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Evaluation of cortical processing of language by use of positron emission tomography in hearing loss children with congenital cytomegalovirus infection☆

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ABSTRACT

Objective: To predict cochlear implant efficacy and investigate the cortical processing of the visual component of language in profoundly deafened patients with asymptomatic congenital cytomegalovirus (CMV) infection.

Methods and cases: The cortical activity of two children with CMV-related hearing loss was evaluated with fluorodeoxyglucose-positron emission tomography (FDG-PET) with a visual language task before cochlear implantation. Total development and auditory perception ability were assessed one year after implantation.

Results: The two children with CMV-related hearing loss showed activation in the auditory association area where no activation was found in the controls, and exhibited nearly identical cortical activation patterns to those seen in patients with profound congenital hearing loss. In contrast, differences in total development in verbal ability and discrimination of sentences between the two cases were revealed one year after implantation.

Conclusion: These results might indicate that the differences of cortical activities according to hearing abilities could have been influenced by CMV infection that involves higher function of the brain directly and/or affects the cochlea peripherally. Additionally, if CMV infection might have affected only the cochlea, these cortical activation patterns were influenced secondary by the time course of hearing loss characterized by CMV infection, which had varied manifestations.

Accurate diagnosis and cochlear implantation at the appropriate time are important for successful speech development, and each patient needs a personalized habilitation program based on their etiology and brain function.

1. Introduction

Functional brain imaging provides important evidence of the plasticity of the central auditory pathway following a profound loss of hearing, and is one of the effective methods for investigating the cortical processing of language [1,2]. Previous studies have shown low levels of auditory cortical activity in subjects with profound deafness, i.e. lower levels of activity are observed with longer durations of deafness [3,4]. The importance of early hearing inputs by hearing aids or cochlear implantation (CI) has also been shown. Children with prelingual deafness can acquire spoken language by CI, but this approach is less effective in older children who have not acquired language during the critical language acquisition periods [5,6]. The development of the auditory cortex is believed to depend on the patient's auditory experience within 'critical periods' in the early lifetime. Positron emission tomography (PET) activation study by visual language task has shown that low glucose metabolism in the temporal auditory cortex predicts a good CI outcome in prelingually deafened children, which suggests that low metabolism in the

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auditory cortex may indicate its potential of plasticity for spoken language acquisition [7].

Congenital cytomegalovirus (CMV) infection is the most common environmental cause of developmental disability and sensorineural hearing loss (SNHL) in children [8]. Approximately 90% of infected infants are born with no clinical symptoms of congenital CMV infection, such as microcephaly, growth retardation, hepatomegaly, jaundice, or abnormal neurologic findings. SNHL is found in 6–23% of these asymptomatic infection cases and is often late-onset, fluctuating and progressive in nature within the first 6 years of childhood [9,10]. Hence, newborn hearing screening often does not detect problems in children with asymptomatic congenital CMV infection, and at the time of eventual SNHL diagnosis, the exact time course and manifestations cannot be determined [11]. The development of auditory skills and experiences of children with congenital CMV infection with associated hearing loss are unclear due to various clinical histories. Hearing impairment resulting from (even asymptomatic) congenital CMV infection might be not only of cochlear origin but also have central nerve involvement and entail possible risk of CMV-associated disorders later in life. Brain function and CI outcomes have not been examined in asymptomatic congenital CMV-associated hearing loss. In this study, we used ^{18}F-fluorodeoxyglucose (FDG)-PET to measure cortical glucose metabolism with a visual language task before CI in two profoundly deaf children with asymptomatic congenital CMV infection in order to assess the activities of the auditory cortex and predict the CI outcomes.

2. Methods and cases

2.1. Diagnosis of congenital CMV infection

To analyze congenital CMV infection, we used CMV DNA quantitative PCR (qPCR) analysis. Before qPCR analysis, total DNA including genomic DNA and CMV DNA was extracted from preserved dried umbilical cords. Each 10 pg total DNA was analyzed by a Step One Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using a TaqMan Universal Master Mix II (Applied Biosystems). The detailed methods of qPCR have been described previously (Furutate et al.) [12].

2.2. FDG-PET scanning and image analysis

FDG-PET scanning and image analysis were performed using the methods described by Fujiwara et al. [7]. During the time period between the intravenous injection of 370 MBq 18 F-FDG (the dose was adjusted according to the body weight of each subject) and the PET scanning of the brain, the patients were instructed to watch a video of the face of a speaking person reading a children's book. The video lasted for 30 min, and several still illustrations taken from the book were inserted (for a few seconds each) to help the subjects to follow the story. The subjects were video-recorded to confirm that they were watching the task video. PET images were acquired with a GE ADVANCE NXi system (General Electric Medical Systems, Milwaukee, WI, USA). The patients were then sedated by an anesthesiologist, and their heads were immobilized with a bandage during the scan. Spatial preprocessing and statistical analysis were performed with SPM2 (Institute of Neurology, University College of London, UK) implemented in Matlab (Mathworks, MA, USA). The cortical radioactivity of each deaf patient was compared with that of a control group by a t test in the basic model of SPM2. The control group consisted of six normal-hearing (pure tone average hearing levels within 20 dB HL) right-handed adult (27.5 ± 3.8 years) subjects. The statistical significance level was set at $p < 0.001$ (uncorrected).

2.3. Measurement of language and total development

Before CI, we evaluated the patients' mental development by the Kyoto scale of psychological development (*K*-test) in which Cognitive-Adaptive development [13] that consists of non-verbal reasoning or visuospatial perceptions is measured. This test is used commonly to assess developmental status for Japanese language users and the results are described as a developmental quotient (DQ) in comparison to normal controls. In the *K*-test, developmental delay is defined by DQ below 80.

One year after CI, auditory perception ability was assessed by word and sentence discrimination tests, which are components of the CI2004 test battery for children. Audible word discrimination tests were administered by a speech therapist with live voice stimuli presented at 70 dB in a soundproof room. We also evaluated intellectual development using the Japanese version of the WISC-III that corresponds to the Wechsler Intelligence Scale for Children (WISC) and contains non-verbal and verbal ability components. The Japanese WISC-III includes five subsets for performance IQ (PIQ) (picture completion, picture arrangement, block design, object assembly and coding) and five subsets for verbal IQ (VIQ) (information, comprehension, similarities, arithmetic and vocabulary).

This study was approved by the Ethics Committee of Shinshu University School of Medicine and prior written consent was obtained from the parents of both children after a full explanation of the study.

2.4. Details of cases

2.4.1. Case 1

This case was a 5-year-old girl. She had no particular events in the perinatal period and passed the newborn hearing screening. However at age 4 years 11 months, her mother suspected hearing loss because of poor response to sound. She only had mild expressive language impairment; her fine motor skills were unaffected. An auditory steady state response (ASSR) test showed bilateral hearing loss (approximately, right: 60 dB, left: 110 dB) (Fig. 1A). She was promptly fitted for bilateral hearing aids. After one month, a follow-up ASSR test indicated deterioration of hearing in her right ear to over 110 dB (Fig. 1C). At this point, DNA testing for hereditary hearing loss e.g. screening for mutations in the *GJB2* and *SLC26A4* genes, and checking for congenital CMV infection using preserved dried umbilical cord (above mentioned) was performed to diagnose the cause of hearing loss. These tests revealed that there were no pathological mutations causing hearing loss, but there were positive results for CMV infection. It was suspected that this late-onset, and rapidly progressive for one month, hearing loss was due to asymptomatic congenital CMV infection. Computed tomography (CT) findings of the middle and inner ear were normal. Hearing aids were not expected to be adequate to acquire spoken language, therefore CI was performed in the left ear at the age of 5 years 5 months.

2.4.2. Case 2

This 4-year-old girl had no particular events in the perinatal period and had not undergone newborn hearing screening. Her parents noticed that she did not respond to their voices when she had just turned 3 years old. She visited a hospital for a checkup where she was diagnosed by ASSR test at the age of 3 years 6 months with hearing loss that was approximately right: 60 dB, and left: 110 dB (Fig. 1B). She attended rehabilitation for hearing, using a combination of finger signing and gestures. In the following year, her hearing deteriorated further to right: 90 dB, left: 110 dB at the age of 4 years five months and her speech development was not

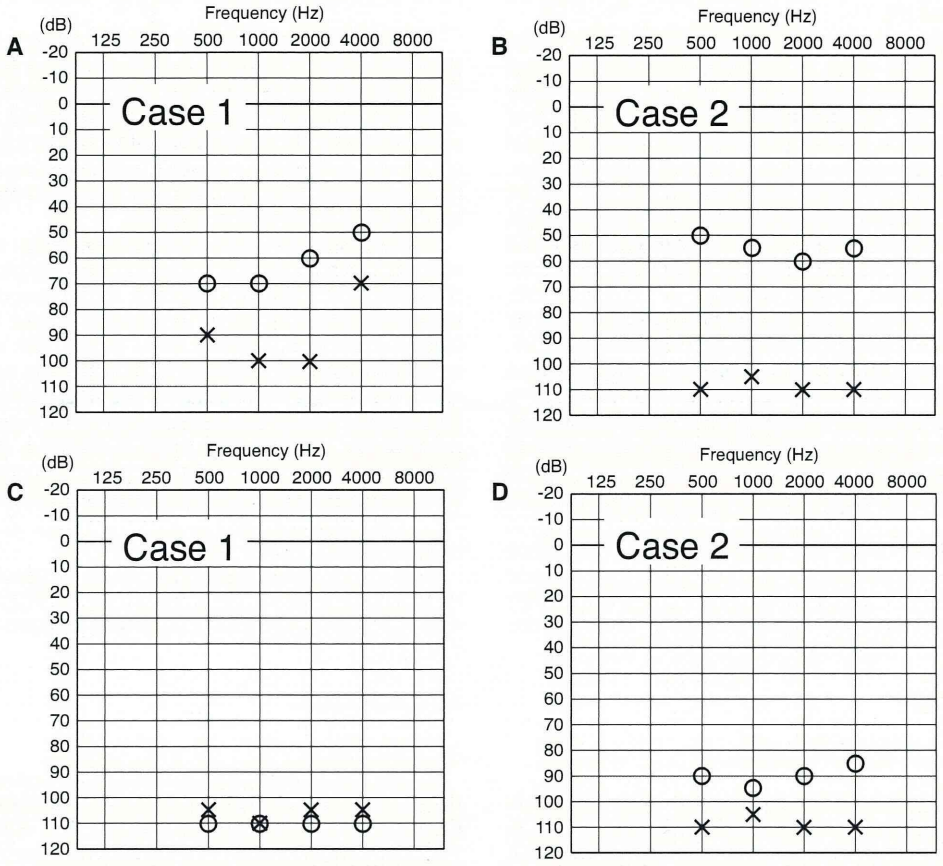

Fig. 1. (A) Case 1; a 5-year-old girl with asymptomatic congenital CMV infection (threshold using ASSR test). (B) Case 2; a 5-year-old girl with asymptomatic congenital CMV infection. These were results of first diagnosed with hearing loss. (C and D) Deterioration in hearing, for one month and for one year, respectively.

significant (Fig. 1D). She was referred to our hospital for further examinations, and her preserved umbilical cord demonstrated a positive result for congenital CMV infection. Late-onset and slowly progressive hearing loss for one year was suggested. There were no inner ear abnormalities seen in the CT findings. She underwent CI surgery in the left ear at the age of 4 years 9 months.

Each child received the same rehabilitation according to auditory oral method by the same speech therapist after implantation.

Table 1
The activated areas of the brain in profoundly deaf individuals during speech-reading.

Case	Gender/age (years)	Activated areas	
		Right hemisphere	Left hemisphere
1	Female/5	Superior temporal gyrus [BA22] Cingulate gyrus [BA31] Middle frontal gyrus [BA9]	Middle temporal gyrus [BA21] Inferior parietal lobe [BA40] Occipital gyrus [BA19] Precueus [BA7]
2	Female/5	Middle temporal gyrus [BA21] Postcentral gyrus [BA3/1/2] Middle occipital gyrus [BA20] Middle frontal gyrus [BA9]	Precentral gyrus [BA4] Precuneus [BA31] Precuneus [BA19] Cingulate gyrus [BA24]

3. Results

3.1. Brain imaging with PET

Table 1 and Fig. 2 show the areas that were activated in each child during a speech-reading task. The following cortical areas showed significantly higher metabolism during speech-reading in the children compared to normal hearing control subjects. In Case 1, the activated areas were the bilateral auditory association area [BA21], the bilateral precuneus, somatosensory cortex [BA7], the left secondary visual area [BA19], and the left inferior parietal lobule [BA40].

The activated areas in Case 2 were similar to those in Case 1, but the activation of the visual association areas in the parietal lobe were lower and smaller than in Case 1.

3.2. Assessment before cochlear implant, and outcome

Table 2 shows the children's scores in the *K*-test before CI, in the word and sentence discrimination tests, and in the Japanese WISC-III at one year after implantation. *K*-test scores that assessed Cognitive-Adaptive development of each child were almost similar. Both cases showed 30–40 dB of aided hearing thresholds at all frequencies with CI. One year after CI, the results of the Japanese WISC-III showed a clearer difference in VIQ than PIQ, in which Case 1 had a better score compared with Case 2. Case 1 did

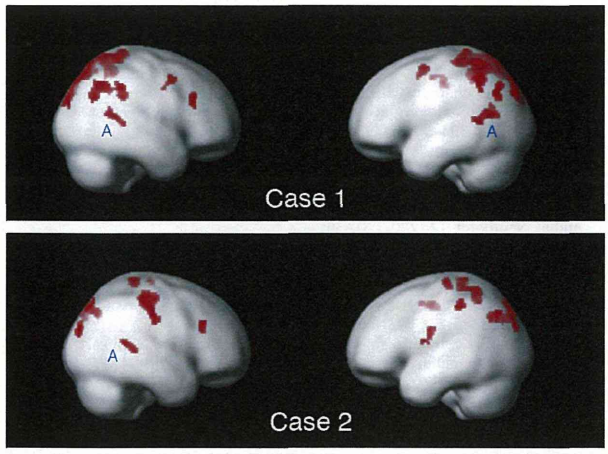

Fig. 2. Cortical activation by language-related visual stimuli in two profoundly deafened with congenital CMV infection cases. Case 1 and 2 showed significant activation in auditory association areas (A) (SPM2, $p < 0.001$, uncorrected).

Table 2
The results of total development before and after cochlear implant, and auditory assessment.

	Before CI	One year after CI	
	K-test (Cognitive-Adaptive)	WISC-III (Japanese version)	Infant word and sentence discrimination
Case 1	99	PIQ 101 VIQ 84	Word 98% Sentence 90%
Case 2	93	PIQ 93 VIQ 56	Word 100% Sentence 53%

CI, cochlear implant; *K*-test, Kyoto scale of psychological development; WISC, Wechsler Intelligence Scale for Children; PIQ, performance IQ; and VIQ, verbal IQ.

better as well in the sentence discrimination component of the auditory perception ability assessment while their results were similar regarding words in the word and sentence discrimination test for children.

4. Discussion

This is the first report on the evaluation of cortical processing of language in hearing loss children with congenital CMV infection. In infants with congenital CMV infections, as many as 20% will suffer from some degree of SNHL, either fluctuating or progressive [14]. This may present a late onset hearing loss, even if the results of newborn hearing screening were normal. The clinical courses of hearing loss in Cases 1 and 2 were typical for asymptomatic congenital CMV infection. Performance and outcome of children with CIs have a strong relation to hearing variables such as onset and course of hearing loss, age of hearing aids fitting, and social background variability, which depends on habilitation and education. According to Fukushima et al. and Kawasaki et al., children with *GJB2* mutations as the etiology for hearing loss have an advantage in their CI outcomes and speech acquisition with normal cognitive development compared with children with unknown etiologies, but this is because the hearing loss is of cochlear origin [15,16]. On the other hand, widely varying conclusions regarding CI outcomes with congenital CMV infection have been reported. Some studies reported the efficacy being not inferior to that of other CI recipients, while others reported it being much poorer [9,17–20]. Accordingly, prediction of CI outcomes for hearing loss with CMV infection is still difficult, unclear, and inconsistent because of various manifestations, progression and the possibility of involvement of higher brain function. Yamazaki et al. suggested that CI with CMV infection outcomes vary widely depending on the psycho-neurological disorders, with their differences in proportion and severity [19].

In this study, the auditory association area in the temporal lobe was activated bilaterally in Case 1 and unilaterally in Case 2. Fujiwara et al., in a FDG-PET study using the same methods and tasks as the present study, showed that subjects with better spoken language skills had less temporal lobe activation [7]. These cases exhibited nearly identical cortical activation patterns to those of congenitally deafened children, suggesting that they did not have enough hearing to develop the cortical network for audition. Previous studies have suggested that plastic changes in auditory cortices were strongly determined by the duration of auditory deprivation [21,22]. However, our two cases of children with CMV-related hearing loss were affected with severe bilateral hearing loss over a short period and were able to acquire spoken language with only a little delay for their age group. It is an interesting but unsolved question why they exhibited results that were the same as previous reports of pre-lingually deafened patients who did not receive sufficient auditory signals and therefore depended on visual cues. One possibility was that high speech-reading activation in the temporal auditory area might be linked to the condition of lacking auditory speech skills at that point, rather than reflecting a consequence of replacement by visual cross-modal plasticity due to a hearing loss of long duration. Besides, visual language activation in the auditory area may change even if affected by hearing loss of a short duration, or it might be influenced by the age-related metabolic changes during the critical period for spoken language acquisition. Another possibility was that these results might indicate that both cases had not received sufficient hearing stimulation as a foundation of language during their early years, which may be attributed to the central nervous system impairment of CMV infection.

Regarding the results of assessment after CI, there was a difference of cognitive ability with VIQ and hearing ability of sentence discrimination, with Case 1 having better CI performance than Case 2 (Table 2). In the assessment of auditory performance, Case 2 especially had difficulty in sentence discrimination despite having the same score in word discrimination as Case 1, who had better CI performance. Sentence discrimination tests require not only audible sound coded by CI, but also recognition of semantics and syntax that would be developed and established with hearing experiences during growth. Indeed, because of the differences between our two cases of the brain imaging, especially in the auditory cortex, we were uncertain whether it might be affected by CMV infection or the onset of their hearing loss itself. However, it raised the possibility that involvement of central nerve and high brain function relevant to CMV infection may lead to retardation of sentence discrimination and speech acquisition in Case 2. On the other hand, there was a difference of activation patterns in the parietal visual association areas. Case 2 showed lower and smaller than in Case 1. Fujiwara et al. predicted that the children with deafness were likely to depend more on vision than normal hearing children do. In Case 1, when someone talked to her, she might have been able to pay much more attention to their facial expression, gestures and visual cues for understanding better than Case 2. Lee et al. reported the comparison of brain metabolic activity between good and poor CI outcomes [23]. The activity patterns in the parietal regions of those with good CI outcomes in their study were similar to our result in Case 1.

We considered that these results might indicate that the differences of cortical activities according to hearing abilities could have been influenced by CMV infection that involves higher function of the brain directly and/or affects the cochlea peripherally. Additionally, if CMV infection might have affected only the

cochlea, these cortical activation patterns were influenced secondary by the time course of hearing loss characterized by CMV infection, which had varied manifestations.

Accurate diagnosis of hearing loss and early cochlear implantation are important for successful speech development. The approach using PET could help those involved in the habilitation and education of pre-lingually deafened children to decide upon the appropriate mode of communication for each individual. Brain imaging technologies to evaluate the neural basis for auditory speech skills have been developed and much evidence has been reported; however, correlation with hearing loss etiology, pathology and cross-modal plasticity of auditory cortex remains contentious. Further evaluations of the cortical metabolism before and after implantation are necessary for establishing appropriate personalized audiologic rehabilitation programs for individuals based on their etiology and brain function.

Conflicts of interest statement

We, the authors, declare that there were no conflicts of interest in conjunction with this paper.

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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, U.S.A.). 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

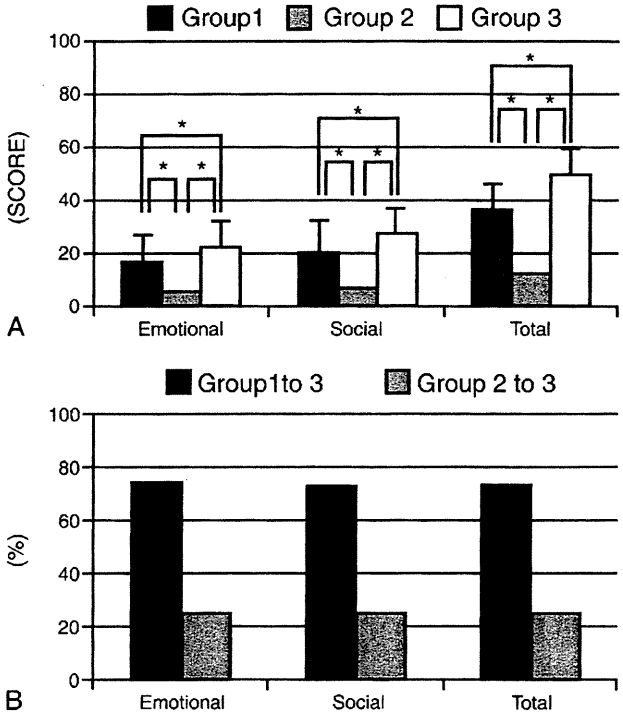

FIG. 1. Hearing Handicap Inventory for Adults (HHIA) scores for Groups 1, 2, and 3. Emotional, social, and total scores on the HHIA scale, in 3 groups of patients: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); Group 2, unilateral severe to profound prelingual 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).

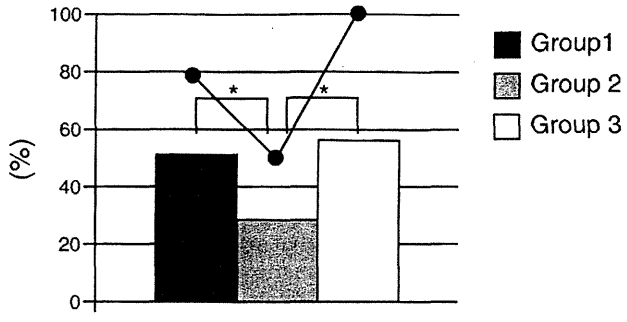

FIG. 2. Visual Analogue Scale (VAS) scores for Groups 1, 2, and 3. VAS scores in 3 groups of patients: Group 1, unilateral severe to profound (>70 dB) sudden sensorineural hearing loss (SNHL); Group 2, unilateral severe to profound prelingual or congenital SNHL; and Group 3, bilateral SNHL. Significant 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

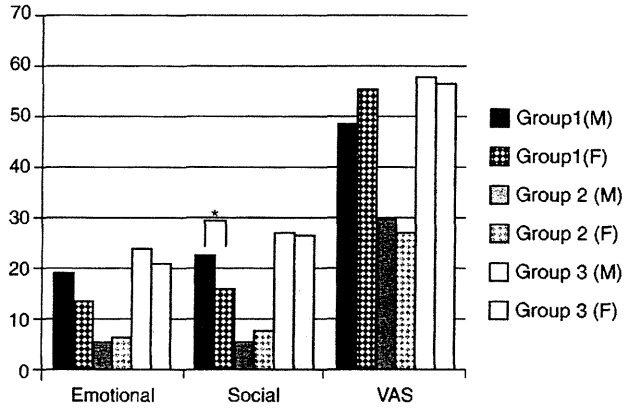

FIG. 3. Mean scores on the emotional and social subscales in the Hearing Handicap Inventory for Adults (HHIA) and Visual Analogue Scale (VAS) according to sex in Groups 1, 2, and 3. Emotional and social scores on the HHIA scale and VAS, in 3 groups of patients: Group 1, unilateral severe to profound (>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. * $p < 0.05$.

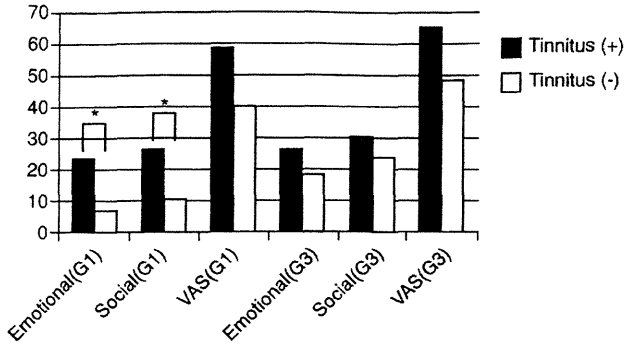

FIG. 4. Differences in the Hearing Handicap Inventory for Adults (HHIA) scores (emotional and social subscale) and Visual Analogue Scale (VAS) between patients who had tinnitus and those who did not in Groups 1 and 3. Emotional and social scores on the HHIA scale and VAS, in 2 groups of patients, some 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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Standards of practice in the field of hearing implants

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HEARRING quality standards: an Introduction

In 2005 the World Health Organization estimated that approximately 278 million people suffered from 'moderate to profound hearing impairment,' 80% of whom lived in low- and middle-income countries (WHO, 2010) where there is less access to competent medical professionals and modern medical procedures and technologies than in high-income countries. Furthermore, with the ageing populations in the developed world (United Nations, 2010) and their associated age-related hearing-loss (presbycusis), the need for assisted hearing solutions – even taking into account a hopefully broader application of preventive measures (e.g. rubella immunization, health education, quieter workplaces, etc.) and health-care infrastructure development – is clearly both significant and continued.

One of such possible hearing solutions is hearing implantation. Indeed, as of December 2010, approximately 219 000 people have been implanted, either uni- or bilaterally (National Institute on Deafness and Other Communication Disorders, 2011). As significant as the benefits of cochlear or middle ear implantation have been for recipients and their families, such implantation is still in its demographic infancy, serving a negligible fraction of those whom

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it could, and will, help integrate or reintegrate into the verbal bustle of everyday life and work.

'The best clinics – providing the best for the patient and comprehensive care' (HEARRING, 2012). With this motto, renowned specialists of four leading hearing implant centers formed the HEARRING group in 2008. Inspired by the collaborative nature of comprehensive cancer center networks, they sought a closer network to better pool their expertise and share information instead of relying solely on medical literature and – beneficial as they are – the individual personal contacts that medical congresses and conferences provide. In the following years, other centers from around the world have joined HEARRING: as of 2012, 23 clinics with numerous surgeons, audiologists, rehabilitationists, and other skilled professionals are collaborating under the HEARRING umbrella.

The 23 clinics in the HEARRING network are committed to creating and maintaining the highest standards of quality. We believe that consensus- and evidenced-based standards are essential to providing each potential implant user, regardless of age or where in the world he/she is treated, with the best possible hearing implant solution for the treatment of her/his individual hearing loss.

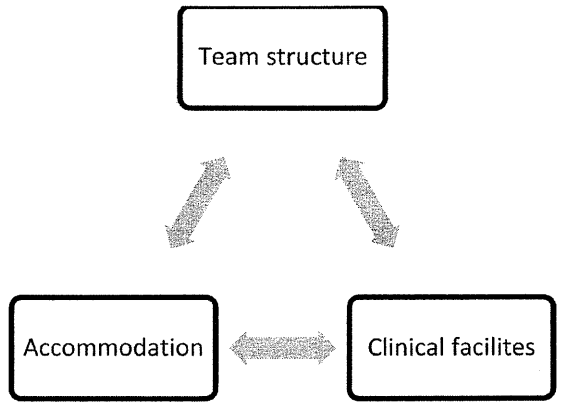
In order to try to ensure the best outcomes and the highest safety levels for every present or potential implant user in every clinic, the HEARRING group – under the direction of experts Prof. Christopher H. Raine, MD, Prof. Dr Rudolf Hagen, Prof. Dr Joachim Müller, Prof. Dr Benoit Godey, and Jane Martin – has created a series of standards that covers all aspects of the hearing implant solution process. These quality standards are based on the British Cochlear Implant Group's (BCIG) own quality standards and can be considered current best practice; indeed they have been approved and adopted by participating HEARRING clinics. These standards are not, however, a static picture; as technology and treatment options continually develop, these standards will be continually updated.

The BCIG was founded in 1989 – not long after implantation became common – to promote good practice and provide information and advice to professionals and the public on cochlear implant solutions. They, with the Royal National Institute for the Deaf, published 'Quality Standards for Adult Cochlear Implantation' (British Cochlear Implant Group and Royal National Institute for the Deaf, 2009), a series of 16 guidelines that are meant to be the *minimum* and *realistically achievable* baseline standards for clinics. HEARRING has used this original document as a blueprint for developing a series of six related sets of evidence-based standards, each tailored to fit a specific age category or procedure:

1. Quality standards for adult cochlear implantation
2. Quality standards for cochlear implantation in children and young adults
3. Quality standards for combined electric and acoustic stimulation (EAS)
4. Quality standards for middle ear implantation (MEI)
5. Quality standards for rehabilitation
6. Quality standards for minimal outcome measurements in adults and children.

With some slight variation (see Table 1), each set of standards has the same basic structure which can be divided into two subsections: (1) resources and (2) processes.

Resources: The Resources section is made up of three



parts: team structure, accomodation, and clinical facilities.

Team structure outlines who every cochlear implant team should include and the minimum training and/or experience each member should have. It also describes the importance of establishing and maintaining a program of continued professional development: with national or international courses, conferences, and meetings each team member should be up to date with the latest cochlear implantation-related developments. Extending beyond the core team, this section also provides a list of 'additional support' professionals whose expertize need not be part of a core team but whom the core team should have ready access to if necessary.

Accommodation is about the provision and differentiation of the clinic's physical space: the size, suitability, comfort, and privacy of areas designated for staff, present or potential implant users, and waiting relatives. As different cultures have different spatial expectations and comforts, the HEARRING standards do not prescribe specific sizes but rather those that are 'suitable', 'sufficient', and 'large enough to comfortable accommodate'. Accomodation is also about access and communication. It covers providing the present or potential implant user with suitable

Table 1 The structural variations by Quality Standard

	Quality Standards for					
	Adult Cochlear Implantation	Cochlear Implantation in Children and Young Adults	Combined Electric and Acoustic Stimulation	Middle Ear Implantation	(Re)habilitation	Minimal Outcome Measurements
			Symbols: = equal	***≠ differs***	***+ in addition***	***– without (compared to basic document)***
Introduction	Individualized	=	Individualized	Individualized	Individualized	Individualized
Structure	Basic document	+ min of two surgeons, audiovestibular physician/ pediatrician, key worker, education, pediatrics	+ hearing aid acoustician – audiological medicine	– clinical scientists, physiologists, rehab therapists, speech and language therapists, clinical physiologists, engineers, tinnitus, balance, medical physics, genetic counseling, interpreter services, social services for the deaf, deaf advocacy	+ teacher of the deaf, key worker, parents, hearing aid acoustician, audiovestibular physician, cooperation with other services – otologist, audiologists, physiologists	NO
Accommodation	Basic document	+ suitable and family-friendly facilities	=	=	=	NO
Clinical Facilities	Basic document	+ spatial awareness	=	– OAE, electrically evoked potentials, balance function testing	NO	NO
Referral and Selection Criteria	CI selection criteria	CI in children/young adults selection criteria	EAS selection criteria	MEI selection criteria	NO	NO
Assessment Process	Basic document	+ ophthalmic assessment, family support and education, associated organizations, final outcome ≠ receptive skills assessment	+ APHAB test	12 weeks – referral for balance testing and genetic counseling, necessity for vaccination (meningitis), determination of UCL, hearing aid testing, electrically evoked response audiometry, promontory stimulation testing, OAE, details for communication, bilateral candidate assessment	≠ structure and content, children and adults are discussed separately – includes pre-op counseling	≠ describes basic sets of outcome measures to be used at routine visits for adults and children
Cooperation with Other Services	Basic document	+ newborn hearing screening	=	NO	NO (included in previous chapter)	NO
Pre-op Information and Counseling	Basic document	+ involvement of child, device	=	=	NO (included in previous chapter)	NO
Device	CI	NO (included in previous chapter)	EAS	MEI	NO	CI, but also applicable to other hearing implants
Surgery and In-patient Care	Basic document	+ monitoring of anesthetics and facial nerve – discussion of surgical procedure	=	– preservation of hearing, radiological examination	NO	NO
Fitting and Tuning	Basic document	+ electrophysiological measurements in the very young	=	+ rehabilitation	NO	NO

Continued

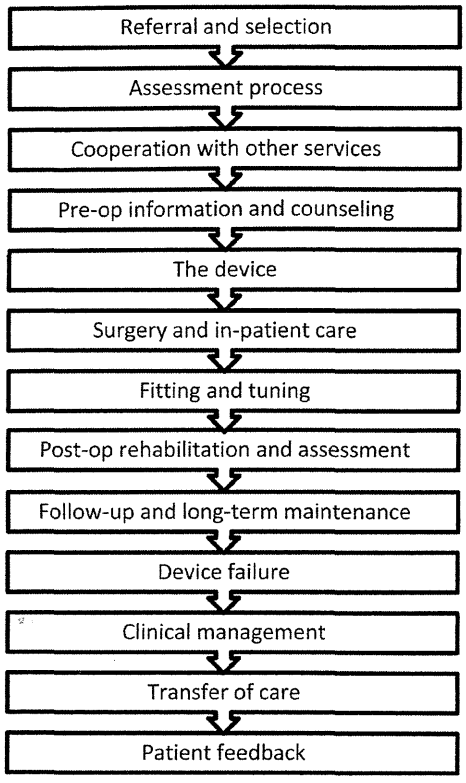
Table 1 ***Continued***

	Quality Standards for						
	Adult Cochlear Implantation	Cochlear Implantation in Children and Young Adults	Combined Electric and Acoustic Stimulation	Middle Ear Implantation	(Re)habilitation	Minimal Outcome Measurements
			Symbols: = equal	***≠ differs***	***+ in addition***	***– without (compared to basic document)***	
Post-op Rehabilitation and Assessment	Basic document	– lip reading, hearing tactics	=	– rehabilitation (included in previous chapter) ≠ post-op assessment	≠ structure and content, children and adults are discussed separately	NO
Follow-up and Long-term Maintenance	Basic document	+ assessment of FM systems	=	=	NO	NO
Device Failure	Basic document	=	+ detailed audiological reevaluation, consideration of a CI	=	=	NO
Clinical Management	Basic document	=	=	=	NO	NO
Transfer of Care	Basic document	=	NO	=	=	NO
Patient Feedback	Basic document	=	=	=	NO	NO

[1]The Quality Standards for Minimal Outcome Measurements in Adults and Children were based on the core elements of the other standards, and in itself describes procedural elements for routine assessment and reporting.

telecommuncations access to the clinic and, while in the clinic, with assistive listening devices and alerts.

As the name would suggest, the clinical facilities section outlines which technology should be available to be able to perform a variety of tests. Further, this section highlights the need to regularly calibrate instruments to nationally recognized standards.



Processes:

The clinics and professionals of the HEARRING network believe that providing users with individualized hearing solutions is a careful and detailed process that does not start and stop at surgical implantation. Each of the individual 13 steps is subdivided to provide more specific and in-depth guidelines. Taken together, the cumulative effect is a wealth of best-practice detail which covers every step of the implant experience from selection criteria to long-term maintenance.

The aforementioned six quality standards are published in full on the forthcoming pages followed by a table highlighting the key differences between the standards. It is the HEARRING group's hope that a wide adoption and implantation of these standards will lead to still a greater delivery of the highest quality comprehensive care and thus happier, better hearing implant users.

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一側性難聴児における先天性サイトメガロウイルス感染症の関与

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Correlation of congenital cytomegalovirus infection in children with unilateral sensorineural hearing loss

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Congenital Cytomegalovirus (CMV) infection and mumps infection are major cause of unilateral sensorineural hearing loss (SNHL), but there were few reports showing the frequency of congenital CMV infection in children with unilateral SNHL. The present study investigated the prevalence of congenital CMV infection diagnosed by detection of CMV DNA in dried umbilical cord specimens from children with unilateral SNHL and other causes of unilateral SNHL.

This study evaluated 88 children with unilateral SNHL who were referred to the Department of Otolaryngology, Shinshu University School of Medicine from May 2008 to April 2012. DNA was extracted from the dried umbilical cords and CMV DNA was examined by quantitative PCR. CMV DNA was identified in 8 (9.1%) of 88 children with unilateral SNHL. Unilateral severe to profound SNHL and mild to moderate SNHL caused by congenital CMV infection were detected in 9.6% (7/73) and 6.7% (1/15), respectively. Genetic deafness mutations could not be found. In conclusion, congenital CMV infection plays a major role as a cause of unilateral SNHL in children.

Key words：congenital cytomegalovirus infection, unilateral sensorineural hearing loss, dried umbilical cord, genetic hearing loss
和文キーワード：先天性サイトメガロウイルス感染症，一側性感音難聴，保存臍帯，遺伝性難聴

論文要旨

サイトメガロウイルス（以下CMV）やムンプスウイルスは一側性難聴を生じる代表的な疾患の1つとされている。しかし、先天性CMV感染が一側性難聴の原因に占める頻度や先天性CMV感染による難聴で一側性難聴を生じる頻度などについて厳密に調べた報告はない。今回我々は一側性難聴児に対して保存臍帯を使用してCMV DNA検査を実施し、その他の難聴の原因を含めて検討した。2008年5月から2012年4月までの48ヶ月間に信州大学附属病院耳鼻咽喉科小児難聴外来を受診した134例のうち、一側性感音難聴を認めた88例（65.7%）を対象とした。採取した保存臍帯からDNAを抽出し、定量的PCRにてCMV DNAの有無を診断した。CMV DNAが陽性であったのは、88例中8例（9.1%）に認められた。一側高度難聴は73例中の7例（9.6%）であり、一側軽度～中等度難聴は15例中の1例（6.7%）であった。難聴遺伝子の変異は1例も確認されなかった。先天性CMV感染は小児の一側性感音難聴の主たる原因の1つである事が確認できた。

はじめに

最近、新生児聴覚スクリーニングの導入に伴い、早期に一側性難聴が診断されるようになり、一側性難聴児の1/4が新生児聴覚スクリーニングで発見されている[1]。一側性高度難聴の場合、患側からの聞き取りの困難、騒音下の聞き取りの低下、音源定位の困難が言われている。また、言語発達遅滞や学業成績への影響を指摘する者もあり、一側性難聴であっても日常生活に支障をきたすことがある[2]。一側性難聴を生じる疾患としては、ムンプスウイルスやサイトメガロウイルス（以下CMV）を代表とするウイルス感染や内耳・内耳道奇形、細菌性髄膜炎、auditory neuropathy spectrum disorder（ANSD）などが上げられている。近年画像技術が向上し、MRIにより内耳道内の神経が個別に描出できるようになり、蝸牛神経の無～低形成が先天性一側高度難聴で高頻度に認められている[3]。

CMVは胎内感染する病原体の中で最も頻度が高く、妊娠中に初感染した場合20～40%に胎盤感染し、先天性CMV感染症は出生児の0.2～2.5%にみられる[4),5)]。先天性CMV感染した出生児の約1割が低出生体重・肝脾腫・脳室周囲石灰化、小頭症、DICなどの症候を示し、運動発達遅滞・精神発達遅滞を伴い、その半数に難聴を生じるとされている。それ以外の約9割の出生児は何ら症状を示さない無症候性感染症として経過するが、その後1～3割に難聴や精神発達遅滞などの神経症状を伴ってくる[6),7)]。難聴は中等度から高度の聴力障害から、遅発性・進行性など臨床症状は様々である[8),9)]。また、両側性難聴が25%で一側性難聴が75%であったとの報告もみられている[10)]。しかし、先天性CMV感染症の診断法には免疫学的検査（妊婦のIgG・IgM、新生児のIgM）、新生児の尿やガスリーカードの血液や臍帯の組織を使ったCMV DNA検査法があるが、先天性CMV感染を診断するための実用的なスクリーニング検査法はないため広く行われているわけではない。また新生児の尿検査は出生後2ないし3週以内に実施する必要があり、それ以降に先天性CMV感染を診断するためにはガスリーカードの血液や臍帯の組織を使ったCMV DNA検査が必要となるため、先天性CMV感染が一側性難聴の原因に占める頻度や先天性CMV感染による難聴で一側性難聴を生じる頻度などについて厳密に調べた報告はない。今回我々は一側性難聴児に対して保存臍帯を使用してCMV DNA検査を実施し、検討したので報告する。

対象と方法

対象は、2008年5月から2012年4月までの48ヶ月間に信州大学附属病院耳鼻咽喉科小児難聴外来を受診した感音難聴児134例のうち、一側性感音難聴を認めた88例（65.7%）とした（表1）。対象児は難聴以外に合併症はなく、難聴と診断された年齢は生後1ヶ月から12歳（平均40.8ヶ月）、男児39例、女児49例であった。難聴耳側は右が43例、左が45例であった。難聴耳の平均聴力は89.5dB、良聴耳は平均13.6dBで、平均聴力70dB以上の一側高度難聴が73例（83.0%）、平均聴力20dBから69dBの一側軽度～中等度難聴が15例（17.0%）であった。

表1　一側性感音難聴88児の内訳

性別	男児	39例（44.3%）
	女児	49例（55.7%）
平均聴力レベル	難聴耳	89.5dB
	良聴耳	13.6dB
難聴耳側	右耳	43例（48.9%）
	左耳	45例（51.1%）
高度・重度難聴	例数	73例（83.0%）
	診断時月齢	41.2±36.3ヶ月
軽度・中等度難聴	例数	15例（17.0%）
	診断時月齢	40.3±36.8ヶ月

平均聴力レベルは4分法。高度・重度難聴：70dB以上。軽度・中等度難聴：20dBから69dB。

難聴の診断は純音聴力検査（年齢によっては遊戯聴力検査）とASSR（auditory steady-state evoked response）検査（Master 580-Navpro; Nihon Kohden Co. Ltd, Tokyo, Japan）によって行った。平均聴力は500、1000、2000、4000Hzの4分法とした。聴力検査は6～12ヶ月おきに実施し、複数の周波数で10dB以上の閾値上昇が見られた場合を進行性とし、10dB以上の閾値の悪化、改善がみられた場合を変動性と定義した。

両親の同意を得た上で、難聴遺伝子検査（インベーダー法：13遺伝子46変異）と保存臍帯の一部（5 mm片）を採取（図1）し、CMV DNA検査を実施した。採取した保存臍帯からQIAGEN-QIAamp DNA Miniを用いてDNAを抽出し、定量的PCRにてCMV DNAの有無を診断した。なお、ポジティブコントロール、ネガティブコントロール、解析方法の詳細は引用文献[11)]に記載した方法と同様である。今回は保存臍帯からのCMV

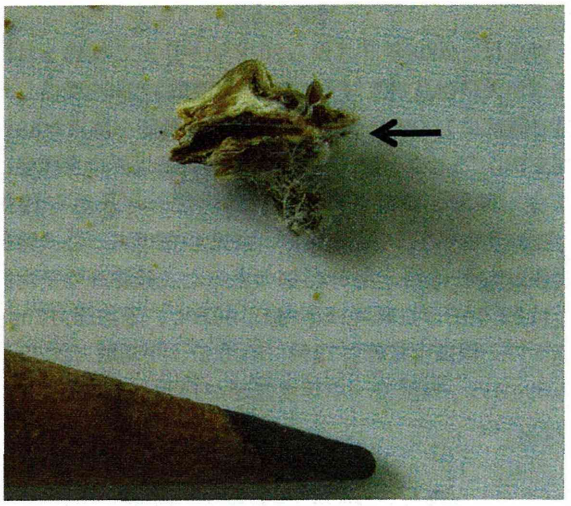

図1　CMV DNA検査のために採取した保存臍帯片

CMV（cytomegalovirus）DNA検査のために必要な約5 mm大に採取した保存臍帯片（矢印）。

DNA検査のみで先天性CMV感染の有無を判断した。

結　果

CMV DNAが陽性であったのは、一側性感音難聴児88例中8例（9.1%）に認められた。一側高度難聴は73例中の7例（9.6%）であり、一側軽度～中等度難聴は15例中の1例（6.7%）であった。CMV陽性であった8例の聴力図を図2に示す。難聴遺伝子の変異は一側性感音難聴児には1例も確認されなかった。表2にCMV DNA陽性を認めた8例の臨床症状の特徴を示す。男児が4例、女児が4例で、難聴の診断時の年齢は生後2ヶ月から98ヶ月、平均50ヶ月であった。難聴耳側は右耳が3例、左耳が5例で、高度難聴の平均聴力は96.3dB、中等度難聴の1例は58.3dBであった。出生児体重は2児以外は不明であったが、1児は2395gと狭義の低出生体重児（2500g未満）であった。しかし、全例頭部MRI検査では異常所見はなく、発達障害もみられていない。難聴の発症時期は新生児聴覚スクリーニング検査で一側REFERと判定された先天性が2例、新生児聴覚スクリーニング検査でPASSが確認されている遅発性発症が2例、不明が4例であった。一側中等度難聴であった1例（12.5%）において変動する聴力が確認された。遅発性発症例、変動＋進行例ともに今回は特に治療は行っていない。CMV DNA陽性が確認された8例においてはCT検査で内耳奇形は認められなかった。

考　察

一側性難聴は日常生活や学校教育においてほとんど支障がないといわれ、自ら訴えができ、左右別の聴力検査ができる就学時頃に発見される事が多かったが、最近、新生児聴覚スクリーニングの導入に伴い、早期に一側性難聴が診断されるようになった。新生児聴覚スクリーニング後の精密検査で一側性難聴と診断される頻度は24.5%～36.8%で、全出生児中の0.07%と報告[12]されている。一側referであっても一側性難聴と診断される頻度は50%前後で、経過観察中に良聴耳が悪化（6%）する例や両側passが最終的に一側性難聴と診断（3～8%）される例がある[13]。信州大学附属病院耳鼻咽喉科小児難聴外来を受診した感音難聴児134例のうち、65.7%に一側性感音難聴を認め、両側性難聴よりも頻度が多かった。

守本ら[14]は94例の一側性難聴児を検討し、36.2%が感音難聴であったが、そのうちの52.9%が原因不明であったと報告している。また、茂木ら[15]（2009年）は2001年から2008年までに信州大学耳鼻咽喉科小児外来を受診した120例の一側性難聴児の原因を調査し、内耳・内耳道奇形が15%、ムンプス難聴が6%、先天性CMV感染症が3%、髄膜炎が2%、突発性難聴が3%、ANSDが4%、原因不明が67%であったと報告している。この時の検討では、120例中20症例のみに保存臍帯からのCMV DNA検査の実施であったため、88例全例に検査を実施した今回の検討に比べると頻度が低くなったと思われる。今回の検討ではCMV DNAが陽性であったのは、一側性感音難聴児の9.1%に認められた。一側高度難聴児にかぎると9.6%であり、一側軽度～中等度難聴にかぎると6.7%であった。一側性難聴における先天性CMV感染児の比率に関してはこれまで25%（1/4例）[16]と19%（8/42例）[17]の報告がみられる。これらの報告より対象者の数は多かったが、頻度は低い結果となった。より正確な頻度を導くには、先天性CMV感染のスクリーニング検査法の確立と普及、さらに前向き研究を実施して行く必要がある。

先天性CMV感染した出生児の約9割は何ら症状を示さない無症候性感染症として経過するが、その後1～3割に難聴や精神発達遅滞などの神経症状を伴ってくる[6),7)]。難聴は中等度から高度の聴力障害がみられ、遅発性（11～18%）・進行性（23～62%）、また難聴が改善する（23～47%）報告[8),9)]がみられている。今回の検討では、先天性CMV感染による一側性難聴の場合、高度難聴が87.5%（7/8例）と高率であった。25%（2/8例）が新生児聴覚スクリーニング検査で一側REFERで