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Original Article

Secondary Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss in the Subacute and Chronic Phases

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This study investigated the efficacy of hyperbaric oxygen therapy (HBOT) as a secondary treatment for patients with idiopathic sudden sensorineural hearing loss (ISSNHL) in the subacute and chronic phases. Forty-eight ISSNHL patients (HBOT group) who had received primary conventional treatment within 4 weeks after onset and underwent HBOT between 4 and 20 weeks post-onset were retrospectively compared with 44 ISSNHL patients (control group) with primary conventional treatment alone. Mean hearing gain was slight, with gains of 5.2 ± 8.9 dB in the HBOT group and 2.0 ± 7.6 dB in the control group. However, no significant difference was recognized between the two groups. In the HBOT group, no significant difference was observed in hearing gain among patients with HBOT initial time at 4-7, 8-11, 12-15 or 16-20 weeks after onset. Meanwhile, hearing gain was significantly higher in patients with profound hearing loss than in the other patients. We conclude that the effectiveness of secondary HBOT for ISSNHL patients in either subacute or chronic phase remains unproven, and thus, the decision administer HBOT should be made with caution.

Key words: sudden sensorineural hearing loss; idiopathic; hyperbaric oxygen therapy; secondary treatment

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a rapid loss of hearing over a period of up to 3 days, and is diagnosed when pure-tone audiometory shows hearing loss (HL) of ≥30 dB in three connected frequencies [1]. Therapeutic measures include administration of systemic and intratympanic corticosteroids, antiviral and hemodilution agents, minerals and vitamins. However, effective treatments have yet to be established [2, 3].

In hyperbaric oxygen therapy (HBOT), a patient breathes 100% oxygen at a pressure level higher than 1 atmosphere absolute (ATA) in a mono-place or multi-place chamber. HBOT is thought to have complex effects on immunity, oxygen transport and hemodynamics, resulting in favorable effects by reducing hypoxia and edema and enabling normal host responses to infection and ischemia [4]. Although the true etiology remains uncertain, vascular pathologies have been proposed as causes of HL in ISSNHL. HBOT is administered for ISSNHL to improve circulatory impairments, including ischemia and hypoxia in the inner ear.

HBOT is applied for ISSNHL as a primary or secondary therapy. A primary single treatment of HBOT showed a significant improvement in hearing in comparison to intravenous injections of either buflomedil or pentoxifylline [5, 6]. Addition of primary HBOT therapy to standard pharmacotherapy did not provide any benefit in some reports [7, 8], while addition of primary HBOT resulted in significantly better outcomes than standard pharmacotherapy alone in other reports [9, 10].

Numerous reports have examined HBOT as a

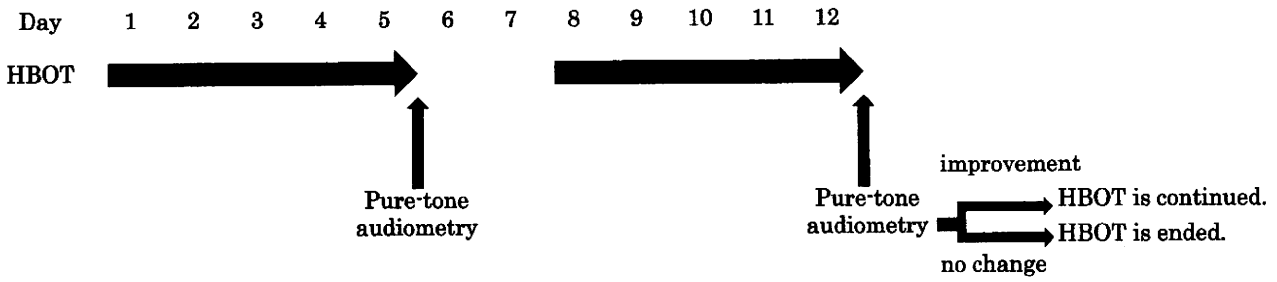

Figure 1 : HBOT protocol
HBOT was performed every weekday for 2 weeks, with PTA measured once a week. HBOT was continued when any improvement in audiometric thresholds was recognized by the end of 10 sessions.

secondary treatment following an unsuccessful treatment regimen. Lamm et al. [11] analyzed of 2,338 patients with ISSNHL, acoustic trauma, or acute noise-induced HL from 46 previously reported papers, and concluded that HBOT was effective for patients who received the therapy between 2 and 6 weeks after primary conventional therapy. However, patients who received HBOT ≥4 weeks after HL onset should be evaluated to determine the effectiveness of for subacute or chronic phases of ISSNHL, as a large proportion of hearing recovery in ISSNHL typically occurs within 1 month after onset [1, 12]. Furthermore, improvements in hearing among patients who received HBOT should be compared with the natural history of ISSNHL, as the possibility of some spontaneous recovery in hearing as late as 4 months post-treatment has been reported [13]. The present study therefore evaluated the efficacy of secondary HBOT in patients who failed to achieve good hearing outcomes from primary standard pharmacotherapy, and to elucidate the point up to which HBOT remains valuable as a treatment for ISSNHL.

Patients, Materials and Methods

Between April 2001 and November 2008, a total of 428 patients with ISSNHL visited the Department of Otolaryngology in Tokyo Medical and Dental University Hospital for treatment and received HBOT at the Hyperbaric Medical Center. Among these 428 patients, we enrolled 48 patients (HBOT group) who underwent HBOT ≥4 weeks after onset of ISSNHL without any other treatments. These patients were referred to our hospital for HBOT as a secondary treatment after primary treatment had failed. The time of initiating HBOT ranged from 4 to 20 weeks, with a mean of 7.4 weeks after HL onset (4-7 weeks, n=29; 8-11 weeks, n=13; 12-15 weeks, n=4; 16-20 weeks, n=2). The multi-place chamber (NHC-412-A; Nakamura Tekko-sho, Tokyo, Japan) is pressurized with air to 2.0 ATA, then the patient breathes 100% oxygen through a mask delivery system for 60 min, every weekday for 2 weeks (10 sessions in total) (Fig. 1). A tympanic tube was inserted in some patients or HBOT was cancelled in other patients if any problems including otalgia or otitis media arose. HBOT was continued when any improvement in audiometric thresholds was recognized at the end of the 10 sessions. The number of sessions was thus adjusted for each patient, with a mean of 13.0 sessions (range, 4-43 sessions).

In addition, the study enrolled 44 patients (control group) with ISSNHL who had received treatment of corticosteroids, vitamins and adenosine triphosphate without HBOT in our department within 4 weeks after onset of ISSNHL, but failed to achieve complete hearing recovery, and had received no further treatments after primary therapy. In our primary therapy, corticosteroids were administered as 10 mg/day of intravenous betamethasone followed by tapered doses for 10 days, or 30 mg/day of oral prednisolone followed by tapered doses for 12 days.

All patients met the following inclusion criteria: 1) rapid onset of unilateral sensorineural HL with unknown etiology; 2) pure-tone average (PTA) at onset of HL ≥30 dB; 3) PTA in the unaffected contralateral ear <30 dB; and 4) no finding of vestibular schwannoma on magnetic resonance imaging. Pure-tone audiometry was performed to evaluate HL by obtaining audiometric thresholds, representing the minimum audible sound levels at frequencies of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. PTA was defined as the average of audiometric thresholds (dB) at frequencies of 250, 500, 1000, 2000 and 4000 Hz. When the patient did not respond to the maximum sound level, 5 dB was added to the level for statistical analysis.

PTA-1 was defined as the PTA of an affected ear

Table Ⅰ. Profiles of HBOT and control groups

	HBOT group (n=48)	Control group (n=44)	*p* value
Age (mean ± SD in year)	46.5 ± 13.5	51.8 ± 17.0	0.06[a]
Sex (male/female in number)	27/21	19/25	0.21[b]
Dizziness and/or vertigo (in number)	14	16	0.46[b]
PTA-1 (mean ± SD in dB HL)	63.8 ± 21.9	57.4 ± 23.6	0.07[a]

HBOT, hyperbaric oxygen therapy; SD, standard deviation; PTA, pure-tone average
[a]Mann-Whitney U test; [b]χ^2 test

Table Ⅱ. HBOT initial time and hearing outcome

	HBOT initial time (weeks)				*p* value
	4-7 (n=29)	8-11 (n=13)	12-15 (n=4)	16-20 (n=2)	
Hearing gain (mean ± SD in dB)	7.8 ± 9.7	1.2 ± 4.8	4.0 ± 6.4	-4.0 ± 8.5	0.06[a]
Classification of hearing gain					
Good	1	0	0	0	
Fair	8	1	1	0	
No change	20	12	3	2	

HBOT, hyperbaric oxygen therapy; SD, standard deviation
[a]Kruskal-Wallis test

immediately before HBOT in the HBOT group, or 4 weeks after onset of HL in the control group. Severity of PTA-1 was categorized as mild (PTA-1 <40 dB), moderate (PTA-1 ≥40 dB but <60 dB), severe (PTA-1 ≥60 dB but <90 dB) or profound (PTA-1 ≥90 dB). PTA-2 was defined as the PTA when no apparent change in PTA was recognized >23 weeks after onset of HL. Hearing gain was estimated from the difference between PTA-1 and PTA-2. The degree of hearing gain was classified as "good" (hearing gain ≥30 dB), "fair" (hearing gain <30 dB but ≥10 dB) or "no change" (hearing gain <10 dB). HBOT initiation time was defined as the time between onset of HL and initiation of HBOT.

Analyses of categorical data (sex, presence of dizziness and/or vertigo and classification of hearing gain) were performed using the χ^2 test or Fisher's exact test. Analyses of continuous data (age, PTA-1 and hearing gain) were performed using the Mann-Whitney U test. Comparisons between HBOT initial time and hearing outcome were performed using the Kruskal-Wallis test. Comparisons between severity of PTA-1 and hearing outcome in the HBOT group were performed using the Kruskal-Wallis test with post hoc Tukey-Kramer test. Differences were considered to be significant for values of $p<0.05$. Statistical analyses were performed using JMP 7.0.1 statistical software (SAS Institute).

The HBOT has already been established as a standard therapy for patients with ISSNHL. The above procedure was preformed after obtaining approval from patients and in accordance with the ethical standards of the Helsinki Declaration.

Results

Patient profiles

Profiles of the HBOT and control groups are summarized in Table Ⅰ. No significant differences in age, sex, presence of dizziness and/or vertigo at onset of HL or PTA-1 were seen between groups. Severity of PTA-1 in the HBOT and control groups was categorized as mild in 3 and 10 patients, moderate in 22 and 20, severe in 16 and 8 and profound in 7 and 6, respectively.

HBOT initial time and hearing outcome in HBOT group

The relationship between HBOT initial time and hearing outcome is shown in Table Ⅱ. Mean hearing gain was 7.8 ± 9.7 dB in patients with HBOT initiation time of 4-7 weeks, slightly higher than in the other

Table Ⅲ. Severity of PTA-1 and hearing outcome in HBOT group

	Severity of PTA-1				p value
	Mild (n=3)	Moderate (n=22)	Severe (n=16)	Profound (n=7)	
Hearing gain (mean ± SD in dB)	2.3 ± 3.5	2.1 ± 5.3	4.4 ± 6.3	18.3 ± 13.2	0.03[a]
Classification of hearing gain					
Good	0	0	0	1	
Fair	0	3	3	4	
No change	3	19	13	2	

PTA, pure-tone average; SD, standard deviation
[a]Kruskal-Wallis test

Table Ⅳ. Overall hearing outcome

	HBOT group (n=48)	Control group (n=44)	p value
Hearing gain (mean ± SD in dB)	5.2 ± 8.9	2.0 ± 7.6	0.09[a]
Classification of hearing gain			0.28[b]
Good	1	0	
Fair	10	5	
No change	37	39	

HBOT, hyperbaric oxygen therapy; SD, standard deviation
[a]Mann-Whitney U test; [b]Fisher's exact test

groups (8-11 weeks, 1.2 ± 4.8 dB; 12-15 weeks, 4.0 ± 6.4 dB; 16-20 weeks, -4.0 ± 8.5 dB). The number of patients categorized as showing "good" or "fair" hearing gain was 9 with HBOT initial time of 4-7 weeks, but 1 at 8-11 weeks, 1 at 12-15 weeks and 0 at 16-20 weeks. One patient with "good" hearing gain started HBOT at 5 weeks after onset of HL. However, no significant difference in mean hearing gain was seen among HBOT initial times (Kruskal-Wallis test, p=0.06).

Severity in PTA-1 and hearing outcomes in HBOT group

The relationship between severity in PTA-1 and hearing outcome in the HBOT group is shown in Table Ⅲ. A significant difference in mean hearing gain was seen between each subgroup (Kruskal-Wallis test, p=0.03). Mean hearing gain was 18.3 ± 13.2 dB in patients with profound HL, significantly higher than the 2.3 ± 3.5 dB with mild HL, 2.1 ± 5.3 dB with moderate HL and 4.4 ± 6.3 dB with severe HL (post-hoc by Turkey-Kramer test: p=0.01, <0.0001 and 0.0005, respectively). Five of the 7 patients (71%) with profound HL obtained "good" or "fair" hearing gain, while all patients with mild HL showed "no change".

Overall hearing outcome

Table Ⅳ shows overall hearing outcomes. Mean hearing gain was 5.2 ± 8.9 dB in the HBOT group, slightly higher than the 2.0 ± 7.6 dB in the control group. However, no significant difference in hearing gain was seen between the two groups (Mann-Whitney U test, p=0.09). According to the hearing gain classification, a "good" hearing gain was obtained in 1 of 48 patients (2%) in the HBOT group, but in no patients from the control group. A "fair" hearing gain was seen in 10 of 48 patients (21%) in the HBOT group and 5 of 44 patients (11%) in the control group, whereas "no change" was seen in 37 of 48 patients (77%) in the HBOT group and 39 of 44 patients (88%) in the control group. However, no significant difference in hearing gain classification was noted between the two groups (Fisher's exact test, p=0.28). Severity according to PTA-1 in 5 control patients with "fair" hearing gain was categorized as moderate in 2, severe in 1 and profound in 2. The "fair" hearing gain recognized in the control group was thought to have occurred naturally. No patients in either group showed complete hearing recovery.

When hearing gain was evaluated at each severity of

PTA-1, mean hearing gains in the HBOT and control groups were 2.3 ± 3.5 dB and -1.6 ± 5.7 dB for mild PTA-1, 2.1 ± 5.3 dB and 2.0 ± 7.7 dB for moderate PTA-1, 4.4 ± 6.3 dB and 4.8 ± 7.4 dB for severe PTA-1 and 18.3 ± 13.2 dB and 4.5 ± 9.2 dB for profound PTA-1, respectively. However, no significant difference in hearing gain was seen at each severity of PTA-1 between HBOT and control groups (Mann-Whitney U test, mild PTA-1: p=0.3, moderate PTA-1: p=1.0, severe PTA-1: p =0.6 and profound PTA-1: p=0.08, respectively).

Discussion

The nature of ISSNHL remains unclear, but vascular insufficiency of the cochlear artery is a popular theory. Yamasoba et al. [14] identified slow blood flow within the vertebrobasilar arteries in some patients with ISSNHL. Capaccio et al. [15] found an association between acquired prothrombotic risk factors and related genetic variants in ISSNHL. These findings support the concept of a vascular pathology. In fact, perilymphatic oxygen tension appears to be significantly decreased in patients with ISSNHL [16]. The results of an experimental animal study showed that cochlear hypoxia could be immediately and fully compensated by HBOT, but not by isobaric oxygenation [17].

In most patients with ISSNHL, hearing improves within 1 month after the onset of HL [1, 12]. However, the natural history of ISSNHL can affect the therapeutic evaluation. Slattery et al. [18] reported the possibility of some spontaneous recovery in hearing as late as 4 months after starting treatment. Yeo et al. [12] demonstrated delayed recovery beyond the first month after discharge in 22% of patients. In the present study, 5 patients (11%) in the control group showed a "fair" hearing gain ≥4 weeks after onset of HL, supporting those previous reports [12, 18].

The period during which HBOT can be effective as a secondary treatment remains uncertain. Kau et al. [19] examined the efficacy of secondary HBOT in 359 patients with acute and chronic inner ear disorders, including ISSNHL. They divided patients into groups with HL duration <3 months and ≥3 months, and found that HBOT was beneficial only to HL <3 months after onset. However, this report did not evaluate the efficacy of HBOT for HL in the subacute phase, as HL in the acute and subacute phases was mixed in the group with HL duration <3 months. Desloovere et al. [20] reported the effectiveness of secondary HBOT at 2.5 ATA for ISSNHL patients who received HBOT within 3 months after onset, with a decrease in hearing gain with increasing time delay. However, that study also did not specifically analyze patients with subacute ISSNHL. The present study compared the HBOT group with the control group at ≥4 weeks after onset. A slightly higher mean hearing gain was obtained in the HBOT group than in the control group. The rate of patients with a "good" or "fair" hearing gain was higher in the HBOT group (23%) than in the control group (11%). However, no significant differences in hearing gain or hearing classification were apparent between the two groups. Findings regarding overall hearing outcome suggested that the effectiveness of secondary HBOT for patients with subacute or chronic ISSNHL remains unproven.

Earlier treatment with HBOT results in better hearing outcomes [11, 20, 21]. In the present study, patients with HBOT initiation time of 4-7 weeks obtained slightly better hearing outcomes than other patients in the HBOT group. Furthermore, only patients with "good" hearing gain were started on HBOT at 5 weeks after onset of HL. However, no significant differences were found in mean hearing gain among each HBOT initial time in the HBOT group.

The association between initial hearing level and prognosis of hearing remains contentious [9, 22, 23]. Fetterman et al. [22] reported that the severity of HL was hard to recover. On the other hand, Topuz et al. [9] reported HBOT as more effective in more severe HL. In the present study, patients with profound HL showed significantly better hearing outcomes than other patients in the HBOT group. Actually, nearly 70% of all patients with profound HL obtained "good" or "fair" hearing gain.

The current statistical findings regarding overall hearing outcome indicate the effectiveness of HBOT for patients with subacute or chronic ISSNHL remains unproven. Furthermore, some patients have also shown worsening of hearing after HBOT [7]. A recent systematic review of randomized controlled trials showed that HBOT improved hearing, but the clinical significance of the level of improvement is unclear [24]. Routine application of HBOT to patients with ISSNHL was not justified according to that review. Taken together, secondary HBOT should only be carefully administered for patients with ISSNHL after unsuccessful conventional treatment.

Strict estimation of the efficacy of HBOT for ISSNHL might be difficult, as the pathological condition of ISSNHL in enrolled patients is potentially heterogenous and the number of HBOT sessions varies widely between patients. To address this problem, a

prospective study of a large number of patients is needed.

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The Laryngoscope

Association of the C677T Polymorphism in the Methylenetetrahydrofolate Reductase Gene With Sudden Sensorineural Hearing Loss

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Objectives/Hypothesis: To investigate the recently reported association of the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene with sudden sensorineural hearing loss (SSNHL), we analyzed data from a community-based Japanese population.

Study Design: Nested case-control study.

Methods: Among 2,174 adults (1,096 males and 1,078 females) aged 40 to 79 years old who participated in the National Institute for Longevity Sciences–Longitudinal Study of Aging, we compared 33 cases of prevalent SSNHL, defined as a self-reported otolaryngologist diagnosis, with the other cases. Multiple logistic regression was used to obtain odds ratios (ORs) for SSNHL in subjects with the MTHFR C677T polymorphism, with adjustment for other possibly influential factors under additive, dominant, and recessive genetic models.

Results: The per-allele ORs for SSNHL risk were 1.687 (95% confidence interval [CI], 1.023–2.780) in model 1, with adjustment for age and sex, and 1.654 (CI, 1.003–2.728) in model 2, with adjustment for smoking status, body mass index, histories of heart disease, hypertension, and diabetes, in addition to the factors in model 1. In model 3, a significant association between SSNHL and the C677T polymorphism was observed under all genetic models independent of factors including folic acid and homocysteine, although there were only 25 cases and 1,677 controls due to the addition of moderating factors.

Conclusions: Our results suggest that the T allele of MTHFR C677T could be associated with susceptibility to SSNHL, and even imply that this mutation could be a risk factor that is independent of blood folic acid and homocysteine.

Key Words: Methylenetetrahydrofolate reductase, polymorphism, sudden hearing loss, nested case-control study.

Level of Evidence: 2b.

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INTRODUCTION

Sudden deafness, or idiopathic sudden sensorineural hearing loss (SSNHL), remains an inexplicable disease with no identified specific cause. In Japan, it is considered a high-priority topic of investigation, and several nationwide epidemiologic surveys on sudden deafness have been performed by the Research Committees on Sudden Deafness, Acute Profound Deafness and Epidemiology of Intractable Diseases in the Ministry of Health and Welfare.[1,2]

Recently, an association between genetic risk factors and SSNHL has been reported. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme involved in the remethylation of homocysteine to methionine. The C677T mutation, which causes an amino acid change from alanine to valine and renders the enzyme thermolabile, is the most common genetic cause of hyperhomocysteinemia.[3] This substitution leads to a 30% decrease in the enzyme's activity in heterozygotes and a 60% decrease in homozygotes.

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Homocysteine is an amino acid that functions in the promotion of platelet activation, hypercoagulability, the oxidative stress response, endothelial dysfunction, and smooth muscle cell proliferation.[4] Hyperhomocysteinemia is believed to promote atherosclerosis and atherothrombosis as risk factors for macroangiopathies such as cerebrovascular disease and coronary disease,[5,6] and for microvessel diseases such as diabetic nephropathy and retinopathy in diabetic patients.[7] Although an association between SSNHL and the MTHFR C677T polymorphism in combination with some other genetic alterations has been reported,[8–10] conflicting results have been presented,[11] and it remains unknown whether the MTHFR C677T polymorphism is associated with SSNHL in isolation.

We retrospectively genotyped the MTHFR gene at position 677 in a case-control study nested within the Longitudinal Study of Aging (33 SSNHL cases and 2,141 controls). The association of the MTHFR polymorphism with a history of SSNHL, defined as a self-reported otolaryngologist diagnosis, was assessed, and possible confounds were considered.

MATERIALS AND METHODS

Subjects

The present study derives its subjects from the comprehensive Longitudinal Study of Aging (NILS-LSA), an ongoing population-based study with a 2-year follow-up, conducted by the National Institute for Longevity Sciences. Participants in the NILS-LSA are citizens selected randomly from a database stratified by both age and gender, in cooperation with the local government. The details of the NILS-LSA have been described elsewhere.[12,13] All procedures for the study were reviewed by the ethical committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

For purposes of the present report, 2,174 participants (1,096 males and 1,078 females) aged 40 to 79 years old, who completed the first-wave examinations of NILS-LSA between November 1997 and April 2000, were selected. Participants filled out a series of questionnaires designed to obtain demographic characteristics and information on the presence of various medical problems. SSNHL was defined as a self-reported otolaryngologist diagnosis, and then the participants were divided for analysis into cases and controls according to the presence or absence of SSNHL history.

MTHFR Genotype Analysis

Genomic DNA was extracted from peripheral blood lymphocytes using the standard procedure. The genotype (C or T) at position 677 of the MTHFR gene was determined by the allele-specific primer-polymerase chain reaction (ASP-PCR) method (Toyobo Gene Analysis, Tsuruga, Japan). The single nucleotide polymorphism region of the gene was amplified by PCR with two ASPs (C-specific primer: 5′-GAAGGTGTCTGCGG GAXCC-3′, T-specific primer: 5′-GAGAAGGTGTCTGCGGGAXTC-3′), and a biotin-labeled common antisense primer (5′-biotin-GAATGTGTCAGCCTCAAAGAAA-3′). Details of MTHFR genotyping in the NILS-LSA have been given elsewhere.[14] The validity of the ASP-PCR method was confirmed with genotyped DNA samples obtained by the standard method reported by Frosst et al.[3] KOD polymerase derived from *Thermococcus kodakaraensis* KOD1 was used.[15] The fidelity of this method is 3.4 times higher than that obtained using Taq DNA polymerase. The mutation rate with this method is 0.35%.[15]

Measures

Audiometric measurements were performed on the same day as the blood draw. Air-conduction pure-tone thresholds at octave intervals from 0.5 to 8 kHz were obtained using a diagnostic audiometer (AA-73A; Rion, Tokyo, Japan). The average hearing threshold (AHT) level for frequencies of 0.5, 1, 2, and 4 kHz was calculated for the better ear to quantify the prevalence of hearing impairment under the common definition across genotypes. Hearing impairment was defined as at AHT >25 dB according to the World Health Organization grades.[16]

Participant information including occupational noise exposure, lifetime smoking, histories of heart disease and hypertension was obtained from the self-reported account. Occupational noise was defined in our questionnaire as background noise in a work environment over which the worker could not hold a conversation in a normal voice. History of occupational noise exposure and lifetime smoking history were categorized as never or ever. The definition of diabetes was based on the medical history obtained by the questionnaire. We also classified as diabetic any subject with a fasting plasma glucose concentration >126 mg/dL and an HbA1c of more than 6.5% and any subject taking medication to lower blood glucose levels. Each of these was treated as a binary variable (presence vs. absence). Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Venous blood samples were collected, with the agreement of the participants, for genetic and other blood analyses. Measurements of blood homocysteine and folate were added midway; therefore, only 1,702 individuals out of 2,174 subjects could be used for analysis of homocysteine and folate as factors.

Blood samples were collected early in the morning after at least 12 hours of fasting. Plasma total homocysteine was determined with high-performance liquid chromatography and fluorimetric detection.[17] Serum concentration of folate was determined by detection of chemiluminescence produced by the enzymatic reaction using Access (Beckman Coulter Inc., Fullerton, CA).

Statistical Analyses

Statistical analyses were conducted using the Statistical Analysis System (SAS) version 9.13 (SAS Institute, Cary, NC). For univariate analysis of continuous variables, a t test was used to assess differences between two groups, and one-way analysis of variance (ANOVA) was used to make comparisons among the three groups. Comparisons of categorical variables were performed using the χ^2 test. All values are expressed as mean ± standard error unless otherwise specified.

For multivariate analysis, a multiple logistic regression was performed to obtain odds ratios (ORs) for SSNHL in subjects with the MTHFR C677T polymorphism. Genotypes were coded as follows: wild-type homozygotes, CC; heterozygotes, CT; and mutant homozygotes, TT. We considered three different modes of inheritance. For the additive per-allele model, the T allele was compared between cases and controls by assigning scores of 0, 1, and 2 to homozygotes for the C allele, heterozygotes, and homozygotes for the T allele, respectively. For the dominant model the comparison was between the CC genotype and the combined CT and TT genotypes. Finally, for the recessive model the comparison was between the TT genotype and the combined CC and CT genotypes. For this analysis, we used three models, each adjusted for a different combination of

TABLE I.
Characteristics of Case and Control Groups.

	All	SSNHL group	Control Group	P
No.	2,174	33 (1.5%)	2,141 (98.5%)	
Sex, % male	50.4	57.6	50.3	NS
Age, yr	59.2 ± 0.2	61.6 ± 1.6	59.1 ± 0.2	NS

*P value tested by *t* test or χ^2 test.
SSNHL = sudden sensorineural hearing loss; NS = not significant.

confounding variables. In model 1, age, sex, and history of occupational noise exposure were taken as possible influential variables. For model 2, the same variables as model 1 were used, with the addition of smoking status, BMI, histories of heart disease, hypertension, and diabetes. In model 3, folic acid and homocysteine were included in addition to the variables from model 2.

RESULTS

Table I shows the profiles of the SSNHL case and control groups. Of the 2,174 participants, 33 case subjects had previously reported SSNHL. No significant differences in gender or age were found between SSNHL cases and controls. The MTHFR (C/T) genotypes of participants are shown in Table II. The distribution of genotypes was not significantly different from that expected based on the Hardy-Weinberg equilibrium (χ^2 test, $P > .05$). There was no significant difference in the prevalence of SSNHL among genotypes according to univariate analysis by χ^2 test.

Table III shows the results from multiple logistic regression regarding the risk of SSNHL. ORs with accompanying 95% confidence intervals (CIs) were calculated for each mode of inheritance. The per-allele odds ratio for SSNHL risk was 1.687 (95% CI, 1.023–2.780) in model 1, with fewer moderating factors; and 1.654 (95% CI, 1.003–2.728) in model 2, which adjusted for smoking status, BMI, histories of heart disease, hypertension, and diabetes, as well as the factors from model 1. Under the recessive model of inheritance, the risk for SSNHL increased significantly in mutant homozygotes in model 1, but after adjustment for additional factors, no significant association of the mutant homozygotes with SSNHL was observed. In model 3, a significant association between SSNHL and the C677T polymorphism was observed under all genetic models independent of possible influential moderating factors including folic acid and homocysteine, although the number of cases and controls were reduced to 25 and 1,677, respectively, due to the selection of the moderating factors.

DISCUSSION

The present findings suggest that the MTHFR C677T gene polymorphism confers susceptibility to SSNHL, and that the T allele is associated with an increased risk of SSNHL.

Among many hypothesized pathologies of SSNHL, impaired inner ear perfusion and ischemic vascular damage of the cochlea are widely recognized as possible pathogenic mechanisms. Several studies have attempted to prove the vascular cause hypothesis using image diagnostic technology or hematologic assessment. High signals on three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging have been observed in affected inner ears, and these signals have been interpreted to reflect minor hemorrhage or an increased concentration of protein in the inner ear due to pathologically increased permeability.[18] Marcucci et al. reported that thrombophilic risk factors including hyperhomocysteinemia are associated with SSNHL, and that this indirectly supports the hypothesis of a vascular occlusion in the pathogenesis of SSNHL.[19] Lin et al. analyzed the risk of stroke development among SSNHL patients during a 5-year follow-up period after hospitalization for acute episodes of SSNHL, and suggested that SSNHL can be an early warning sign of impending stroke.[20]

In recent years, several genetic risk factors have been found for the vascular pathogenesis of SSNHL, of these, the MTHFR C677T polymorphism has been most extensively investigated. Capaccio et al. studied the relationship between SSNHL and two MTHFR gene polymorphisms (C677T and A1298C), and more recently have further investigated prothrombin G20210A, platelet Gly $IIIa^{A1/A2}$, factor V Leiden G1691A genotypes, and other hematologic tests in patients with SSNHL.[8,9,21,22] Although most studies attempting to determine the impact of MTHFR polymorphisms on SSNHL have found significant compound effects of MTHFR C677T with other possible susceptibility gene polymorphisms,[9,10,21] no studies have demonstrated a solitary effect of the MTHFR C677T polymorphism on SSNHL risk. The present results suggest that the T allele at MTHFR position 677 could be associated with an increased risk of SSNHL by itself, and even that this mutation could be a risk factor from SSNHL that is independent of blood folic acid and homocysteine. When the present data were compared using univariate analysis, blood homocysteine (nmol/mL) was significantly higher in mutant homozygotes (CC genotype: 10.33 [95% CI, 9.97–10.68], CT genotype: 10.67 [95% CI, 10.36–10.99], TT genotype:

TABLE II.
Characteristics of Subjects According to MTHFR 677 (C/T) Genotype.

	Genotype			
	CC	CT	TT	P
No. (%)	806 (37.1)	1,039 (47.8)	329 (15.1)	
Age, yr	59.4 ± 0.4	59.3 ± 0.3	58.3 ± 0.6	NS
AHT, dB	17.6 ± 0.4	17.0 ± 0.4	17.6 ± 0.7	NS
Sex, % male	49.8	50.1	53.2	NS
Hearing impairment, %	22.5	19.2	19.2	NS
SSNHL, %	0.99	1.54	2.74	NS

*P value tested by the analysis of variance or χ^2 test.
Hearing impairment: AHT >25 dB.
CC = wild-type homozygotes; CT = heterozygotes; TT = mutant homozygotes; NS = not significant; AHT = average hearing threshold (level for frequencies 0.5, 1, 2, and 4 kHz for the better ear); SSNHL = sudden sensorineural hearing loss.

TABLE III.
Odds Ratios of SSNHL According to MTHFR 677 Genotype.

Mode of Inheritance						
			CC (T = 0)	CT (T = 1)	TT (T = 2)	*P*
Additive genetic model*	Number		806	1,039	329	
	Per-allele odds ratios	Model 1	1	1.687 (1.023–2.780)/T-allele		.0404
		Model 2	1	1.654 (1.003–2.728)/T-allele		.0486
		Model 3†	1	2.475 (1.324–4.627)/T-allele		.0045
			CC	CT/TT		*P*
Dominant genetic model	Number		806	1,368		
	Odds ratios	Model 1	1	1.765 (0.790–3.944)		NS
		Model 2	1	1.753 (0.779–3.946)		NS
		Model 3†	1	3.194 (1.067–9.561)		.0379
			CC/CT	TT		*P*
Recessive genetic model	Number		1,845	329		
	Odds ratios	Model 1	1	2.238 (1.024–4.891)		.0434
		Model 2	1	2.162 (0.984–4.750)		NS
		Model 3†	1	3.253 (1.288–8.217)		.0126

Ranges in parenthesis indicate the 95% confidence interval.

Moderating variable model 1: age, sex, history of occupational noise exposure; model 2: smoking status, body mass index, histories of heart disease, hypertension, and diabetes in addition to those of model 1; model 3: folic acid, homocysteine levels in addition to those of model 2.

*The additive genetic model assumes that a linear gradient in risk across the CC, CT, and TT genotypes (CC genotype base). This is equivalent to a comparison of the T allele against the C allele. The per-allele odds ratio for sudden sensorineural hearing loss risk is shown under the additive genetic model.

†The numbers of cases and controls were reduced to 25 and 1,677, respectively, due to the addition of moderating variables (folic acid and homocysteine) in model 3.

CC = wild-type homozygotes; CT = heterozygotes; TT = mutant homozygotes; NS = not significant; SSNHL: sudden sensorineural hearing loss.

14.40 [95% CI, 13.84–14.95]) and blood folic acid (ng/mL) was significantly lower in mutant homozygotes (CC genotype: 6.20 [95%CI: 6.02–6.39], CT genotype: 5.67 [95% CI, 5.51–5.84], TT genotype: 4.76 [95% CI, 4.47–5.05]), but no significant difference was observed between SSNHL cases and controls in either blood homocysteine or folic acid.

As stated earlier, hyperhomocysteinemia is believed to promote atherosclerosis and atherothrombosis as risk factors for macroangiopathy and microangiopathy[5–7]; however, recently a theory has been put forth that the role of circulating homocysteine on the pathogenesis of vascular disease should be questioned. It has been reported that the circulating form of folic acid, 5-methyltetrahydrofolate (5-MTHF) has beneficial effects on endothelial function and vascular superoxide production, and that the genetic polymorphism MTHFR C677T affects vascular 5-MTHF, but not homocysteine.[23,24]

The prevalence of the MTHFR C677T allele varies widely among different populations (T allelic frequency: 0.06–0.59; homozygosity frequency: 0–0.35). The 677T allele frequency is over 30% in many ethnic groups in Mediterranean or Asian countries.[24] In Japan, according to the Japanese in Tokyo from the HapMap data (http://www.hapmap.org/index.html.en), the T allele frequency is 0.367 (vs. 0.390 in the present study). Japan is an area suitable for studying the impact of the MTHFR 677T allele, in contrast to other factors such as the V Leiden G1691A mutation, which has been reported to be significantly associated with SSNHL,[9] but is rarely observed in Japanese people.[25]

Some limitations to the present study should be considered when interpreting its findings. One major weakness is that the prevalence of SSNHL was based on self-reporting, which is susceptible to inaccuracy. Furthermore, the variables adjusted as confounders in the present analyses, such as lifestyle diseases, BMI, and the presence of a smoking habit, may not reflect the patient's situation at the onset of SSNHL. A hospital-based study is absolutely essential to capture the core of the disease, including audiologic feature, severity, and recovery condition. The present study lacks such clinical audiologic information around the time of onset of SSNHL.

In contrast, a community-based study has various advantages. The strength of the present study is a nested case-control study design within a cohort of inhabitants, who were selected randomly from a register stratified by both age and gender. The risk of recall bias was eliminated. Also, the risk of genotypic bias in controls is likely to be less than controls in a hospital-based study. In addition, because a number of candidate genes for geriatric diseases have been typed in the NILS-LSA, further epidemiologic evidence, such as evidence for gene-gene interactions or gene-environment interactions, would also be of interest.

CONCLUSION

The present study has demonstrated a significant association between the MTHFR C677T gene polymorphism and SSNHL, defined as a self-reported otolaryngologist diagnosis with consideration of possible confounding factors. The results suggest that the MTHFR C677T gene polymorphism confers susceptibility to SSNHL, that the T allele may be associated with an increased risk of SSNHL, and that this mutation could even be a risk factor that is independent of blood folic acid and homocysteine.

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ORIGINAL ARTICLE

3 Tesla magnetic resonance imaging obtained 4 hours after intravenous gadolinium injection in patients with sudden deafness

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Abstract

Conclusion: 3 Tesla (3T) magnetic resonance imaging (MRI) performed 4 h after intravenous gadolinium (Gd) injection provides sufficient anatomic resolution of the inner ear fluid spaces in sudden deafness. The signal intensity ratio (SIR) between the cochlea and cerebellum may be a good indicator of disruption of the blood–labyrinthine barrier. *Objectives:* We evaluated the inner ear 4 h after intravenous Gd injection to determine whether 3T MRI enables the acquisition of images of the affected inner ear in sudden deafness. *Methods:* Ten patients underwent 3T MRI scanning 4 h after intravenous Gd injection. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MRI was performed. *Results:* The SIR varied from 0.45 to 2.17 in 11 affected ears and from 0.43 to 1.48 in 9 unaffected ears. The difference of contrast (affected ear vs unaffected ear) could be detected in five of the nine patients with unilateral sudden deafness. The Gd distribution was recognized in the vestibule of 10 affected ears and in the cochlea of 5 affected ears, in which no significant hydrops was observed. In the remaining vestibules and cochleas of affected ears, the Gd enhancement was too faint to evaluate the endolymphatic hydrops.

Keywords: *Inner ear fluid spaces, blood–labyrinthine barrier, gadolinium distribution, fluid-attenuated inversion recovery, endolymph, perilymph, signal intensity ratio*

Introduction

Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) has been developed to detect high concentrations of protein or hemorrhage. Our previous study using a 3 Tesla (3T) MRI unit showed that 31 of 48 patients with sudden deafness had high signals in the affected inner ear before intravenous gadolinium (Gd) injection [1]. Immediately after intravenous Gd injection, 16 of the 31 ears showed Gd enhancement that suggested disruption of the blood–labyrinthine barrier. Gd enhancement of the inner ear was most intense 4 h after intravenous Gd injection [2,3]. In the present study, we evaluated the signal intensity of the inner ear 4 h after intravenous Gd injection and compared the intensity with that of the cerebellar hemisphere in patients with sudden deafness.

In patients with Ménière's disease, 1 day after the intratympanic Gd injection, 3T 3D-FLAIR MRI shows Gd enhancement in the perilymph and visualize the enlarged endolymphatic space [4]. This method requires intratympanic Gd injection. However, Gd is generally administered intravenously for contrast enhancement in MRI. In the present study, we also evaluated whether images obtained by 3T MRI 4 h after intravenous Gd injection provide sufficient anatomic resolution to image the inner ear fluid spaces in patients with sudden deafness.

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Material and methods

Subjects

Ten patients with sudden deafness who visited Nagoya University Hospital between April 2008 and June 2009 were enrolled in this study. The criterion for sudden deafness used in this study was that the patient could describe the day of onset of sudden deafness but did not know its cause. Before the onset, no hearing loss had been noted except in one patient, who had experienced left sudden deafness 8 months after the appearance of right sudden deafness. We excluded patients with fluctuating or progressive hearing loss.

Hearing levels were evaluated using an audiometer (Model AA-79S; Rion, Tokyo, Japan) in a sound-insulated chamber. The initial audiograms were obtained at the first visit, and the final audiograms were taken 2 months after the onset of deafness, except for patients who recovered completely within this period. If the patient did not respond to the maximum sound level produced by the audiometer, we defined the threshold as 5 dB above the maximum level.

Age; sex; the affected side; the presence or absence of vertigo; average hearing level at 500 Hz, 1 kHz, and 2 kHz; injected Gd dose; the signal intensity ratio in the affected and unaffected ears; differences in contrasting density (affected ear vs unaffected ear); Gd distribution; and hearing outcome are presented in Table I.

The hearing outcome of sudden deafness was made according to the criteria of the Ministry of Health, Labour and Welfare in Japan [5]. Recovery was ranked as follows: no change (improvement in hearing loss of 10 dB on average); slight improvement (improvement in hearing of 10 dB or more but less than 30 dB on average); marked improvement (improvement in hearing of 30 dB or more on average); and complete recovery (all five frequencies on the final audiogram were 20 dB or less or the same degree of improvement in hearing as in the contralateral ear).

Patients underwent 3T MRI scanning after the intravenous administration of the nonionic contrast agent, gadoteridol (ProHance; Eisai, Tokyo, Japan), at a total dose of 0.2 ml/kg (0.1 mmol/kg) or 0.4 ml/kg (0.2 mmol/kg). Although the standard dose of gadoteridol is 0.2 ml/kg, a concentration of 0.4 ml/kg is permitted by the Japanese governmental health insurance system if the aim is to visualize metastatic brain tumors. The magnetic resonance image was obtained 4 h after the injection using the method reported previously [2].

The protocol of the study in accordance with the Declaration of Helsinki was approved by the Ethics Review Committee of Nagoya University School of Medicine (approval number 587). All patients gave their informed consent to participate in this study. Their written informed consent was attached to the electronic medical record after permission was given by the patient, in accordance with the suggestion of the Ethics Review Committee.

Table I. Gadolinium (Gd) distribution in inner ear after intravenous injection.

Patient no.	Age (years)	Sex	Side	Vertigo	HL (dB) initial/final	Hearing outcome	Gd dose (ml/kg)	SIR (affected ear)	SIR (unaffected ear)	Gd distribution	
										Cochlea	Vestibule and SCCs
1	56	M	Right	No	54/56	No change	0.2	0.58	0.58	Faint	Partial
2	82	M	Left	No	88/23	Complete improvement	0.2	0.72	0.68	No	Faint
3	43	M	Left	No	48/45	No change	0.2	0.45	0.43	Faint	Partial
4	55	F	Right	Yes	71/45	Slight improvement	0.2	2.17 (1.11)	1.48 (0.50)	Whole	Whole
5	47	F	Left	No	44/33	Slight improvement	0.2	0.68	0.49	Partial	Partial
6	72	M	Left	Yes	105/105	No change	0.2	1.09 (0.68)	0.67 (0.63)	Whole	Whole
7	65	F	Right	Yes	58/21	Complete improvement	0.4	1.21 (0.56)	0.78 (0.44)	Partial	Whole
8	44	F	Left	No	70/19	Complete improvement	0.4	0.87	0.86	Faint	Partial
9	57	F	Both	No	Left 80/25, right 104	Marked improvement	0.4	Left 0.83 (0.36), right 1.14 (0.63)	–	Whole	Whole
10	67	M	Right	Yes	105/99	No change	0.4	1.82	0.87	Whole	Whole

Gd, gadolinium; HL, average of hearing level of 500 Hz, 1 kHz, and 2 kHz (dB); SCCs, semicircular canals; SIR, signal intensity ratio between the cochlea and cerebellum; SIR values shown in parentheses indicate the values of the precontrast images. Patient no. 9 had experienced left sudden deafness 8 months after she experienced right sudden deafness.

MRI

MRI was performed with a 3T MRI unit using a 32-channel array coil to obtain a high signal-to-noise ratio [6]. Heavily T2-weighted 3D constructive interference in the steady-state imaging was obtained for anatomic reference and 3D-FLAIR was then performed to detect perilymph enhancement while suppressing the signal from the endolymph. The details of the MRI protocol were described previously [4,7,8]. All images were attached to the electronic medical record and reviewed by a radiologist who was blinded to the patient's medical history.

The contrasting effects of cochlear fluid were evaluated semiquantitatively. A region of interest (ROI) was set manually in the basal turn of the cochlea on the 3D-FLAIR image. The signal intensity ratio (SIR) was defined as the signal intensity of the basal turn divided by that of a circular ROI in the cerebellar hemisphere. An example of ROI setting is shown in Figure 1. The averaged SIR value was measured three times and designated as the SIR for each ear. The SIR values were compared between the precontrast images and between the affected ear and the unaffected ear.

Grading of endolymphatic hydrops was evaluated in the vestibule and cochlea according to the criteria described previously [9].

Results

The clinical findings in 10 patients with sudden deafness are summarized in Table I. The patients were five men and five women whose mean age (± SD) was 58.8 (± 12.0) years. MRI revealed an asymptomatic left dural arteriovenous fistula in patient no. 5. Patient no. 9 had experienced left sudden deafness 8 months after she experienced right

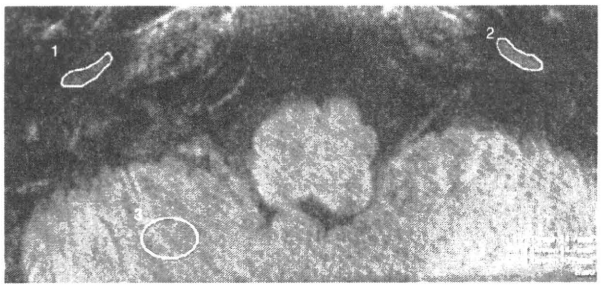

Figure 1. An example of the region of interest (ROI) setting on a contrast-enhanced 3D-FLAIR image. The ROI for the cochlear fluid signal intensity measurement was drawn manually around the basal turn of the cochlea. The circular ROI for the signal intensity measurement of the cerebellum was set in the most artifact-free area of the ipsilateral cerebellum. The signal intensity ratio was calculated as the value shown in the lower right of the figure.

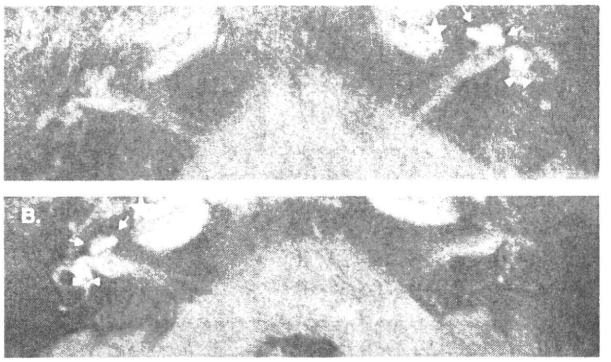

Figure 2. 3D-FLAIR MRI after intravenous Gd injection. (a) A 72-year-old man with left sudden deafness (patient no. 6). (b) A 67-year-old man with right sudden deafness (patient no. 10). Gd enhancement was obtained in both ears, and the affected ear (asterisks) showed bright signals compared with the unaffected ear. Arrows indicate the cochlea and arrowheads indicate the endolymphatic spaces in the vestibule.

sudden deafness. Four patients (nos 4, 6, 7, and 10) experienced vertigo in addition to hearing loss. The average interval between the onset of hearing loss and undergoing MRI was 10.3 ± 5.2 days. Hearing recovery was complete in three patients, marked in one patient, slight in two patients, and unchanged in four patients despite intravenous and/or intratympanic steroid therapy.

Precontrast MRI was performed in four patients and the SIR between the cochlea and cerebellum varied from 0.36 to 1.11 (0.55 ± 0.08). The SIR at contrast varied from 0.45 to 2.17 (1.05 ± 0.50) in 11 affected ears and from 0.43 to 1.48 (0.78 ± 0.29) in nine unaffected ears. In five of nine patients with unilateral sudden deafness, a difference in the contrasting effect (affected ear vs unaffected ear) could be obtained. 3D-FLAIR MRI showed low signals of the endolymph surrounded by high signals of the perilymph. The Gd distribution was recognized in the vestibule and semicircular canals of 10 affected ears, in which no significant vestibular hydrops was observed. Meanwhile, it was recognized in the cochlea of five affected ears, in which no cochlear hydrops was observed. In the remaining vestibules and cochleas of affected ears, the Gd enhancement was too faint to evaluate the endolymphatic hydrops. Typical MRI images for patient nos 6 and 10 are shown in Figure 2; Gd distribution was sufficient to observe inner ear fluid spaces.

Discussion

Intravenous Gd injection has three advantages in the evaluation of the inner ear. First, the affected ear can be compared with the unaffected ear; second, the

clinician can observe whether the blood–labyrinthine barrier is disrupted; and third, the Gd injection method is readily available.

We previously reported pre- and post-contrast high signals in the affected inner ear of patients with sudden deafness who were examined with 3D-FLAIR MRI [1,10]. Such high signals may reflect minor hemorrhage or an increased concentration of protein in the inner ear fluid and a disrupted blood–labyrinthine barrier. Our present study revealed that waiting 4 h after intravenous Gd injection and using a double dose of Gd increases the post-contrast signals.

The ratio between the signal intensity of the inner ear and that of the cerebellar hemisphere has been reported in healthy ears [2]: in four ears of two healthy volunteers, the SIR values were 0.22 ± 0.12 before the injection and 0.90 ± 0.11 at 4 h after the Gd injection of 0.1 mmol/kg. We found SIR values of 0.55 ± 0.08 in precontrast images of the unaffected ear. In the affected ears of five patients, contrasting effects were recognized and the SIR was higher than in healthy subjects. The SIR may be a good indicator for the semiquantitative evaluation of disruption of the blood–labyrinthine barrier. Semiquantitative expression of the signal intensity may be useful for comparing the results between patients or between ears. However, we acknowledge that the SIR was based on signals only at the basal turn of the cochlea in this study.

Because the blood–endolymph barrier is extremely tight compared with the blood–perilymph barrier, Gd administered intravenously enters the perilymph but does not enter the endolymph [11]. This difference makes it possible to visualize the endolymphatic spaces of the inner ear using 3D-FLAIR MRI after intravenous Gd injection. The present study showed a distinction between the endolymph and perilymph in the vestibule on MRI after intravenous Gd injection in patients with sudden deafness. One limitation of this study relates to the distinction between the endolymphatic and perilymphatic images. Although the endolymphatic spaces of the vestibule were recognized in 10 affected ears, we could acquire images of the enhanced structure of the cochlea only in 5 affected ears. It was more difficult to observe the contrast in the cochlea than in the vestibule, possibly because the endolymphatic space volume is smaller in the cochlea than in the vestibule. In a 3D computerized model made from specimens of the temporal bone, the average of the cochlear endolymphatic volume was calculated to be one-fifth that of the vestibular endolymphatic volume in normal ears [12]. The endolymphatic space may be visualized more easily in patients with endolymphatic hydrops in the cochlea [13].

At present, even with advanced technology, we cannot achieve constant visualization of all of the cochlear endolymphatic space after intravenous Gd administration. However, increasing the permeability of the blood vessels in the blood–labyrinthine barrier by the intravenous injection of Gd enhances the perilymphatic spaces, allowing recognition of the endolymphatic spaces, which are not enhanced. To increase the precision of the diagnosis, additional technological development and improvement of the contrasting effect are needed. It is also important to clarify the relationships between the MRI findings and clinical manifestations. Further studies with a large number of subjects are warranted to investigate the disease further.

Conclusion

This is the first report to demonstrate the distinction between the endolymph and perilymph on MRI after intravenous Gd injection in patients with sudden deafness. The ratio between the signal intensities of the inner ear and the cerebellar hemisphere may be a good indicator for evaluating the disruption of the blood–labyrinthine barrier in sudden deafness. This study protocol has potential as a method for the fine detection of the pathology of various inner ear diseases.

Acknowledgments

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Edaravone, a free radical scavenger, in the treatment of idiopathic sudden sensorineural hearing loss with profound hearing loss

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Abstract

Objective: Edaravone, a free radical scavenger, is a clinical drug that is widely used to reduce neuronal damage after acute cerebral infarction in Japan since 2001. The aim of this study was to investigate whether edaravone could improve treatment result in idiopathic sudden sensorineural hearing loss (ISSHL) patients with severe hearing loss.
Methods: Between 2004 and 2006, 14 patients of ISSHL with the mean hearing levels equal or over 90 dB at the initial visit were treated with edaravone. 14 counterpart control patients were selected from 45 patients who had similar prognostic factors and were treated with hyperbaric oxygenation therapy (HBO) in the past decade.
Results: There were no significant differences between edaravone group and the control group in hearing recovery.
Conclusion: We considered that edaravone was not able to bring remarkable effect compared with conventional treatment regimen for ISSHL.

Keywords: ISSHL; Profound hearing loss; Free radical scavenger; HBO

1. Introduction

There is only a few treatment that was proved to be effective in randomized controlled study (RCT) for idiopathic sudden sensorineural hearing loss (ISSHL) [1–7]. We consider the following reasons make the randomized study for ISSHL difficult: (1) planning a study compared with natural course is difficult because early treatment is considered to be critical for ISSHL, (2) there might be several causes and pathogeneses in ISSHL, (3) clinical courses of ISSHL are variable from complete recovery to deterioration, and (4) some of the patients might have spontaneous recovery [8,9]. However, several prognostic factors which might affect treatment results for ISSHL have been reported, thus the prognosis of ISSHL could be partly predicted [8–12]. To make an ideal design of clinical study for investigating the effect of new treatment of ISSHL, well selected entry criteria in respect to prognostic factors could be important.

Edaravone (MCI-186, 3-methyl-1-phenyl-pyrazolin-5-one) is a clinical drug that is widely used to reduce neuronal damage after acute cerebral infarction in Japan since 2001. Edaravone scavenges hydroxyl radical and has inhibitory effects on peroxynitrite and peroxylradicals [13,14]. It was reported that edaravone markedly reduced the loss of inner hair cell after transient cochlea ischemia in Mongolian gerbils [15]. Although the pathogenesis of ISSHL is still unknown, ischemia and reperfusion dysfunction could be possible pathogeneses. Furthermore, inflammation, which is presumed to be another cause of ISSHL, might be related to the production of free radicals that resulted tissue injury. Therefore, edaravone might have possibility of therapeutic effect for ISSHL.

The purpose of this study was to detect the possibility whether this newly proposed medicine improves the treatment result in ISSHL patients with severe hearing loss, who had been known to have markedly poor prognosis compared with other patients.

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Table 1
Treatment regimen in the study.

Edaravone	30–60 mg	Intravenous	7–14 days
Alprostadil alfadex	60 mg	Intravenous	7 days
Betamethasone	8 mg	Intramuscle	1 day
	4 mg, 2 mg, 1 mg	Peroral	Tapering in 9 days
ATP	300 mg	Peroral	Two months
Vit. B	3 cap	Peroral	Two months
Ubidecarenone	30 mg	Peroral	Two months

2. Methods

The diagnosis of ISSHL was made under the following criteria: (1) acute onset from instant to several hours or notice on awakening, (2) hearing loss was severe enough that could be recognized by the patients, (3) sensorineural hearing loss of unknown etiology. The entry criteria for this study was (1) treatment can be started within three days from the onset, (2) ages range from 20 to 65 years old, (3) the average of five frequency (from 250 to 4000 Hz) pure tone hearing levels was equal or over 90 dBHL, (4) without severe general complications, (5) patients with signed informed consent document. The institutional ethical committee of Kitasato University Hospital approved the study protocol. The laboratory work-up including blood count, blood chemistry, viral antibody screening, and TPHA, which could be related to the etiology of sensorineural hearing loss, was evaluated. Magnetic resonance imaging was performed to exclude the vestibular schwannoma.

Between 2004 and 2006, 15 patients with ISSHL compatible with above mentioned entry criteria were treated with edaravone at the department of Otolaryngology of Kitasato University Hospital. Excluding a patient with insufficient follow-up, a total of 14 patients were investigated in this study. All patients were treated at admission setting and the treatment regimen including other drugs was shown in Table 1. Former three patients were administrated by 30 mg edaravone once a day intravenous infusion, later 11 patients were administrated by 30 mg twice (total 60 mg) a day. Three patients were further treated with hyperbaric oxygenation therapy (HBO) following edaravone infusion complying with their wishes. Blood count and blood chemistry were evaluated for checking up side effect during and after edaravone treatment.

2.1. Selection of the patients in control group

Between 1995 and 2004, there were 45 patients with ISSHL suitable for the entry criteria from (1) to (4). A control counterpart patient to each case in the edaravone group was selected from these 45 patients. The case with most similar conditions at initial visit was selected based on the following factors: with or without vertigo, date from onset, age, hearing level, and type of audiogram. Prognostic factors of the patients in this study and their counterpart control patients were summarized in Table 2. The treatments for 14 control patients were basically same with the edaravone group except edaravone and HBO treatments. All patients in the control group received HBO.

Pure tone audiometry was performed two or three times per week within one or two week admission, and one or two times per month after discharge. The final hearing levels were obtained from the stabilized status at three months or more after the onset.

3. Results

The mean hearing levels of initial and final pure tone audiograms in both groups were shown in Fig. 1. The average levels of each frequency of both groups were almost

Table 2
Prognostic factors in control and edaravone group.

Control				Edaravone				
Vertigo	Date	Hearing levels	Age	Vertigo	Date	Hearing levels	Age	Treatment
–	2	101	25	–	1	103	29	60 mg
+	2	111	43	+	1	111	44	60 mg
+	2	107	59	+	2	108	34	30 mg
+	3	107	47	+	3	108	45	30 mg
+	1	111	65	+	2	111	64	30 mg
+	2	102	29	+	1	101	32	60 mg + HBO
+	1	111	59	+	2	111	60	60 mg + HBO
+	2	106	62	+	1	104	61	60 mg
+	1	110	41	+	2	108	32	60 mg+HBO
+	3	98	41	+	3	96	31	60 mg
+	3	92	41	+	2	96	49	60 mg
+	2	111	48	+	2	111	56	60 mg
+	2	111	54	+	2	111	54	60 mg
+	3	111	52	+	3	111	58	60 mg
Average	2.1	106.4	47.6		1.93	106.4	46.6	

Treatment: 30 mg or 60 mg mean dose of edaravone per day.

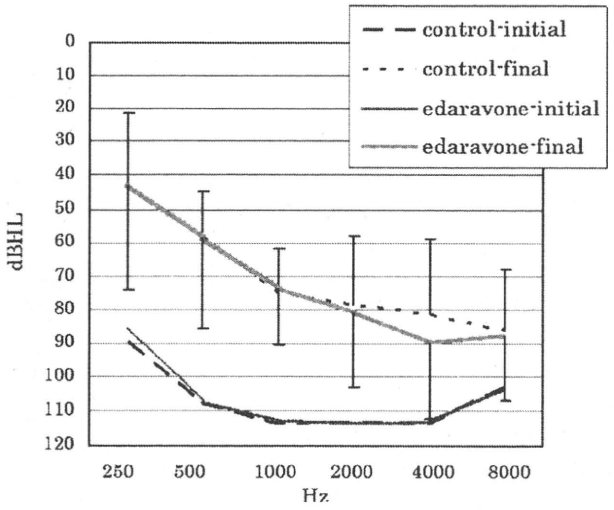

Fig. 1. Initial and final mean hearing levels of both groups in pure tone audiograms. Error bars with final hearing levels indicate standard deviation.

same in the initial and final audiogram except the level at 4000 Hz from final audiogram. Although the final mean hearing level at 4000 Hz in edaravone group was worse than that in the control group, the difference was not statistically significant (t-test, $p = 0.29$). Fig. 2 shows initial and final averaged hearing level from five frequencies (from 250 to 4000 Hz) in both groups. Distribution of final hearing levels in edaravone group was slightly larger than that in the control group. In edaravone group, whether with or without HBO seemed to have no obvious effect for final hearing levels, and there were two cases with markedly poor recovery. There was no difference in final hearing levels between the dosage of edaravone 30 and 60 mg/day (data not shown). Fig. 3 shows degree of recovery (the difference between initial and final five frequencies averaged hearing levels) linked the cases to the control in a line. The distribution of degree of recovery in edaravone group was larger than that in the control group. There was no statistical significant difference in the averages of the degree of hearing recovery between two groups (paired t-test, $p = 0.80$).

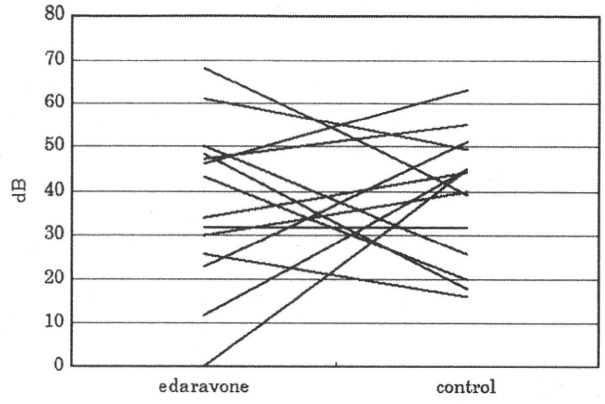

Fig. 3. The degree of hearing recovery in edaravone case and counterpart control.

There were no side effects evidenced by subjective symptoms and laboratory data; eruption, acute renal failure, liver dysfunction, thrombocytopenia and so on, in all patients treated with edaravone.

4. Discussion

For the past decade, several RCT studies for investigating the treatment effect of ISSHL have been performed, there is limited treatment that was proved to be effective [1–7]. As mentioned before, we consider some reasons did influence the trend: variety of causes and pathogeneses, variety of severity, variety of clinical course including spontaneous recovery [8,9]. Evaluation of treatment effect is difficult in the group of cases who might have different causes and with a variety of clinical features. Several prognostic factors in the early stage of ISSHL have been reported to affect final treatment result, especially three factors; degree of hearing loss, time delay from the onset, and with or without vertigo, were well known to have significant impact [8–12]. Previously, we reported that the averaged hearing level of 90 dB was a critical border for predicting prognosis [11,12]. Hearing recovery of the patients over 90 dB remarkably

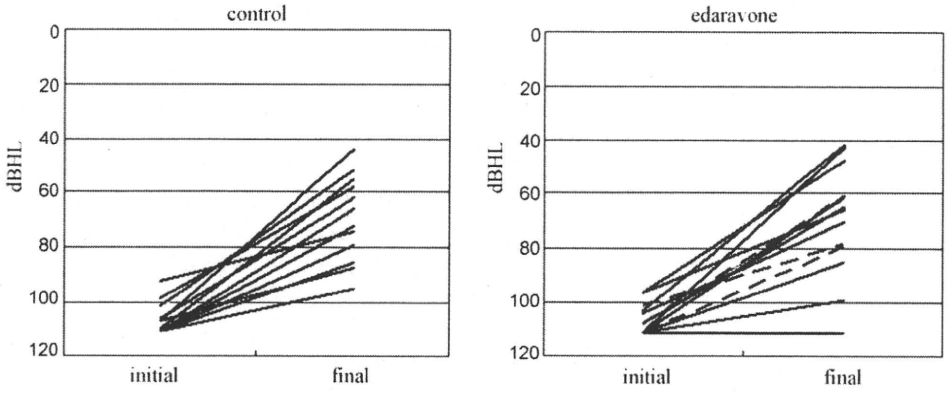

Fig. 2. Changes between initial and final averaged five frequencies hearing levels in both groups. Dot lines in edaravone group indicate the changes in patients with HBO after edaravone regimen.