表 3. フォローアッププラン

暦齢	神経診察	血液検査	尿検査	聴力検査	KIDS/新版 K 式/WISC	眼科診	頭部 MRI
1か月齢	○	○	○	○		○	○
4 か月齢	○	○	○				
7 か月齢	○	○	○	○	○		
1 歳	○	○	○	○		○	
2 歳	○	○	○	○	○		○
3 歳	○	○	○	○	○		
4 歳	○	○	○	○	○		
5 歳	○	○	○	○	○		

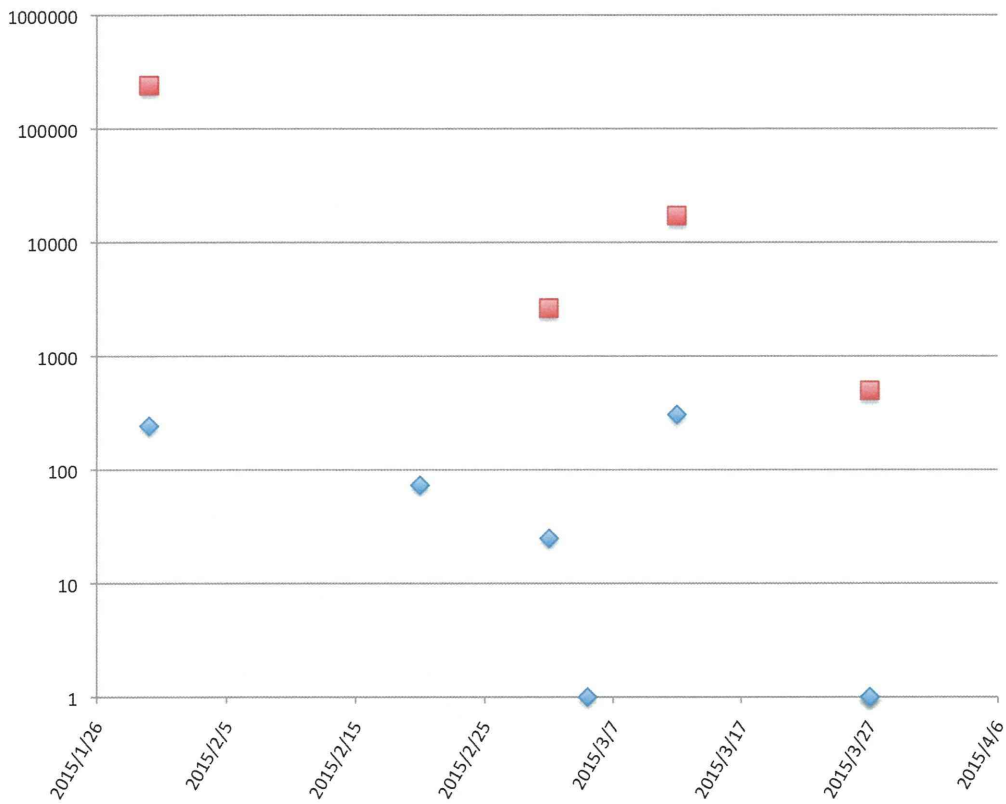

図１　ガンシクロビル治療を実施した児の血液中サイトメガロウイルスのコピー数の変化

ガンシクロビル治療を実施した児の血液中サイトメガロウイルスのコピー数の変化（２例）を示す。
いずれの児も投与後徐々にコピー数の低下を認めている。

Ⅳ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

[1] Moteki H, Suzuki M, Naito Y, Fujiwara K, Oguchi K, Nishio S, Iwasaki S, Usami S. Evaluation of cortical processing of language by use of positron emission tomography in hearing loss children with congenital cytomegalovirus infection. Int J Pediatr Otorhinolaryngol. 78: 285-289. 2014

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V.　研究成果の刊行物・別刷

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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

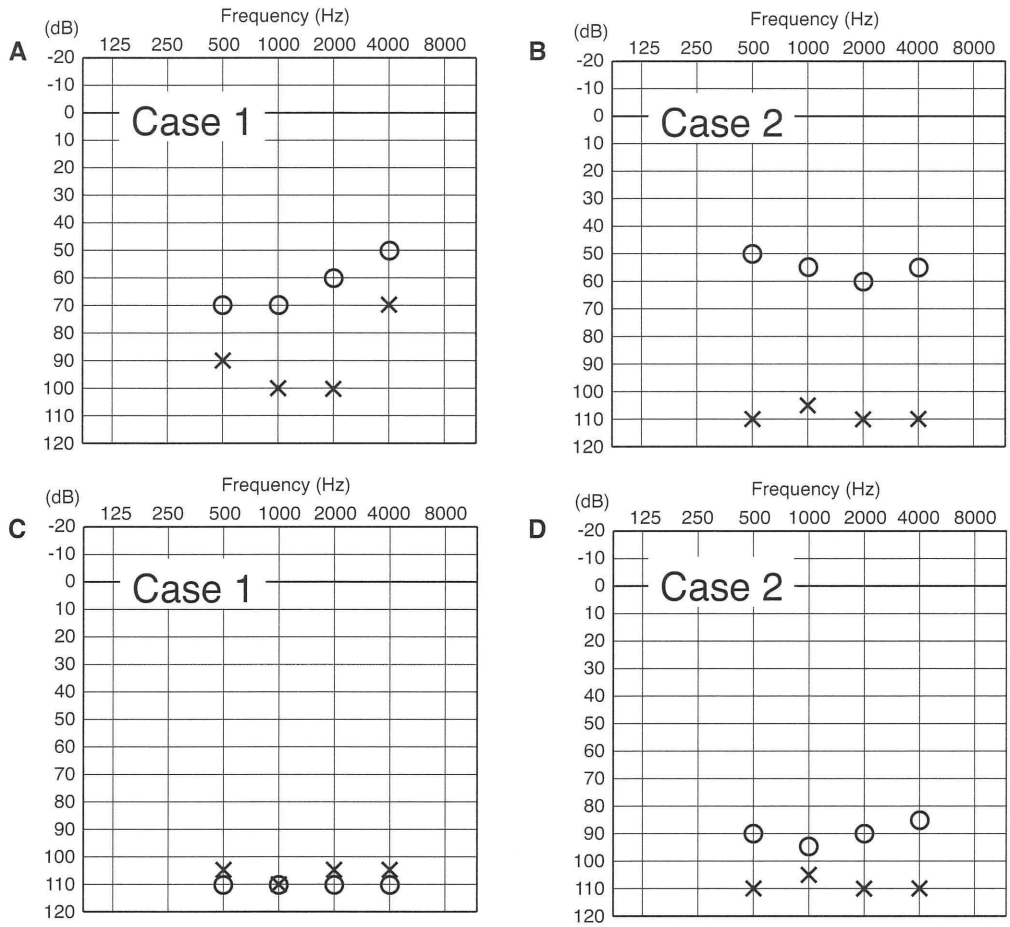

Fig. 1. (A) Case 1; a 5-year-old girl with asymptomatic congenital CMV infection (threshold using ASSR test). (B) Case 2; a 5-year-old girl with asymptomatic congenital CMV infection. These were results of first diagnosed with hearing loss. (C and D) Deterioration in hearing, for one month and for one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

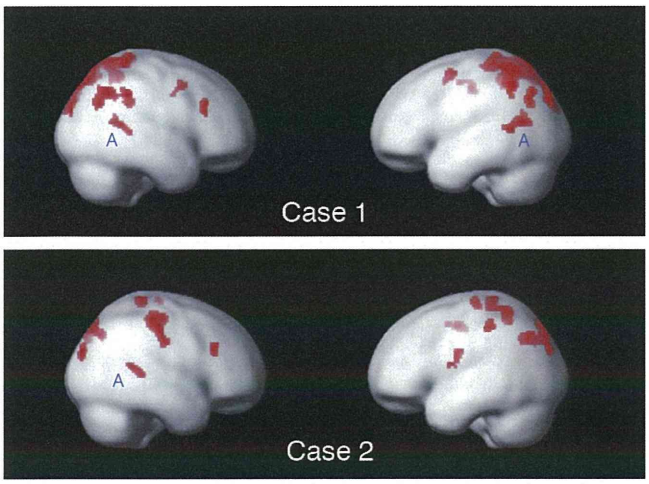

Fig. 2. Cortical activation by language-related visual stimuli in two profoundly deafened with congenital CMV infection cases. Case 1 and 2 showed significant activation in auditory association areas (A) (SPM2, $p < 0.001$, uncorrected).

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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