252	0.247
S-15	Does your hearing difficulty cause you trouble to watch TV or listen to the radio?	0.000	0.000
S-16	Does your hearing difficulty make you go out shopping less often than you would like to?	0.067	1.000
E-17	Does your hearing difficulty make you annoyed or unhappy?	0.277	0.671
E-18	Does your hearing difficulty make you prefer to be alone?	0.467	0.797
S-19	Does your hearing difficulty make you want to talk less to the people in your family?	0.140	0.137
E-20	Do you think that your hearing difficulty reduces or limit your personal or social life somehow?	0.959	0.999
S-21	Does your hearing difficulty make you trouble when you are in a restaurant with family or friend?	0.011	0.773
E-22	Does your hearing difficulty make you feel sad or depressed	0.109	0.564
S-23	Does your hearing difficulty make you watch less TV or listen to the radio less often than you would like to?	0.344	0.001
E-24	Does your hearing difficulty make you feel embarrasses or less comfortable when you talk to a friends?	0.635	0.289
E-25	Does your hearing difficulty make you feel isolated or feel aside within a group of people?	0.177	0.000

E indicates emotional subscale; G, group; S, social subscale.

"sometimes" (2 points), or "no" (0 points). Care was taken not to induce answers and to avoid interviewer bias.

In addition, subjects were asked to rate their hearing handicap in various everyday situations on a VAS, which is a psychometric measurement instrument for quantifying subjective phenomena. A VAS is presented as a horizontal line, 100 mm in length, with one end as 0 (absence of perception of hearing handicap) and the other as 100 (maximum). The subjects mark on the line the point that represents their current state; the VAS score is the distance in millimeters from the left ("absence") to the mark.

Statistical Methods

All statistical values were calculated using IBM SPSS Statistics 18 (IBM Corp. Armonk, NY, USA). We used the *t* test to compare each score of 25 items in the HHIA between groups (Group 1 to Group 2 and Group 1 to Group 3). Correlations and standard deviations within each group were examined. The significance level was set at 0.05. Pearson's correlation coefficient was used to study the relationship between the average hearing loss and subscales of HHIA or VAS score as well as the correlation between the duration of hearing loss and subscales of HHIA or VAS score. We used a multiple logistic regression analysis to assess the independent effects of age, sex, average hearing loss level, presence/absence of tinnitus, and unilateral precongenital SNHL versus unilateral sudden SNHL versus bilateral SNHL.

RESULTS

Seventy-one subjects (33 male and 38 female subjects) with a mean age of 52 years (range, 21–81 yr) were included in the unilateral sudden SNHL group (Group 1). Of these, 34 subjects (48%) were affected in the right ear. The average level of hearing loss was 92 dB (range, 70–115 dB). The average period between onset of hearing loss and completion of the questionnaires was 77 months (range, 6–237 mo). One hundred twenty-one subjects (58 male and 63 female subjects) with a mean age of 60 years (range, 20–97 yr) were included in the bilateral SNHL group (Group 3). The average levels of hearing loss in the better hearing ear, right ear, and left ear were 67 dB (range, 35–115 dB), 70.8 dB, and 71.5 dB, respectively. The average period between onset of hearing loss and completion of the questionnaires was 15 years (range, 1–56 yr). Seventeen subjects (10 male and 7 female subjects) with a mean age of 31 years (range, 20–77 yr) were included in the unilateral precongenital SNHL group (Group 2). Of these, 8 subjects (47%) were affected in the right ear. The average level of hearing loss was 109 dB (range, 75–115 dB). The causes of hearing loss were congenital deafness in 8 subjects, mumps in 7 subjects (average onset of hearing loss: 6.7 yr of age), and unknown in 2 subjects.

The mean total scores and emotional (E) and social (S) subscores together with the standard deviation values obtained from the HHIA questionnaire for the participants of Group 1, 2, and 3 were 35.8 ± 13.9 (total), 16.4 ± 13.5 (E) and 19.3 ± 14.2 (S); 12.5 ± 10.4 (total), 5.7 ± 4.4 (E) and 6.7 ± 6.5 (S); and 49.3 ± 13.6 (total), 22.4 ± 13.9 (E) and 27.0 ± 13.3 (S), respectively (Fig. 1A). Significant differences were found between all groups. Relative percentages of the HHIA scores in Group 1 and 2 compared with Group 3 were 72.6% (total), 73.2% (E) and 71.5% (S) and 25.1% (total); 25.4% (E) and 24.8% (S), respectively (Fig. 1B). The subjective handicap assessed by VAS was 51.8 ± 28.7 (Group 1), 28.5 ± 21.8 (Group 2), and 56.7 ± 29.0 (Group 3). Relative percentages of the VAS in Groups 1 and 2 compared with Group 3 were 81.0% and 50.3%, respectively (Fig. 2). Significant differences in the VAS scores ($p < 0.05$) were found in Groups 1 and 3 when compared with Group 2. Table 1 shows the comparison between the mean scores of HHIA for each item obtained for Groups 1 and 2 (G1-G2) or Group 3 (G1-G3). One item of the emotional subscale (E-5) and 5 items of the social subscale (S-6, S-8, S-13, S-15, and S-21) revealed significantly higher scores in Group 1 when compared with Group 2. Three items of the emotional subscale (E-2, E-7, and E-25) and 4 items of the social subscale (S-1, S-10, S-15, and S-23) revealed significantly higher scores in Group 3 when compared with Group 1.

Tables 2 and 3 show the Pearson's correlation between the hearing handicap (HHIA; emotional and social subscale and VAS scale) and degree and duration of hearing loss in Groups 1 and 3. A mild correlation ($0.2 < r \leq 0.4$) between

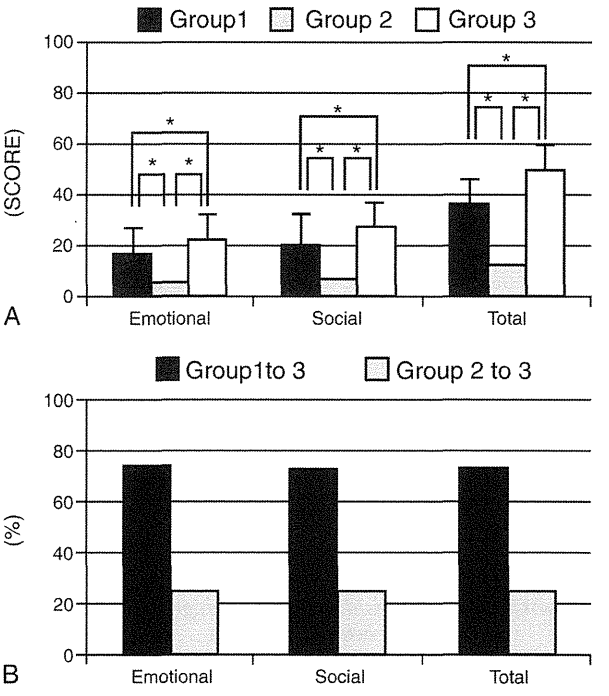

FIG. 1. Hearing Handicap Inventory for Adults (HHIA) scores for Groups 1, 2, and 3. Emotional, social, and total scores on the HHIA scale, in 3 groups of patients: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); Group 2, unilateral severe to profound prelingual or congenital SNHL; and Group 3, bilateral SNHL. Significant differences were found between groups (*A*). *$p < 0.05$. Relative percentages of the HHIA scores compared with Group 3 were 73.2% (E), 71.5% (S) and 72.6% (total) in Group 1 and 25.4% (E), 24.8% (S), and 25.1% (total) in Group 2 (B).

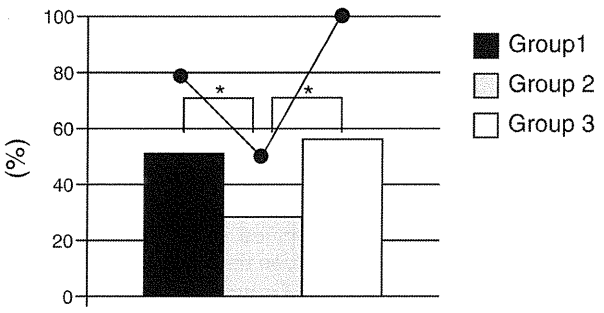

FIG. 2. Visual Analogue Scale (VAS) scores for Groups 1, 2, and 3. VAS scores in 3 groups of patients: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); Group 2, unilateral severe to profound prelingual or congenital SNHL; and Group 3, bilateral SNHL. Significant differences were found in Groups 1 and 3 when compared with Group 2. * $p < 0.05$. Relative percentages of the VAS were 81.0% in Group 1 to Group 3 and 50.3% in Group 2 to Group 3.

the HHIA subscale or VAS scores and degree of hearing loss could be found in Group 3. No significant correlation between the HHIA subscale or VAS scores and duration of hearing loss could be found in either Group 1 or Group 3. Figure 3 shows the mean scores of the emotional and social subscales in the HHIA and VAS related to sex in Groups 1, 2, and 3. Higher scores were found in male subjects compared with female subjects. Figure 4 shows the mean difference in the scores of HHIA (emotional and social subscale) and VAS between patients who had tinnitus and those who had no tinnitus in Groups 1 and 3. Patients with unilateral sudden SNHL (Group 1) who had tinnitus scored higher in the HHIA (E: $p < 0.05$ and S: $p < 0.05$).

We performed a multiple logistic regression analysis to determine the influence of age, sex, average hearing loss level, presence of tinnitus, and 3 groups (unilateral precongenital SNHL versus unilateral sudden SNHL versus bilateral SNHL) for the HHIA total score (Table 4). Patients who had tinnitus demonstrated a greater than 3-fold increased risk (odds ratio, 3.171) of high score (>42) in the HHIA compared with those who did not have tinnitus. High score (>42) in the HHIA indicated severe hearing handicap (10). A greater risk of high score in the HHIA

TABLE 2. *Relationship between average hearing loss and hearing handicap*

		Case	Average of HL (dB)	Average score	Pearson's correlation: *r*
HHIA (E)	Group 1	43	92.7	16.4	0.125
	Group 3	110	67.5	22.4	0.282
HHIA (S)	Group 1	43	92.7	19.3	0.182
	Group 3	110	67.5	27.0	0.385
VAS	Group 1	42	93.2	51.8	0.013
	Group 3	91	68.4	56.7	0.276

HHIA (E) indicates Hearing Handicap Inventory for Adults (emotional); HHIA (S), Hearing Handicap Inventory for Adults (social); HL, hearing level; VAS, visual analog scale.

TABLE 3. *Relationship between the duration of hearing loss and hearing handicap*

		Case	Average of DHL	Average score	Pearson's correlation: *r*
HHIA (E)	Group 1	43	78.5 Mo	16.4	0.124
	Group 3	56	189.0 Mo	21.1	0.084
HHIA (S)	Group 1	43	78.5 Mo	19.3	0.144
	Group 3	56	189.0 Mo	23.8	0.006
VAS	Group 1	42	74.7 Mo	51.8	0.106
	Group 3	51	181.2 Mo	56.5	0.135

DHL indicates duration of hearing loss.

(odds ratio, 6.690) was found in the patients with bilateral SNHL compared with those with unilateral sudden SNHL and in the patients with unilateral sudden SNHL compared with those with unilateral precongenital SNHL. The association was also significant in the patients with older age and higher average hearing loss level (Table 4).

DISCUSSION

The original HHIA (13) is in English and has high internal consistency with regard to its questions, test-retest reliability, and low standard error (14). The HHIA questionnaire has been translated into Italian (15), Brazilian Portuguese (16), and Japanese (17). The validity and reliability of the translated versions of the HHIA have also been reported in the literature. The average scores of the HHIA in adult patients with bilateral hearing loss were reported to be 52.2 ± 26.6 (total); 26.7 ± 15.3 (E) and

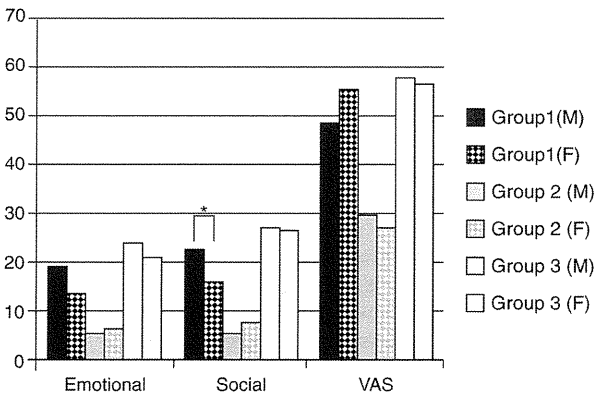

FIG. 3. Mean scores on the emotional and social subscales in the Hearing Handicap Inventory for Adults (HHIA) and Visual Analogue Scale (VAS) according to sex in Groups 1, 2, and 3. Emotional and social scores on the HHIA scale and VAS, in 3 groups of patients: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); Group 2, unilateral severe to profound prelingual or congenital SNHL; and Group 3, bilateral SNHL. Higher scores were found in male subjects compared with female subjects. The score of the social subscale of the HHIA in male subjects was significantly higher than that in female subjects. * $p < 0.05$.

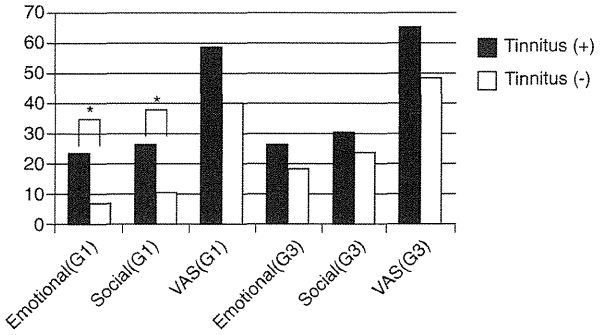

FIG. 4. Differences in the Hearing Handicap Inventory for Adults (HHIA) scores (emotional and social subscale) and Visual Analogue Scale (VAS) between patients who had tinnitus and those who did not in Groups 1 and 3. Emotional and social scores on the HHIA scale and VAS, in 2 groups of patients, some of whom also have tinnitus: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); and Group 3, bilateral SNHL. Those patients with unilateral sudden SNHL (Group 1) who also had tinnitus revealed significantly higher scores in the HHIA than those who were not affected. *: $p < 0.05$.

25.9 ± 12.1 (S) in Brazil (14) and 37.3 ± 16.7 (total); 21.9 ± 8.9 (E) and 15.4 ± 7.8 (S) in Italy (13). In the present study, the average score was 49.3 ± 13.6 (total); 22.4 ± 13.9 (E) and 27.0 ± 13.3 (S). Our results are therefore similar to those in the Brazilian study. The average score in the Italian study was slightly low because it seemed that the hearing threshold (hearing level from 29 to 71 dB) was also lower compared with the Brazilian subjects (hearing level from 26 to 93 dB) and the present subjects (hearing level from 35 to 115 dB). Some studies showed high correlations between the hearing handicap and degree of hearing loss in the population with bilateral hearing loss (15,17), and we confirmed weak correlations between the scores of HHIA or VAS and better ear pure-tone average in the bilateral SNHL group. Otherwise, the correlation could not be confirmed in the unilateral SNHL population. Among the population in our study, logistic regression analysis revealed that higher hearing loss level increased risk of severe hearing handicap in the HHIA score. We were also unable to confirm significant correlations between the duration of hearing loss and hearing handicap in the present study.

The HHIA and VAS scores of patients with unilateral sudden SNHL were significantly higher than in those with unilateral prelingual or congenital SNHL. This result reveals that unilateral postlingual deafness including sudden SNHL may be perceived as a hearing handicap for adults. Many patients with unilateral sudden hearing loss experience a hearing handicap in emotional and social situations. Hearing handicap, based on a score of greater than 18 in the HHIA, was previously reported in 73.1% (16) and 74.6% (17) of unilateral hearing impaired subjects. In our study, a hearing handicap was found in 69.8% of the subjects and high relative percentages of the HHIA (72.6%) and VAS (81.0%) scores were confirmed in the patients with unilateral sudden SNHL compared with those with bilateral SNHL. These scores showed that their experience of sudden SSD was almost as bad as the experience of patients with bilateral SNHL. However, subjects with unilateral prelingual or congenital SNHL revealed low relative percentages of the HHIA (25.1%) and VAS (50.3%) scores compared with subjects with bilateral SNHL. These findings thus emphasize that adults with sudden SSD experience this as a serious handicap. A greater risk of 6.69 times for severe hearing handicap in the HHIA score was found among the 3 groups. The factor of bilateral SNHL increased risk of hearing handicap in the HHIA score compared with that of unilateral sudden SNHL and the factor of unilateral sudden SNHL increased risk of the hearing handicap compared with that of unilateral precongenital SNHL.

Vicci de Araùjo et al. (10) have demonstrated a lower hearing handicap in male subjects compared with female subjects having unilateral hearing loss. However, our results show the opposite outcome, demonstrating a greater hearing handicap in male subjects compared with female subjects with either unilateral sudden or bilateral SNHL. Particularly, the outcome of the social subscale of HHIA in the unilateral sudden SNHL group was statistically significant. These findings reveal that unilateral sudden deafness may cause difficulties in life in a social environment. Disability of auditory function because of unilateral sudden deafness affects speech perception, communication in the presence of background noise, and social interaction. However, sex differences were insignificant risk factor for severe hearing handicap in the HHIA score.

The majority of people with unilateral sudden deafness experience tinnitus. Severe tinnitus can seriously impair the ability of patients to perform their activities in daily life and lower their quality of life. In the present study, the scores of HHIA and VAS were higher in patients who had tinnitus compared with those who did not feel tinnitus in Groups 1 and 3. The emotional and social subscales of HHIA were significantly higher in patients with unilateral sudden SNHL who had tinnitus. It is noteworthy that the risk of severe hearing handicap in the HHIA score among patients with tinnitus was approximately 3.71 times higher than that among those without tinnitus. The present study might indicate that unilateral sudden SNHL in adults with tinnitus causes significant hearing handicap with respect

TABLE 4. *Multiple logistic regression analysis predicting the risk of high score (>42) in the Hearing Handicap Inventory for Adults*

Variable	Odds ratio	*p*
Tinnitus	3.171	0.013
Age	1.021	0.041
Group	6.69	0.06
Average HL	1.031	0.001

HHIA indicates Hearing Handicap Inventory for Adults; Ave. HL, average hearing loss level.

Group: bilateral SNHL versus unilateral sudden SNHL versus unilateral precongenital SNHL.

to emotional and social consequences. Tinnitus adds a significant burden to those who experience this in addition to hearing loss. In recent years, cochlear implants have successfully been used to treat severe tinnitus in patients with SSD (8,9,18,19). In tinnitus cases treated with implants, 60% to 90% of patients with hearing loss revealed an improvement in perception (19). Moreover, the rehabilitation of patients with unilateral deafness with cochlear implants yields better results in speech comprehension and localization (9). We conclude that it is necessary to highlight treatment for unilateral sudden deafness in adults with tinnitus because adults who experience sudden unilateral hearing loss, particularly those who also experience tinnitus, find this a handicap in their daily lives.

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Correlations of Inflammatory Biomarkers With the Onset and Prognosis of Idiopathic Sudden Sensorineural Hearing Loss

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Hypothesis: We investigated whether inflammatory biomarkers and stress are involved in the pathophysiology of idiopathic sensorineural hearing loss (ISHL).
Study Design: Individual cohort study.
Setting: Two tertiary centers.
Patients: Forty-three ISHL and 10 non-ISHL patients seen in our ENT departments from 2004 to 2010 within a week from the onset of new symptoms and without steroid administration before visiting our departments.
Intervention: Multiple audiologic evaluations, blood tests including leukocyte counts, natural killer cell activity (NKCA), interleukin 6 (IL-6), tumor necrosis factor, high-sensitivity CRP (hCRP), and the General Health Questionnaire were used to evaluate the systemic stress and inflammatory response.
Main Outcome Measures: Correlations between biomarkers and ISHL severity and prognosis were evaluated by statistical analysis.
Results: In the ISHL patients, a neutrophil count above the reference range was associated with severe hearing loss and poor prognosis, and was accompanied by low NKCA and high IL-6. In the non-ISHL patients, these associations were not present. The abnormal neutrophil count was independent of preexisting vascular diseases. The abnormal counts responded to treatment and decreased into the reference range.
Conclusion: Neutrophil counts above the reference range of a facility will be a useful indicator of poor prognosis of ISHL. Synchronism of different types of NF-κB activation pathways could be required to cause severe ISHL. An NKCA decrease, an acute neutrophil count increase, and an IL-6 increase can induce NF-κB activation in the cochlea and cause severe ISHL. Further epidemiologic surveys should be conducted to evaluate whether stressful life events increase the risk of severe ISHL onset. **Key Words:** Idiopathic sensorineural hearing loss—Natural killer cell—Neutrophil—Stress response theory.

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A number of etiologies of idiopathic sudden sensorineural loss (ISHL) have been proposed, including viral infection, vascular disturbance, immune-mediated mechanisms, and membrane breaks. However, there is no conclusive evidence for any particular hypothesis (1–3). Recently, Merchant et al. (1,4) and Adams et al. (5) hypothesized that different kinds of systemic stress converge at abnormal activation of a transcriptional factor named NF-κB in the unilateral cochlear lateral wall and cause ISHL. In general, NF-κB plays a pivotal role in immune and inflammatory responses. Adams (6) demonstrated that intraperitoneal injection of lipopolysaccharide endotoxin (LPS) consistently resulted in activation of NF-κB in the lateral wall of the unilateral inner ear. Our past experiments using animals also demonstrated that NF-κB activation in the cochlear lateral wall is a cause of sensorineural hearing loss (7). In addition, we demonstrated that interleukin 6 (IL-6) upregulation in the lateral wall and tumor necrosis factor (TNF) upregulation in the cochlea tissue induced sensorineural hearing loss (8,9); both cytokines are involved in NF-κB–associated cellular stress pathways (10–12).

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TABLE 1. *Criteria for diagnosis of sudden deafness*

Main symptoms
1. Sudden onset of hearing loss; patient can say clearly when it appeared
2. Sensorineural hearing loss, usually severe
3. Unknown cause
Accessory symptoms
1. May be accompanied by tinnitus
2. May be accompanied by vertigo, nausea, and/or vomiting without recurrent episodes
3. No cranial nerve symptoms other than from the VIIIth nerve
I. Definite: all of the above criteria
II. Probable: main symptoms 1 and 2

Criteria established by the Sudden Deafness Research Committee of the Ministry of Health and Welfare in Japan (1973). It should be noted that patients with vertigo are not excluded, and there is no stated period and no definition of the level of hearing loss in the Japanese criteria.

To evaluate the systemic stress response theory of ISHL, we screened several biomarkers related to systemic stress and cochlear inflammation. First, we analyzed white blood cell counts and natural killer cell activity (NKCA), as they are enhanced and suppressed by systemic stress and have critical roles in the immune system (13,14). In addition, white blood cell counts are involved in the pathogenesis, reflect the severity, and predict the prognosis of cardiovascular and cerebrovascular diseases (15–18). Next, we analyzed the IL-6 and TNF. IL-6, in particular, could have an important role in NF-κB–associated cochlear injuries because there is a positive feedback loop involving IL-6 and NF-κB (10). Finally, we analyzed high-sensitivity C-reactive protein (hCRP) because higher levels of hCRP and IL-6 are associated with a higher likelihood for small tissue damage such as a cerebral infarction less than 10 mm in diameter (19–21).

METHODS

Subjects

Diagnosis of ISHL was based on the criteria of the Sudden Deafness Research Committee of the Japanese Ministry of Health, Labor and Welfare (Table 1). Patients with vertigo were not excluded as in recent reports (22–24) because there is no internationally verified evidence that the acute sensorineural hearing loss with vertigo results from a specific cause, and it is thus still considered idiopathic.

Other inclusion criteria for this study were as follows: visiting our departments within 1 week (1w) after onset of symptoms, no history of steroid treatment by a previous physician, and no abnormal findings causing hearing loss on a magnetic resonance imaging. HL was defined as an average of pure-tone threshold at 0.25, 0.5, 1, 2, and 4 kHz. Patients with abnormal HL of the contralateral ear were excluded. We calculated the 95 percentile HL of otologically normal population at a given age using International Organization for Standardization 7029. If HL was above the 95 percentile, we defined the HL as abnormal. The past and present medical history was taken in detail, and the patients with current symptoms of infection and with medications modulating the immune system were excluded. Forty-three patients with ISHL (male:female, 23:20; age, 57 ± 15 yr) fit within the above conditions.

To compare the biomarker profile, 10 non-ISHL patients (male:female, 2:8; age, 52 ± 15 yr) were also included in the present study. They were 4 patients with Ménière's disease, 3 with fluctuating sensorineural hearing loss without vertigo, 2 with suspected perilymph fistula, and 1 with bilateral progressive sensorineural hearing loss. They visited our departments within 1w after onset of the acute change of symptoms, such as acute deterioration of hearing or acute increase of tinnitus

TABLE 2. *Variables of the idiopathic sensorineural hearing loss and non–idiopathic sensorineural hearing loss patients*

	ISHL	n	non-ISHL	n
Hearing level[a] of affected ear, dB	76 ± 24	43	68 ± 13	10
Average recovery rate[b] at 1w, %	52 ± 37	40	Not calculated[c]	
Average final recovery rate, %	73 ± 35	43	Not calculated	
Neutrophil count, /μl	4220 ± 1743	38	3313 ± 1098	10
No. of patients whose neutrophil counts was above the normal limit	5 (13%)		0 (0%)	
Lymphocyte count, /μl	1753 ± 548	38	1589 ± 384	10
Monocyte count, /μl	308 ± 105	38	217 ± 58[d]	10
IL-6, pg/ml	1.3 ± 0.8	43	1.5 ± 2.1	10
TNF, pg/ml	1.0 ± 0.4	43	1.2 ± 0.3	10
hCRP, ng/ml	706 ± 1549	38	754 ± 1547	10
NKCA, %	30 ± 13	40	31 ± 14	10
GHQ	5 ± 4	21	No data	

Variables at the first visit are shown. Variables are shown in mean ± standard deviation.

1w indicates 1 week after starting the treatment; final, the values 2 months or more after starting the treatment; GHQ, General Health Questionnaire; hCRP, high-sensitivity C-reactive protein; HL, hearing level; IL-6, interleukin-6; ISHL, idiopathic sudden sensorineural hearing loss; NKCA, natural killer cell activity; TNF, tumor necrosis factor;

[a]HL, average hearing level of 250 Hz, 500 Hz, 1 kHz, 2 kHz, and 4 kHz;

[b]Recovery rate. Please note that recovery rate does not represent how many patients are cured at a certain time. Rather, it represents how much hearing loss is recovered at a certain time, compared with the affected hearing level at the first visit (please see Methods for details).

[c]The HL of non-ISHL patients fluctuated, and the contralateral HLs were not necessarily normal. Therefore, recovery rate could not be calculated.

[d]Only monocyte counts were significantly different between the 2 groups (t test, $p < 0.05$).

loudness. They had no history of steroid treatment by a previous physician after the latest acute change of symptom. Their contralateral HLs were not necessarily within normal limit.

Blood samples were taken at the first visit, and then, all ISHL patients were given intravenous administration of corticosteroid, vitamin B_{12} and adenosine triphosphate from 7 to 12 days as a standard treatment. The patients were followed for more than 2 months or less than 2 months if hearing loss disappeared completely before that time.

The study was approved by the local ethics committee of both universities, and informed consent was obtained from the patients.

Hearing Level Evaluation

HL was evaluated at the initial visit and at 1w, 3 or 4 w, and 2 months or more afterward. If the patient did not respond to the maximum sound level produced by the audiometer, we defined the threshold as 5 dB more than the maximum level.

Recovery rate (RR) (%) was calculated by dividing the hearing gain by the difference in initial hearing level between the affected and unaffected sides according to previous articles (25,26). The formula is as follows: RR (%) = (initial HL of the affected ear – HL of the affected ear at a time point on the time course) / (initial HL of the affected ear – HL of the unaffected ear).

Biomarker Examinations

No patients were given any corticosteroids before collecting the first blood samples. If possible, blood samples were taken 2 times at the first visit and 1w or more after completing the standard treatment. By collecting samples before steroid administration and by waiting to collect samples until a week or more after completion of steroid treatment, we excluded confounding factors of biomarkers from steroid administration like wide fluctuation of neutrophil counts and differences in patients' acute responses to steroid at the 2 time points. The following variables were measured and analyzed: neutrophil, lymphocyte, and monocyte counts, NKCA, IL-6, TNF, and hCRP. NKCA was measured with ^{51}Cr-releasing assay. IL-6 was measured with chemiluminescent enzyme immunoassay. TNF was measured with enzyme-linked immunosorbent assay.

These measurements were performed by SRL, Inc. (Tokyo, Japan), except for the leukocyte counts, which were analyzed by the on-site clinical laboratories of each university. All measurements were made by the same laboratory for each patient during the measurement time course. Neutrophil counts, NKCA, and IL-6 of ISHL patients were taken in 38, 40, and 43 patients at the first visit, respectively. The sample numbers of other variables were shown in Table 2. A neutrophil count was taken multiple times after the first visit in 19 patients.

It is known that baseline neutrophil counts are relatively stable in individuals but have a considerable normal range in healthy humans (27). Consistent with this knowledge, reference ranges of the neutrophil count at Keio University Hospital and Iwate University Hospital are 1,400 to 5,950 and 1,610 to 5,950/μl, respectively, and the ranges are the same for male and female subjects. Therefore, the upper limit of the normal neutrophil count was defined as 5,950/μl. For NKCA, IL-6, and TNF, reference ranges of Japanese population were not determined.

General Health Questionnaire

Subjective physical and psychological statuses of 21 patients were assessed via the Japanese version of the 28-item General Health Questionnaire (GHQ) (28,29); the Likert method was used to score the GHQ values, including somatic symptoms, anxiety and insomnia, social dysfunction, and depression subscales (30). The maximum score is 28, and a healthy person should have a score of less than 5.

Data Analysis

To analyze the strength of the relationships between HL, RR, and biomarkers, we conducted Pearson's or Spearman's correlation analysis. The latter method was used to analyze correlations between hCRP and variables because the standard deviation of the values was high and not appropriate for Pearson's analysis. Although the correlation analysis is useful for showing linear association between variables, associations between clinical symptoms and biomarkers are not necessarily linear. Therefore, the associations were also evaluated by categorizing patients into biomarker quartiles. In addition, the differential counts of leukocytes are well-documented standardized markers of inflammation in every clinical laboratory in the world. Therefore, the patients were classified into 2 groups: either outside of or within the reference range of the neutrophil count. To evaluate the differences of the means of the biomarkers between 3 or more patient groups, analysis of variance (ANOVA) followed by Tukey's multiple comparison test was used. To evaluate the differences and changes of variables between the 2 groups, the *t* test,

TABLE 3. *Correlation coefficients and p values of correlation analysis between severity, prognosis, biomarkers, and General Health Questionnaire in patients with idiopathic sensorineural hearing loss*

	HL	1w RR	Final RR	Neut
HL		−0.67, 0.000009	−0.60, 0.00005	0.64, 0.00001
1w RR	−0.67, 0.000009		0.87, 5×10^{-12}	−0.63, 0.00003
Final RR	−0.60, 0.00005	0.87, 5×10^{-12}		−0.63, 0.00002
Neut	0.64, 0.00001	−0.63, 0.00003	−0.63, 0.00002	
Lym	NS	NS	NS	NS
Mono	NS	NS	NS	NS
NKCA	NS	NS	NS	−0.46, 0.005
IL-6	NS	NS	NS	0.44, 0.005
TNF	NS	NS	NS	NS
hCRP	0.38, 0.03	NS	NS	0.49, 0.004
GHQ	NS	NS	NS	NS

The first value in each parenthetical set is the correlation coefficient and the second one is *p*.
HL indicates HL at the first visit; Lym, lymphocyte count; Mono, monocyte count; Neut, neutrophil count; NS, not significant; RR, recovery rate.

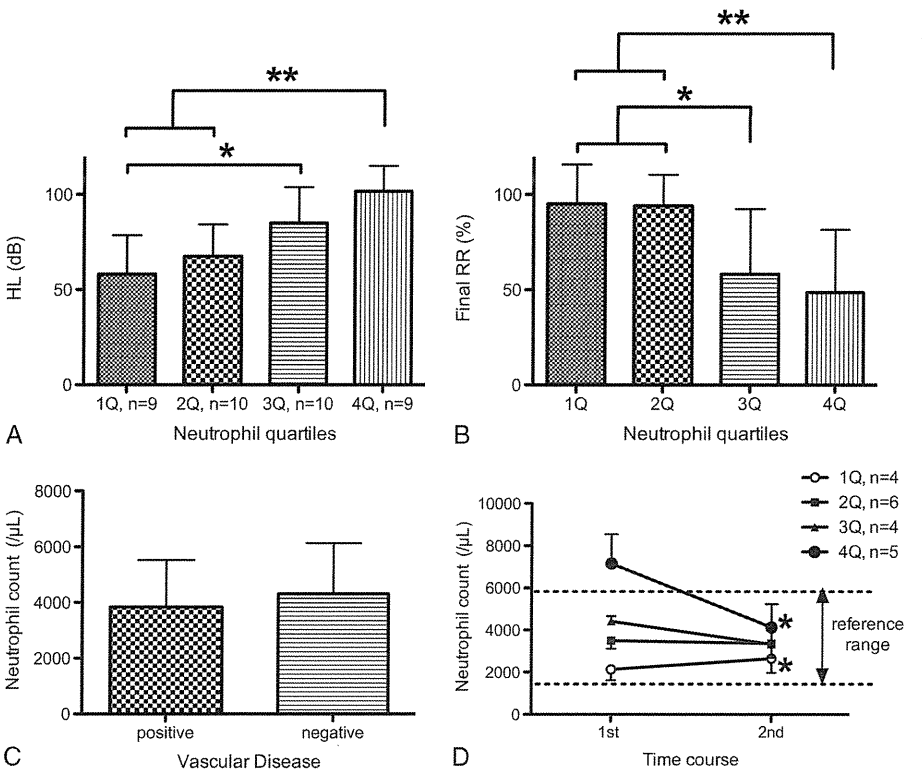

FIG. 1. The relationship between neutrophil quartile at the first visit, hearing level at the first visit (HL), and the final recovery rate (RR). The patients were classified according to the quartile of neutrophil counts: the first quartile (1Q, <2890/μl), the second (2Q, 2890–3912/μl), the third (3Q, 3912–4963/μl), and the fourth (4Q, >4963/μl). The 4Q patients showed worse HL (*A*) and the final RR (*B*) than patients of lower 2 quartiles. Patients in 3Q showed worse HL and the final RR than those in 1Q and 2Q, respectively. The neutrophil count did not show a significant difference between patients with and without vascular diseases (*C*). The change of neutrophil counts was observed at the first visit (first) and 1w or more after completion of steroid administration (second) (*D*). The counts of 4Q significantly changed from above the reference range to within the range. The change of 1Q was also significant, but the values were within the reference range at both time points. ** and * indicate $p < 0.01$ and $p < 0.05$, respectively, with ANOVA followed by Tukey's test.

Mann-Whitney *U* test, or the paired *t* test were used as shown in the legend. $p < 0.05$ was considered significant.

RESULTS

Variables of ISHL and non-ISHL evaluated in the first visit are summarized in Table 2. There was no statistical difference in the variables between the 2 patient groups, except for monocyte counts. Five of 38 ISHL patients showed neutrophil counts above the reference range, whereas no non-ISHL patients showed counts above the range. No patients showed counts below the range in either group.

Correlations between variables are summarized in Table 3. The correlation between RR 1w after starting treatment (1w RR) and RR at the final time point (final RR) showed strong statistical significance in ISHL patients ($r = 0.87$, $p = 5 \times 10^{-12}$). The neutrophil count at the first visit (Neut) was correlated with HL at the first visit, the 1w RR, and the final RR ($r = -0.64$, -0.63, and -0.63; $p = 0.00001$, 0.00003, and 0.00002, respectively). It was also correlated with NKCA and IL-6 ($r = -0.46$ and 0.44; $p = 0.005$ and 0.005, respectively). The total values of 4 subscales of GHQ did not show correlation with any variable. TNF was not significantly correlated with HL, the 1w RR, and the final RR.

In non-ISHL patients, biomarkers were not correlated with other variables.

Consistent with the correlation analysis, the uppermost quartile of the neutrophil counts (the fourth quartile, 4Q in Fig. 1, ≥4963/μl) showed significantly higher HL (A) and worse final RR (B) than the lower 2 quartiles (the first and the second quartiles, 1Q and 2Q, <3912/μl) ($p < 0.001$). The second uppermost quartile (the third quartile, 3Q, 3912-4963/μl) also showed significantly higher HL and the final RR than the first quartile (1Q, <2890/μl) and the lower two quartiles ($p < 0.05$), respectively. In addition, there was no difference of neutrophil counts between patients with and without past or present histories of vascular diseases (e.g., hypertension, coronary artery disease, stroke, diabetes, hyperlipidemia) ($p = 0.44$; Fig. 1C).