Auris Nasus Larynx 39 (2012) 638–640

Contents lists available at SciVerse ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

A postmeningitic cochlear implant patient who was postoperatively diagnosed as having X-linked agammaglobulinemia

Ryosei Minoda [a,*], Haruo Takahashi [b], Satoru Miyamaru [a], Masako Masuda [a], Toru Miwa [a], Tetsuji Sanuki [a], Toshinori Hirai [c], Eiji Yumoto [a]

[a] Department of Otolaryngology Head and Neck Surgery, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo Kumamoto 860-8556, Japan
[b] Division of Otorhinolaryngology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Sakamoto 171, Nagasaki 852-8501, Japan
[c] Departments of Diagnostic Radiology, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo Kumamoto 860-8556, Japan

ARTICLE INFO

Article history:
Received 17 October 2011
Accepted 20 January 2012
Available online 16 February 2012

Keywords:
X-linked agammaglobulinemia
Primary immunodeficiency
Cochlear implant

ABSTRACT

X-linked agammaglobulinemia (XLA) is caused by a mutation in the Bruton tyrosine kinase, leading to an arrest in B cell development. Consequently, patients with XLA show significant decreases in gammaglobulin. Here, we describe a child with postmeningitic deafness and XLA who underwent a cochlear implantation. His psychomotor development had been normal and his congenital immunodeficiency was noticed only postoperatively. Immunoglobulin replacement treatment was started, but he still suffered repeated infections. Eventually, his cochlear implant was removed. A preoperative check of immunological status might be advisable in postmeningitic patients undergoing cochlear implantation to reduce the risk of postoperative infectious complications.

1. Introduction

Cochlear implantation is generally accepted as a safe and effective treatment to rehabilitate patients with bilateral severe-to-profound hearing loss. The complication rate is relatively low. The most common non-device-related complications occur around the skin flap, and the incidence of infectious complications has been reported as 12.9% [1].

Primary immunodeficiency affects as many as 10 million people worldwide. More than 150 primary immunodeficiency diseases have been identified, and they range widely in severity. Immunodeficient conditions likely increase the risk of postoperative infectious complications even in cochlear implant patients.

To the best of our knowledge, only five patients with cochlear implants who had primary immunodeficiencies have been reported to date. Hopfenspirger et al. [2] described two patients with primary immunodeficiency: one with neutropenia/chemotactic neutrophil dysfunction and one with IgA deficiency. Although they had been diagnosed with primary immunodeficiencies preoperatively, they suffered postoperative infections at the surgical sites. Eventually, the cochlear implants in both patients were removed. Yu et al. [3] reported two patients with immunodeficiency who also suffered postoperative infections after cochlear implant surgeries and were then diagnosed with primary immunodeficiencies based on results of their IgG isohemagglutinin titers decreasing postoperatively. They reported that the cochlear implant in one of the two patients was preserved with daily low-dose oral antibiotic administration, without intravenous immunoglobulin therapy [3]. More recently, Brookes et al. [4] reported on a patient who was diagnosed with deafness-dystonia-optic neuronopathy (DDON) syndrome and X-linked agammaglobulinemia (XLA). His XLA was preoperatively diagnosed and antibody replacement therapy was initiated. He did not appear to have any wound troubles after cochlear implantation.

Here, we report on the clinical course of a child with a cochlear implant who was diagnosed with XLA postoperatively. To the best of our knowledge, this is the second report of a patient with XLA who underwent cochlear implantation.

2. Case report

A 3-year-old boy with a postmeningitic profound sensorineural hearing loss (SNHL) was referred to our department in May 2006, to obtain an evaluation for cochlear implantation. A physical examination at the first visit to our department revealed that he had a partial severe retraction of tympanic membrane pars tensa in the right ear and accumulated effusions in the left ear, with purulent rhinorrhea in his nasal cavities. Play audiometry and an auditory brainstem response examination revealed bilateral profound SNHL. A CT scan and MRI examinations revealed

* Corresponding author. Tel.: +81 96 373 5255; fax: +81 96 373 5256.
E-mail address: minoda@gpo.kumamoto-u.ac.jp (R. Minoda).

0385-8146/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.anl.2011.12.005

ossification of the basal turn of the scala tympani of the bilateral cochleae.

In June 2006, we performed cochlear implantation surgery on the left ear. Although ossification was observed in the basal turn of the scala tympani, all electrodes (CI24RE (CA); Cochlear, Ltd., Cove, NSW, Australia) were inserted into the scala tympani. He received ceftriaxone for 10 days postoperatively. His postoperative clinical course and postoperative speech recognition ability were good.

However, in December 2007, he complained of pain where the device had been implanted, and his mother noticed swelling at the site. The swelling and his symptoms became worse (Fig. 1), although he was receiving an oral antibiotic. We then performed surgical drainage, revealing that the content of the swelling was a purulent secretion. Drain tubes were placed during the surgery. Bacteriological examination of the purulent secretion revealed *Streptococcus pneumoniae* (PISP). The local condition improved with daily postoperative lavage through the drain tubes and antibiotic administration.

In April and July 2008, the localized swelling and pain re-appeared again twice. We performed surgical drainage. The content of the swelling revealed a blood clot, and bacteriological examinations of the contents were negative. The local condition again improved with the same treatment as before. During his hospital stay, he underwent patch tests against the materials used in the cochlear implant, provided by the implant company; all the tests were negative. In June 2008, he was treated at a hospital for pneumonia. In September 2008, he underwent an immunological evaluation. His peripheral blood B cell subset was less than 1%, and his serum IgG, IgA, and IgM were 7 mg/dL, 3 mg/dL, and 30 mg/dL, respectively. Gene analysis revealed a mutation in the Bruton tyrosine kinase gene.

He was finally diagnosed with XLA. He started to undergo antibody replacement therapy every 3 weeks: his physical activity level improved significantly; and, his repeated purulent nasal discharges stopped spontaneously without usage of antibiotics,

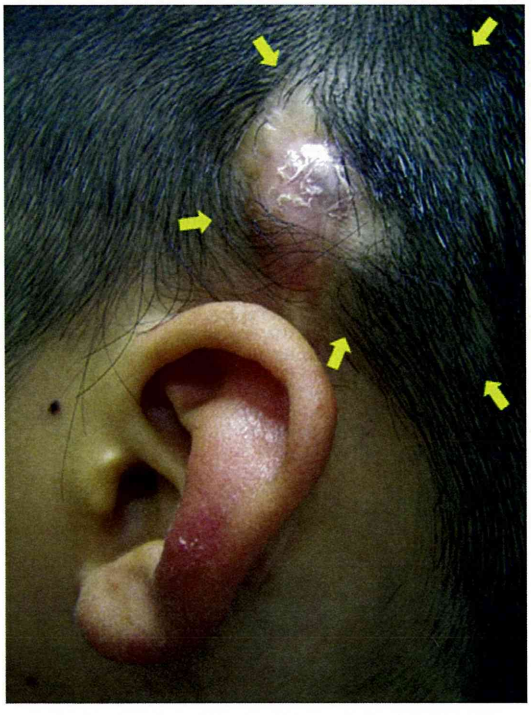


Fig. 1. Swelling at the site where the cochlear implant was implanted.

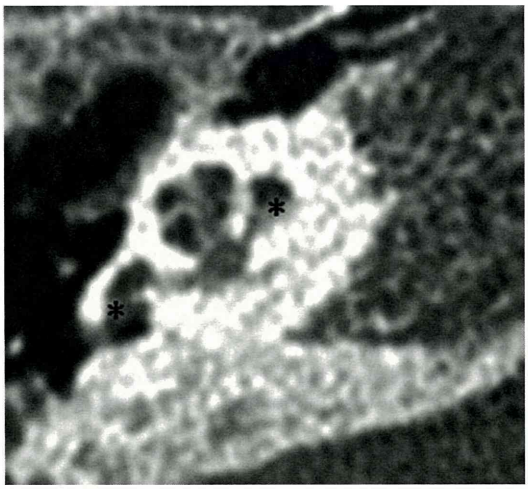


Fig. 2. A CT scan image of right ear at the second cochlear implantation. The asterisks indicate ossification of the scala tympani in the basal turn of the cochlea.

after this treatment. Despite the antibody replacement therapy, subsequently, local swelling around the implant recurred twice more. On the second occurrence, we removed granulation tissue surrounding the cochlear implant in addition to surgical drainage under general anesthesia. During the surgery, we held electrode bundle near the implant, turned it over, removed all granulation tissue surrounding the cochlear implant, to the extent possible, and washed the wound gently with saline many times, after which the cochlear implant was covered with the temporal muscle. Nevertheless, he experienced local swelling and pain again, and self-destruction of wound skin was observed. Finally, we decided to remove the cochlear implant. In February 2010, we performed cochlear implant surgery on the right ear (PULSAR; Med-El, Innsbruck, Austria) and subsequently removed the cochlear implant from the left ear. We inserted the electrode into the scala vestibule because a preoperative CT scan study revealed ossification of the scala tympani in the right ear (Fig. 2). We successfully inserted all except one electrode. Postoperatively, he received flomoxef and clindamycin for 12 days and his serum IgG level was maintained at 1000–1700 mg/dL by intravenous administration of γ-globulin perioperatively. His postoperative clinical course was good. For 22 months, no recurrence of local swelling occurred since the surgery. Postoperative speech recognition ability testing revealed 56% (words) by the Japanese speech recognition test battery, "CI–2004" under the auditory-only listening condition.

3. Discussion

XLA is caused by mutations in the Bruton tyrosine kinase, located at chromosome Xq22, leading to arrested B cell development at a pre-B cell stage. As a result, patients have no mature B cells, and IgG is less that 200 mg/dL. XLA accounted for 7.3% of primary immunodeficiency conditions in a 2007 survey in the United States. The immunodeficient condition allows bacterial meningitis, although most patients who present with bacterial meningitis do not have XLA or any other obvious deficiency in immune function [5]. Additionally, only 7.1% of child patients experience bilateral profound hearing (>90 dBSPL) after childhood bacterial meningitis [6]. Given these numbers, very rarely will a patient with postmeningitis who is a candidate for cochlear implant surgery have an immunodeficiency condition.

The most reliable strategy for the management of postoperative wound infections after cochlear implantation may be to explant

the device. Tambyraja et al. [1] summarized data from the Manufacturer User Facility and Distributor Experience (MAUDE) database, which is maintained by the Food & Drug Administration and has mandatory reporting requirements. In the pre-2002 period, 102 cases of flap problems were reported, which included flap necrosis, flap infection, flap dehiscence, and device extrusion. Approximately 70% of cochlear implants were explanted in those patients. However, current recommendations call for conservative measures [7]. Yu et al. [3] reported four patients with postoperative infections including two primary immunodeficiency patients, who showed decreased IgG isohemagglutinin titers. The postoperative cochlear implant infections in three of the four were controlled effectively with limited surgical approaches and prolonged postoperative antibiotic administration [3]. The cochlear implant was explanted due to failure of infection control in one patient with a primary immunodeficiency although antibody replacement therapy and intravenous antibiotics administration were continued [3]. Considering these reports, prolonged medical management may be effective. However, in the patient with primary immunodeficiency who did not need device removal, the report did not provide detailed levels of immunoglobulin, and her infection was successfully controlled using only a daily low-dose oral antibiotic (cephalexin) with no antibody replacement therapy; her immunodeficiency thus may not have been severe. Taken together, the conservative approach probably has limited efficacy in patients who are immunodeficient.

Controlling infectious complications after cochlear implant surgery can be difficult even in healthy patients. Recently, biofilm formation on the surface of a cochlear implant receiver–stimulator device was suggested to probably contribute to persistent cochlear implant infection. Such a bacterial biofilm on the device is highly resistant to antibiotic therapy and to removal by direct washing of the device [8]. Moreover, Pawlowski et al. [8] reported that the biofilm on the device was most substantial in the depressions along the surface of the device that were created by the manufacturer. Considering these points, the first infection on our patient was likely due to his untreated immunodeficiency condition, and biofilm on the surface of the device probably contributed to the persistent local infection.

If the patient's immunodeficiency is diagnosed preoperatively, one can add supplemental treatments perioperatively to help avoid postoperative complications. Brookes et al. [4] reported on a patient who was diagnosed with DDON syndrome and XLA. His XLA was preoperatively diagnosed and antibody replacement therapy was initiated. He did not appear to have any wound troubles after cochlear implantation. However, if the patient has not been diagnosed preoperatively, like our patient, the immunodeficient condition probably tends to increase infectious complications, ultimately leading to extraction of the implant. Also, in patients who are postmeningitic, cochlear implant surgery on the opposite side probably becomes more formidable because of postmeningitic ossification in the cochlea. Thus, considering the presence of an immunodeficient condition in patients is important, especially from symptoms suggesting such conditions such as recurrent infections. In most patients with XLA, they typically present with recurrent pyogenic infections starting at 5–6 months of age when passively placentally transferred maternal antibodies have waned [9]. Our patient had repeated purulent rhinorrhea preoperatively, which continued postoperatively. He also suffered from pneumonia once postoperatively. With hindsight, these were likely signs of his immunodeficient condition. Physicians should pay attention to the possibility of an immunodeficient condition in a patient before and after surgery. To reduce the risk of complications after a cochlear implant, we think that in addition to obtaining a careful history about any repeated infections, preoperative checks of serum immunoglobulins (IgG, IgA, IgM) and IgG subclass analyses might be needed for the diagnosis of major primary immunodeficient deficits on cochlear implant candidates who have had repeated infectious episodes. Moreover, the prevalence of acquired immune-deficiency syndrome (AIDS) continues to increase, so a preoperative check of the CD4/CD8 ratio might also be useful.

4. Conclusion

An immunodeficient condition may allow bacterial meningitis. However, most patients who present with bacterial meningitis do not have an immunodeficiency [5] and less than 10% of children with meningitis experience bilateral profound hearing after bacterial meningitis [6]. Thus, the chance of seeing a patient with XLA as a candidate for cochlear implant surgery is very low. However, we should consider an immunodeficient condition as a possible cause of meningitis in patients who are candidates for cochlear implants in helping to avoid postoperative infectious complications.

Conflicts of interest

None.

References

[1] Tambyraja RR, Gutman MA, Megerian CA. Cochlear implant complications: utility of federal database in systematic analysis. Arch Otolaryngol Head Neck Surg 2005;131:245–50.
[2] Hopfenspirger MT, Levine SC, Rimell FL. Infectious complications in pediatric cochlear implants. Laryngoscope 2007;117:1825–9.
[3] Yu KC, Hegarty JL, Gantz BJ, Lalwani AK. Conservative management of infections in cochlear implant recipients. Otolaryngol Head Neck Surg 2001;125:66–70.
[4] Brookes JT, Kanis AB, Tan LY, Tranebjaerg L, Vore A, Smith RJ. Cochlear implantation in deafness-dystonia-optic neuronopathy (DDON) syndrome. Int J Pediatr Otorhinolaryngol 2008;72:121–6.
[5] Overturf GD. Indications for the immunological evaluation of patients with meningitis. Clin Infect Dis 2003;36:189–94.
[6] Adachi N, Ito K, Sakata H. Risk factors for hearing loss after pediatric meningitis in Japan. Ann Otol Rhinol Laryngol 2010;119:294–6.
[7] Cunningham 3rd CD, Slattery 3rd WH, Luxford WM. Postoperative infection in cochlear implant patients. Otolaryngol Head Neck Surg 2004;131:109–14.
[8] Pawlowski KS, Wawro D, Roland PS. Bacterial biofilm formation on a human cochlear implant. Otol Neurotol 2005;26:972–5.
[9] Mahmoudi M. Allergy and asthma: Practical diagnosis and management. McGraw-Hill Professional Publishing; 2007.

Auris Nasus Larynx 40 (2013) 435–439

Contents lists available at SciVerse ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Long term speech perception after cochlear implant in pediatric patients with *GJB2* mutations

Haruo Yoshida [a,b,*], Haruo Takahashi [b], Yukihiko Kanda [b,c], Shin-ichi Usami [d]

[a] *Department of Otolaryngology-Head and Neck Surgery, National Hospital Organization Ureshino Medical Center, Saga, Japan*
[b] *Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[c] *Nagasaki Bell Hearing Center, Nagasaki, Japan*
[d] *Department of Otorhinolaryngology, Shinshu University School of Medicine, Asahi, Matsumoto, Japan*

ARTICLE INFO

Article history:
Received 4 September 2012
Accepted 24 January 2013
Available online 9 March 2013

Keywords:
GJB2 hearing impairments
Cochlear implant
Genetic testing
Hereditary hearing loss

ABSTRACT

Objectives: To determine the long term effect of cochlear implant (CI) in children with *GJB2*-related deafness in Japan.
Methods: Genetic testing was performed on 29 children with CI. The speech perception in 9 children with *GJB2* gene-related deafness fitted with CI was compared with those in matched 10 children who were diagnosed as having no genetic loci. The average follow-up period after CI was 55.9 months and 54.6 months, respectively.
Results: A definitive inherited hearing impairment could be confirmed in 12 (41.4%) of the 29 CI children, including 10 with *GJB2*-related hearing impairment and 2 with SLC26A4-related hearing impairment. The results of IT-MAIS, word or speech perception testing under the noise, and development of speech perception and production testing using the Enjoji scale were slightly better for the *GJB2* group after CI than for the control group without statistical significant difference.
Conclusion: The long-term results of this study show that CI is also effective in the development of speech performance after CI in Japanese children with *GJB2*-related hearing impairments as HL due to other etiologies.

1. Introduction

Recent progress in the research on hereditary hearing loss is remarkable. Since 1992, more than 125 genetic loci have been reported to be involved in nonsyndromic hearing loss (HL) [1], and over 67 of those loci are involved in autosomal recessive nonsyndromic HL [2]. Among these, the *GJB2* gene encoding the connexin (Cx) 26 protein (chromosomal 13q11-12) is the most common, of which about 100 different *GJB2* mutations have been reported globally [3]. It is reported to account for between 20 and 50% of all recessive nonsyndromic cases [4].

On the other hand, the benefits of cochlear implantation (CI) for spoken language, reading skills, and cognitive development have been clearly demonstrated [5,6]. Recently, the outcomes of CIs in patients with *GJB2* mutations have also been reported. Several studies have shown that patients with *GJB2* mutations (OMIM 121011) usually exhibit excellent speech perception and language performance after CI, when compared with those without identifiable *GJB2* mutations [7–11]. However, other studies have demonstrated that when the control group is appropriately matched with regard to age at implantation and length of post CI, there is no significant difference when comparing those with *GJB2*-related deafness to those without it [12–15]. Results analyzing post-CI speech performance in patients with *GJB2* mutations are still controversial.

In this study, in order to know whether the long term effect of CI is better in children with *GJB2*-related deafness or not, we have studied the speech perception outcome of CI in children with *GJB2* gene mutations, and compared them to those in matched children without inherited hearing loss.

2. Materials and methods

2.1. Subjects

We have performed CI in 301 cases in our clinic since 1997. Genetic testing was performed in 29 children with CI, and definitive *GJB2*- and *SLC26A4*-related hearing impairment was confirmed in 10 (34.5%) and 2 (6.9%) children with CI, respectively.

* Corresponding author at: Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel.: +81 95 849 7349; fax: +81 95 849 7352.
E-mail address: y-haruo@f6.dion.ne.jp (H. Yoshida).

0385-8146/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.anl.2013.01.006

Table 1
Clinical information of cases in the 2 groups.

Group	Control	GJB2	*P* value
Number of cases	10	9	
Sex (male:female)	3:7	2:7	
Age at CI (months)	36.7	37.4	0.5996
Post CI (months)	54.6	55.9	0.6736
Pre-CI education	Auditory-verbal/oral	Auditory-verbal/oral	

CI: cochlear implantation.

Finally, 19 children whose selection criteria were as follows were enrolled for this study.

1. Their age at CI was 6 years or less
2. Their guardian accepted gene mutation analysis
3. There was no any other apparent cause of deafness such as inner ear anomaly, central disorders/learning difficulties, or cytomegalovirus (CMV) infection

We divided them into two groups: the first, a control group consisting of 10 children who were diagnosed as having no genetic loci, while the second was the actual *GJB2* study group consisting of 9 children with *GJB2* gene-related deafness. Detail of their clinical information is shown in Table 1. HL was diagnosed at a different age in each child, but showed 90 dB or more severe HL before the age of 6 on auditory brainstem response (ABR) test. Preoperative imaging studies (CT and MR) showed no abnormal findings in any of the children in each group. None of the children showed any cognitive delay. The average age at CI in the two groups was 36.7 months (ranging from 21 to 67 months old; 3 male and 7 female) and 37.4 months (ranging from 22 to 63 months old; 2 male and 7 female), respectively. Thus, there is no significant difference between the two groups (Student's *t*-test, $t = -0.5339$, $P = 0.5996$). Their average follow-up period after CI was 54.6 months (ranging from 24 to 110 months) and 55.9 months (ranging from 47 to 62 months), respectively (Student's *t*-test, $t = -0.4278$, $P = 0.6736$). All the cases in this study had an intensive auditory-verbal education without visual information since childhood. Both the CI operation and the (re)habilitation after CI took place in the same clinic.

All patients were fitted with a CI system from either nucleus multichannel cochlear implant system (Cochlear Corporation, Englewood, CO, U.S.A.) or Combi40+ cochlear implant system (MED-EL, Innsbruck, Austria). All electrode arrays were inserted in all patients. There were no perioperative complications in any of the patients.

We examined the hearing level (both with CI and with hearing aids), the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), speech perception skills, and development of articulation in the two groups before and after CI several times in the postoperative period ranging from 6 months to 4 years. The best results from this period were used in evaluating the hearing level and the speech perception skills in the two groups. The speech perception skills were evaluated using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89) tested at 70 dB SPL (sound pressure level) using an open-set questionnaire. We also examined the development of speech perception and production by using the Enjoji Scale of Infant Analytical Development (Enjoji Scale), which was developed in Japan and is now established as one of the standard developmental examinations for evaluating the development of children from birth to about the age of 6 [16]. In this examination, the development of a child can be assessed by checking his or her performance on the chart, in which standard developmental items at each month are described in the three fields including motor, social and language skills. The results allow us to clearly assess to what extent a child is successfully developing in each of the three fields and the six subdivided categories. These tests were conducted up to 2 years after CI.

2.2. Mutation detection

15 ml peripheral venous blood using standard procedure was sent to the Institute of Otorhinolaryngology, Shinshu University School of Medicine, Matsumoto, Japan for Genomic DNA extraction. All subjects underwent mutation screening for 47 common mutations of 10 hearing loss related genes in Japan by using invader assay [17,18].

Written informed consent was obtained from the guardians of all the subjects and the study was approved by the ethical committee of our institute (approval number: 07122106). The differences between in the two groups were analyzed statistically using the paired *t*-test and the unpaired Student's *t*-test. All the acceptance criterion for a significant addition to the explained variance was set at *P* values under 0.05.

3. Results

A definitive *GJB2*-related hearing impairment was confirmed in 9 (32.2%) of the 29 children with CI. Table 2 shows the details of detected *GJB2* gene-mutations. *GJB2 c.*235delC was observed in 3 cases, while six children each had one distinct mutation as listed in the table.

Fig. 1 shows the preoperative aided hearing thresholds. The preoperative hearing level was over 90 dB in all the cases, and the average level of preoperative aided hearing thresholds was nearly 60 dB in the two groups presenting no significant difference between the two groups.

Fig. 2 shows the postoperative hearing thresholds with CI. After CI, the hearing level improved to 25–30 dB in both groups, thus there was no significant difference between the groups.

Fig. 3 shows the results of the IT-MAIS for the two groups. Preoperative scores were worse in the *GJB2* group than in the control group, however, these improved from 1 year to 3 years after CI. The averaged IT-MAIS score in the GJB2 group was 9.8 ± 12.9 (range, 0–31) preoperatively. The averaged IT-MAIS score at 2 years after CI increased up to 33.6 ± 7.8 (range, 20–39), and this improvement was statistically significant (paired *t*-test, $P = 0.017$). The averaged IT-MAIS score in the control group at 2 years after CI

Table 2
Mutations with GJB2 gene in 9 cases.

Mutation	Number of cases
GJB2 c.[235delC];[235delC]	3
GJB2 c.[511insAACG];p.[T86R]	1
GJB2 c.[235delC];[299-300delAT]	1
GJB2 p.[G45E;Y136X];[R143W]	1
GJB2 c.[176-191del16];[299-300delAT]	1
GJB2 c.[235delC];p.[G45E;Y136X]	1
GJB2 c.[235delC];p.[R143W]	1

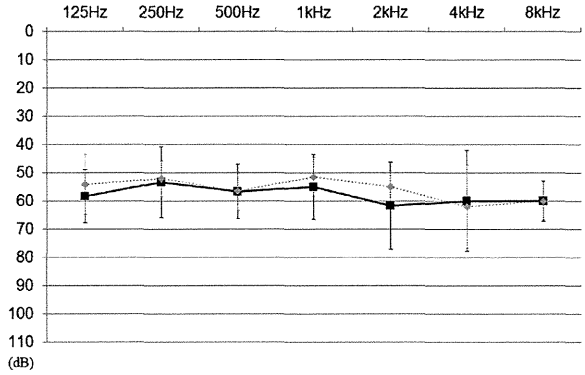


Fig. 1. Results of the average level of preoperative aided hearing thresholds at each frequency. Diamond dots and solid line: control group; square dots and solid line: *GJB2* group; bars: indicate two standard deviations.

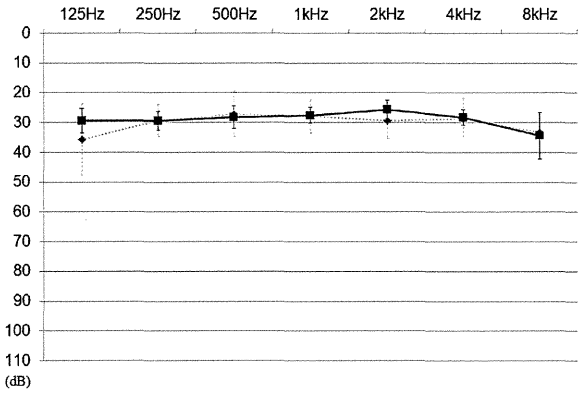


Fig. 2. Results of the average level of postoperative hearing thresholds with CI at each frequency. Diamond dots and solid line: control group; square dots and solid line: *GJB2* group; bars: indicate two standard deviations.

was 30.4 ± 7.6 (range, 19–38). There was no significant difference in the scores between the two groups at 4 years after CI.

Fig. 4 shows the results of speech perception skills in the two groups after CI. Longitudinal axis indicates the results (%) when tested at 70 dB SPL using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89) in the two groups. There was no significant difference between the two groups, but the percentage of correct answers (%) examined under the noise tended to be better in the *GJB2* group.

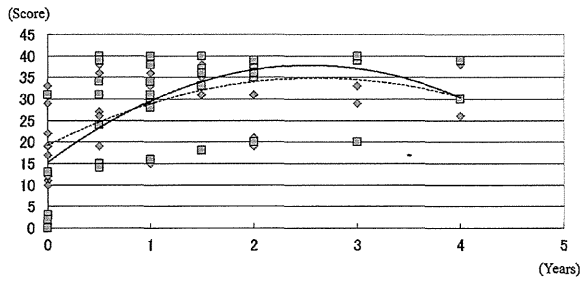


Fig. 3. Results of the difference of IT-MAIS scores from 0 years (=preoperative) to 4 years after CI. Diamond dots: scores in the control group; square dots: scores in the *GJB2* group; dotted line: trend line in the control group; solid line: trend line in the *GJB2* group.

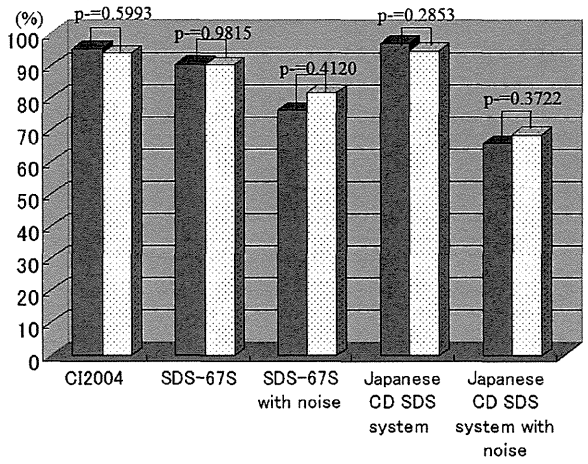


Fig. 4. Results of speech perception skills examined by using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89). Longitudinal axis indicates the correct answer rate (%). Gray bars: control group; dotted bars: *GJB2* group.

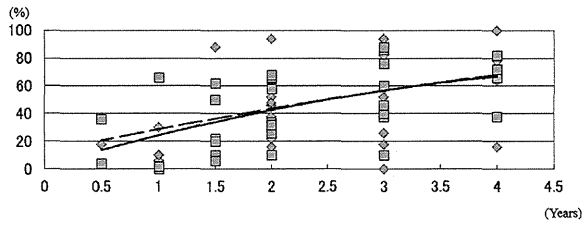


Fig. 5. Results of the development of articulation from 0.5 to 4 years after CI. Diamond dots: accuracy rates in the control group; square dots: accuracy rates in the *GJB2* group.

Fig. 5 shows the results of development of articulation in the two groups after CI. There was no significant difference in the scores between the two groups.

Fig. 6 shows the results in the development of speech perception (Fig. 6a) and production (Fig. 6b) in the two groups after CI. Values of month in the ordinate were calculated by subtracting the developmental months assessed by the Enjoji Scale from the actual age at each period, thus, smaller values indicate better development of speech perception and production. Postoperative language perception and production in the *GJB2* group tended to be slightly better, especially at one and half years after surgery, but there was no significant difference in these scores.

4. Discussion

The incidence of HL is approximately 0.1% among newborns, and hereditary HL is identified in at least 60% of patients with congenital HL, for whom the proportion of syndromic and non-syndromic is 30% and 70%, respectively [19]. The most common trait of nonsyndromic HL is autosomal recessive, which accounts for about 80% of cases [20], and *GJB2* is the gene most frequently associated with hereditary HL. The incidence of *GJB2* mutations in the Japanese population with HL is 14.2% overall and 25.2% in patients with congenital hearing loss [21], and 35 of the 119 cases (29.4%) with non-syndromic deafness [22]. In children with CI, 135 hearing-impaired patients (270 alleles) were tested, and *GJB2* mutations for the c.235delC were found in 39 alleles of 270 alleles (14%). Especially the homozygous of c.235delC was detected in 26

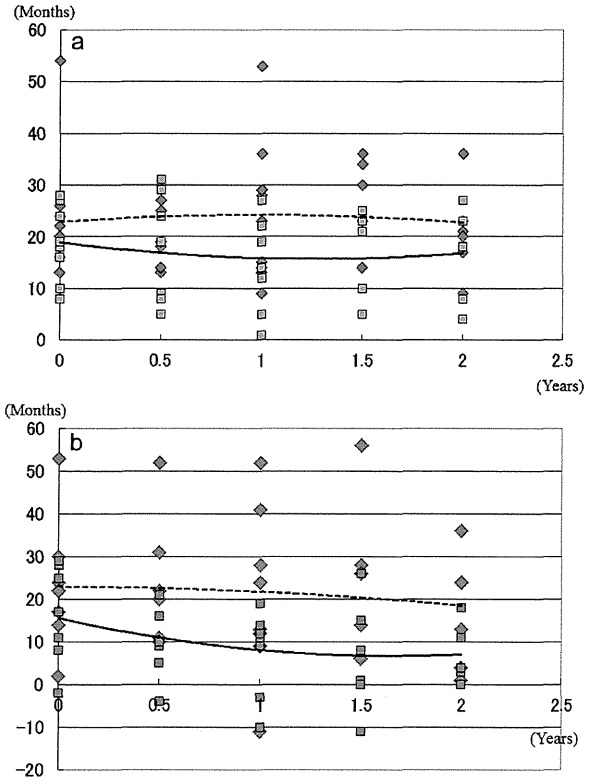


Fig. 6. Results of the developmental course of language perception (a) and production (b) in the control and *GJB2* groups examined by Enjoji Scale of Infant Analytical Development test. Diamond dots: scores in the control group; square dots: scores in the *GJB2* group; dotted line: trend line in the control group; solid line: trend line in the *GJB2* group.

alleles (9.6%), single heterozygous of c.235delC was detected in 1 allele (0.4%) and compound heterozygous of c.235delC was found in 12 alleles (4.4%) [23].

In this study, a definitive inherited hearing impairment could be confirmed in 11 (37.9%) of the 29 CI children, including 9 with *GJB2*-related hearing impairment, 2 with *SLC26A4*-related hearing impairment. These percentages are quite high and remind us of the importance of performing the mutation detection for CI patients.

The *GJB2* group underwent the IT-MAIS, word or speech perception testing under the noise, and development of speech perception and production testing using the Enjoji scale. The finally achieved performances in the two groups were not significantly different, but the averaged IT-MAIS score at 2 years after CI was significantly better in the GJB2 group than in the control group. This result may indicate that the necessary period to achieve the actual age development was shorter in the *GJB2* group than in the control group, and the difference may become smaller as they acquire language through CI in longer term. Matsushiro evaluated 4 CI children with GJB2 gene mutation and reported that the postoperative IT-MAIS score at 6 months was significantly higher in comparison with that of other prelingual CI patients [24]. In this study, children such as those having inner ear anomaly or cytomegalovirus infection, whose postoperative performance after CI is not necessarily good, were excluded from the control group. Considering that these children may also be candidates for CI in general, we can expect CI is efficient for Japanese children with *GJB2* gene mutation as well as for those reported previously [8,23,24].

GJB2 and *GJB6*, mapping to the DFNB1 locus and encoding the gap-junctions Cx 26 and 30, respectively [25]. Cx 26 and 30 are widely expressed in the cochlea at the level of the organ of Corti's supporting cells and connective tissues, and have an important role in forming homomeric or heteromeric hemichannels [26,27]. Mutations in Cx26 are presumed to result in altered potassium recirculation, leading to an accumulation of potassium in the cochlear endolymph and causing hair cell dysfunction and deafness [28]. In other words, mutations in the Cx26 protein mainly lead to the impairment of the endolymph potassium concentrations, which are required for auditory signal transduction, but may not lead to severe damage or decreasing the number of hair cells. It is generally assumed that the results of CI are poorer for inner ear malformation and in cases with neural and/or central damage than in cases with disorders within the inner ear causing the hair cells damage because the auditory pathway including the first neuron, spiral ganglion cells, may well be preserved in the latter. We speculate that the reason why the *GJB2* group had better results in this study is perhaps due to a comparatively good survival and preservation of electrical excitability of the cochlear spiral ganglion cells and the auditory nerve, which is important in the successful CI results [29].

There are some specific reports which support the present results and our speculations. In a rat model, Cx26 was shown to be expressed in nonsensory epithelial and connective tissue cells, but not in the inner or outer hair cells or cochlear nerve fibers [30]. Anatomically, Cx26 mutations result in a dysgenesis of the stria vascularis and hair cells in the organ of Corti, but with minimal neural degeneration and a normal population of spiral ganglion cells in both the apical and basal turns of the cochlea. [31] In the electrophysiological study, children with *GJB2*-related HL had greater similarities between low- and high-frequency residual hearing and between neural activity electrically evoked at apical and basal regions of the cochlea than children with non-*GJB2*-related HL [32]. These results may suggest more consistent spiral ganglion survival along the length of the cochlea in *GJB2*-related HL, which appears to involve a decreasing gradient of spiral ganglion survival from the apex to the base of the cochlea.

Most genotype-phenotype correlation studies have indicated that HL of the subjects with *GJB2* mutations shows a non-progressive pattern [33,34], however, some studies indicated a progressive pattern. [23,35,36]. Considering that early CI is well known to be one of the most important factors for the better postoperative performance for children with congenital HL, even in children with progressive hearing loss due to *GJB2* mutation, we might be able to prepare for early CI for those children if we were aware of it. The early screening of *GJB2* mutation for newborns with severe to profound HL might be advisable.

5. Conclusions

Despite the limits imposed by the small sample size, this study points to the importance of routine genetic assessments. The long-term results of this study also show that CI is also effective in the development of speech performance after CI in Japanese children with *GJB2*-related hearing impairments as HL due to other etiologies. If a child through genetic assessment is diagnosed as having a *GJB2*-related hearing impairment, CI can provide considerable benefits.

Conflict of interest

None.

References

[1] Morell RJ, Kim HJ, Hood LJ, Goforth L, Friderici K, Fisher R, et al. Mutations in the connexin 26 gene (*GJB2*) among Ashkenazi Jews with nonsyndromic recessive deafness. N Engl J Med 1998;339:1500–5.

[2] Van Camp G, Smith RJ. Hereditary hearing loss homepage, http://web-h01.ua.ac.be/hhh/ [accessed 25.01.12].

[3] Xavier E, Paolo G. The Connexin-Deafness homepage, http://davinci.crg.es/deafness/ [accessed 25.01.12].

[4] Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, et al. Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene. Hum Mol Genet 1997;6. 2173Y7.

[5] Balkany TJ, Hodges AV, Eshraghi AA, Butts S, Bricker K, Lingvai J, et al. Cochlear implants in children—a review. Acta Otolaryngol 2002;122:356–62.

[6] UK Cochlear Implant Study Group. Criteria of candidacy for unilateral cochlear implantation in postlingually deafened adults. II. Cost-effectiveness analysis. Ear Hear 2004;25:336–60.

[7] Green GE, Scott DA, McDonald JM, Teagle HF, Tomblin BJ, Spencer LJ, et al. Performance of cochlear implant recipients with *GJB2*-related deafness. Am J Med Genet 2012;109:167–70.

[8] Fukushima K, Sugata K, Kasai N, Fukuda S, Nagayasu R, Toida N, et al. Better speech performance in cochlear implant patients with *GJB2*-related deafness. Int J Pediatr Otorhinolaryngol 2002;62:151–7.

[9] Sinnathuray AR, Toner JG, Geddis A, Clarke-Lyttle J, Patterson CC, Hughes AE. Auditory perception and speech discrimination after cochlear implantation in patients with connexin 26 (*GJB2*) gene-related deafness. Otol Neurotol 2004;25:930–4.

[10] Wu CC, Lee YC, Chen PJ, Hsu CJ. Predominance of genetic diagnosis and imaging results as predictors in determining the speech perception performance outcome after cochlear implantation in children. Arch Pediatr Adolesc Med 2008;162:269–76.

[11] Chora JR, Matos TD, Martins JH, Alves MC, Andrade SM, Silva LF, et al. DFNB1-associated deafness in Portuguese cochlear implant users: prevalence and impact on oral outcome. Int J Pediatr Otorhinolaryngol 2010;74:1135–9.

[12] Lustig LR, Lin D, Venick H, Larky J, Yeagle J, Chinnici J, et al. *GJB2* gene mutations in cochlear implant recipients: prevalence and impact on outcome. Arch Otolaryngol Head Neck Surg 2004;130:541–6.

[13] Cullen RD, Buchman CA, Brown CJ, Copeland BJ, Zdanski C, Pillsbury IIIrd HC, et al. Cochlear implantation for children with *GJB2*-related deafness. Laryngoscope 2004;114:1415–9.

[14] Dahl HH, Wake M, Sarant J, Poulakis Z, Siemering K, Blamey P. Language and speech perception outcomes in hearing-impaired children with and without connexin 26 mutations. Audiol Neurootol 2003;8:263–8.

[15] Mesolella M, Tranchino G, Nardone M, Motta S, Galli V. Connexin 26 mutations in nonsyndromic autosomal recessive hearing loss: speech and hearing rehabilitation. Int J Pediatr Otorhinolaryngol 2004;68:995–1005.

[16] Enjoji M, Goya N. Enjoji-shiki Bunsekiteki Kensahou. Tokyo: Keioutusin; 1992.

[17] Abe S, Yamaguchi T, Usami S. Application of deafness diagnostic screening panel based on deafness mutation/gene database using invader assay. Genet Test 2007;11:333–40.

[18] Usami S, Nishio SY, Nagano M, Abe S, Yamaguchi T, Deafness Gene Study Consortium. Simultaneous screening of multiple mutations by invader assay improves molecular diagnosis of hereditary hearing loss: a multicenter study. PLoS One 2012;7:e31276.

[19] Taitelbaum-Swead R, Brownstein Z, Muchnik C, Kishon-Rabin L, Kronenberg J, Megirov L, et al. Connexin-associated deafness and speech perception outcome of cochlear implantation. Arch Otolaryngol Head Neck Surg 2006;132:495–500.

[20] Van Camp G, Willems PJ, Smith RJ. Nonsyndromic hearing impairment: unparalleled heterogeneity. Am J Hum Genet 1997;60:758–64.

[21] Tsukada K, Nishio S, Usami S, Deafness Gene Study Consortium. A large cohort study of *GJB2* mutations in Japanese hearing loss patients. Clin Genet 2010;78:464–70.

[22] Hayashi C, Funayama M, Li Y, Kamiya K, Kawano A, Suzuki M, et al. Prevalence of *GJB2* causing recessive profound non-syndromic deafness in Japanese children. Int J Pediatr Otorhinolaryngol 2011;75:211–4.

[23] Yoshikawa S, Kawano A, Hayashi C, Nishiyama N, Kawaguchi S, Furuse H, et al. The clinical features of patients with the homozygous 235delC and the compound-heterozygous Y136X/G45E of the *GJB2* mutations (Connexin 26) in cochlear implant recipients. Auris Nasus Larynx 2011;38:444–9.

[24] Matsushiro N, Doi K, Fuse Y, Nagai K, Yamamoto K, Iwaki T, et al. Successful cochlear implantation in prelingual profound deafness resulting from the common 233delC mutation of the GJB2 gene in the Japanese. Laryngoscope 2002;112:255–61.

[25] Nance WE. The genetics of deafness. Ment Retard Dev Disabil Res Rev 2003;9:109–19.

[26] Zhao HB, Kikuchi T, Ngezahayo A, White TW. Gap junctions and cochlear homeostasis. J Membr Biol 2006;209:177–86.

[27] Lautermann J, ten Cate WJ, Altenhoff P, Grümmer R, Traub O, Frank H, et al. Expression of the gap-junction connexins 26 and 30 in the rat cochlea. Cell Tissue Res 1998;294:415–20.

[28] Lefebvre PP, Weber T, Rigo JM, Delree P, Leprince P, Moonen G. Potassium-induced release of an endogenous toxic activity for outer hair cells and auditory neurons in the cochlea: a new pathophysiological mechanism in Menière's disease? Hear Res 1990;47:83–93.

[29] Lousteau RJ. Increased spiral ganglion cell survival in electrically stimulated, deafened guinea pig cochleae. Laryngoscope 1987;97:836–42.

[30] Kikuchi T, Kimura RS, Paul DL, Adams JC. Gap junctions in the rat cochlea: immunohistochemical and ultrastructural analysis. Anat Embryol (Berl) 1995;191:101–18.

[31] Jun AI, McGuirt WT, Hinojosa R, Green GE, Fischel-Ghodsian N, Smith RJ. Temporal bone histopathology in connexin 26-related hearing loss. Laryngoscope 2000;110:269–75.

[32] Propst EJ, Papsin BC, Stockley TL, Harrison RV, Gordon KA. Auditory responses in cochlear implant users with and without *GJB2* deafness. Laryngoscope 2006;116:317–27.

[33] Denoyelle F, Marlin S, Weil D, Moatti L, Chauvin P, Garabédian EN, et al. Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: implications for genetic counselling. Lancet 1999;353:1298–303.

[34] Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, et al. *GJB2* mutations and degree of hearing loss: a multicenter study. Am J Hum Genet 2005;77:945–57.

[35] Gopalarao D, Kimberling WJ, Jesteadt W, Kelley PM, Beauchaine KL, Cohn ES. Is hearing loss due to mutations in the Connexin 26 gene progressive? Int J Audiol 2008;47:11–20.

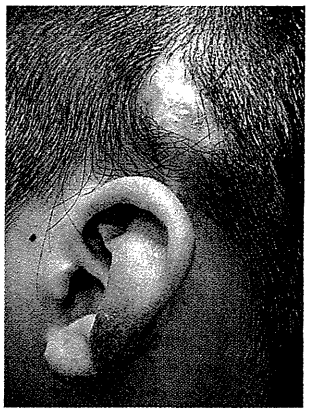
[36] Bartsch O, Vatter A, Zechner U, Kohischmidt N, Wetzig C, Baumgart A, et al. *GJB2* mutations and genotype-phenotype correlation in 335 patients from Germany with nonsyndromic sensorineural hearing loss: evidence for additional recessive mutations not detected by current methods. Audiol Neurotol 2010;15:375–82.

先天性低ガンマグロブリン血症児の髄膜炎後難聴に対する人工内耳手術

髙橋晴雄，蓑田涼生

髄膜炎で失聴し，人工内耳手術後に感染して再手術を余儀なくされた症例

8歳男児．生下時から難聴の訴えはなく言語発達も問題なかったが，4歳時に髄膜炎で両耳とも失聴した．右耳には真珠腫性中耳炎があり，それに対する鼓室形成術と左耳への人工内耳埋め込み術が行われ，術後問題なく経過していた．6歳時，左埋め込みレシーバー部に反復性に感染，膿瘍形成がみられるようになり，抗菌薬による保存治療や局所の肉芽掻破などの外科的治療にも抵抗した．まもなく先天性低ガンマグロブリン血症と診断され，終生のガンマグロブリン補償療法が開始された．ガンマグロブリン治療開始1年後に再びレシーバー周囲に膿瘍形成がみられ，以前と同様に治療に抵抗して難治化した（❶）．



❶ 感染を起こした人工内耳埋め込みレシーバー部位（⟶）

言語習得に対する影響や再感染のリスクを考えて，最良の方法を見いだす

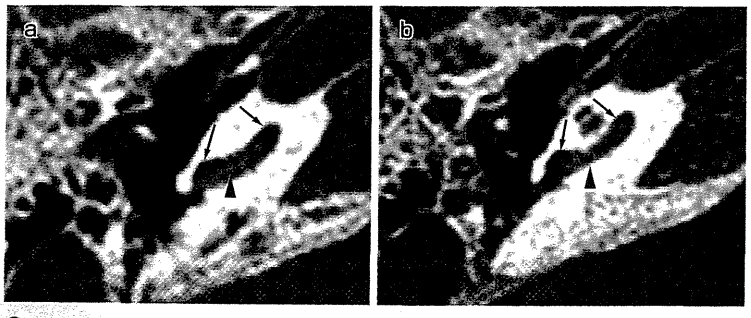
ここで，本症例の治療について次のような選択が考えられた．感染した左人工内耳は抜去する以外には方法はないと思われたが，人工内耳再埋め込みの方法として以下の3つを考えた．

①同時に同側に位置を変えて再埋め込み

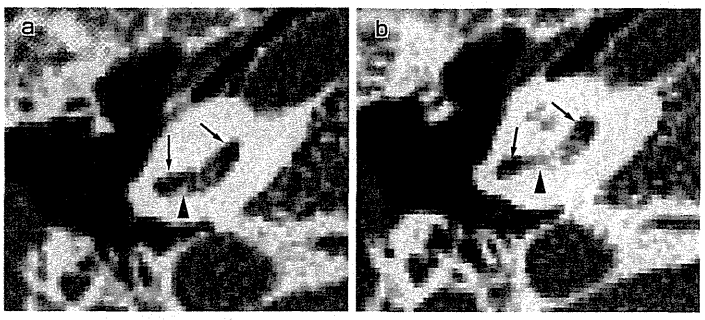
②数か月おいて同側に再埋め込み

③反対側に埋め込み

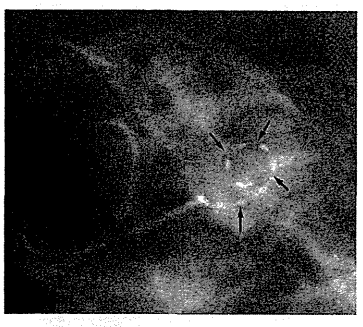
案①には言うまでもなく再感染のリスクがあり，先天性低ガンマグロブリン血症を考えると通常よりそのリスクは高いと思われ，案②では人工内耳装用を中断するため言語習得に障害が生じる可能性があり，数か月おくことにより同側創部の感染は治癒するが広範囲の瘢痕拘縮で再手術が難しいという可能性もある．案③では感染のリスクは低く，言語習得後失聴なので反対側への埋め込



❷ 4歳時の右耳CT所見
蝸牛基底回転の鼓室階にやや濃度が高い陰影がみられ（►），前庭階（⟶）とは対照的な所見を示す．



❸ 7歳時の右耳CT所見
❷でみられた蝸牛基底回転鼓室階のやや濃度が高い陰影は骨新生に変化していたが（►），前庭階（⟶）は依然として開存している可能性が高いと考えられた．



❹ 術後の耳X線所見
電極は蝸牛内に1回転以上挿入されている（⟶）．

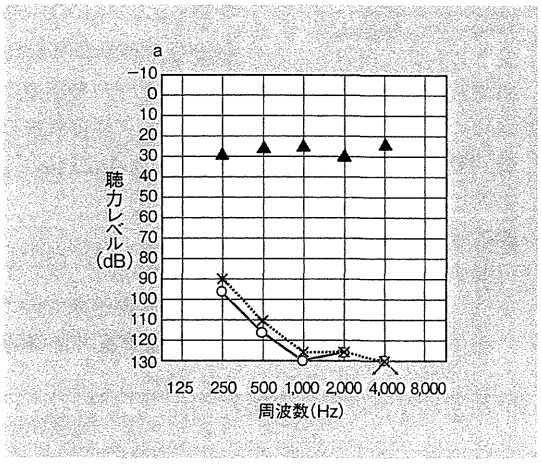
みでも言語獲得は可能と考えられたが，1つ大きな問題があった．それは過去の髄膜炎による蝸牛の変化であった．

蝸牛の立体的解剖の理解をオリエンテーションへ応用する

4歳時の髄膜炎後の側頭骨CTでは蝸牛基底回転に通常よりやや高濃度の陰影があり肉芽，瘢痕形成が疑われ（❷），7歳時には基底回転には明らかな骨新生がみられた（❸）．しかし詳細に観察すると，骨化は鼓室階で生じており，前庭階にはスペースがみられることがわかった．

そこで卵円窓直下に開窓して電極を前庭階に挿入し，卵円窓前下部の蝸牛第2回転にも開窓して電極のより深部への挿入を補助し，全活動電極が挿入できた（❹）．

現在術後2年9か月経過したが，術創感染はみられず，半年時人工内耳装用時純音聴力検査にて，



❺ 術後半年時の裸耳、人工内耳装用時（音場）純音聴力検査結果
十分な環境音聴取能が得られたことが分かる。

良好な聴取能を示し（❺），語音聴取は，術後8か月の単語聴取は聴覚のみで64%，術後1年時において単語聴取は聴覚のみで96%となっている．

ブレークスルーのポイント

- 人工内耳手術を行う際には，通常の手術に必要な範囲以上の詳細かつ広範囲の蝸牛の立体解剖を十分に理解し，非定型的な例でもCT読影や手術でのオリエンテーションを考案できるようにしておくことが重要である．
- 人工内耳という異物を移植する手術は通常でも感染すると難治化するため，免疫不全という不利な点がある場合には，可能な限り術後感染のリスクを排除する戦略を立てることが必須である．

聴覚系検査から鑑別する

急性難聴は迅速な処置ができるかどうかで予後が異なる

- 難聴は耳鼻咽喉科領域でも最も頻繁に遭遇する主訴の一つであり，そのなかでも急性のものは迅速な処置ができるかどうかによって予後がはっきり異なるものが少なくない．
- その意味で急性難聴の的確な診断，ひいてはそれに必要な検査の進め方は日常臨床において知っておくべき必須の部分であるといえる．
- ちなみに難聴の程度として軽度，中等度などの表現がよく使われるが，それぞれの聴力レベルと日常での聞こえの状態は案外知られていないので，❶に一般的なものをまとめる．
- 本項では諸検査の羅列は避け，必要最小限の，しかも多くの耳鼻咽喉科診療所で所有している診察手段，検査機器でどこまで診断でき，それによりどう対処できるかを中心に述べる．ここでは耳垢栓塞や鼓膜穿孔などのように外耳道，鼓膜に明らかな異常がない耳での急性難聴に限って解説する．

ポイントとなる検査

病歴

特徴的病歴は非常に有力な診断の手がかり

- 本項のタイトルは検査の進め方ではあるが，特徴的病歴は検査を行う前の段階で非常に有力な診断の手がかりとなるため，病歴でのポイントを述べる．

上気道炎

- 上気道炎が先行した病歴がある場合には，滲出性中耳炎，また小児で一側性ならムンプス難聴の可能性が考えられる．

❶難聴のレベル

難聴の程度	聴力（dB）	日常生活での状態
軽度	21～40	ささやき声が耳元でないと聞こえない．
中等度	41～70	会話中に聞き落としがあるが対面しての会話は可能．70 dB となると大声でなければ通じない．
高度	71～90	聞き落としが多く，会話はほとんど不可能．耳元に口を近づけて話しかける必要がある．
聾	91≦	言語音，一般環境音ともに聴取不能．

pop 音などの耳内雑音

- とくにいきみや力みの直後の耳内での pop 音に続いて難聴，さらにめまいが生じた病歴があれば，外リンパ瘻が強く疑われる．

頭部打撲，外傷

- 交通事故，転落事故などの頭部打撲，外傷の病歴があれば耳小骨離断が，さらにめまい，ふらつきが加われば内耳障害による感音難聴が疑われる．

その他

- 当然ではあるが，爆発や突発事故的な大音響に曝露した場合には音響外傷の可能性が高く，航空機搭乗やスキューバダイビングなどの急激な気圧変化に曝露した病歴があれば圧外傷（barotrauma），さらにめまいを伴えば内耳障害の可能性が高い．
- また，アミノグリコシド系抗菌薬や白金製剤の抗癌剤投与後には薬物性難聴が考えられる．

純音聴力検査

- いうまでもなく最も基本の重要な検査である．
- 難聴の程度とともにまずみるのは気骨導差である．
- 急性の伝音難聴，感音難聴にそれぞれどのような疾患があるかはここでは割愛するが，急性の混合難聴をみることはまれで，その場合には上半規管裂隙症候群や前庭水管拡大症候群での急性内耳障害なども否定できない．
- 以下に示す聴力型（パターン）も診断に有用なことが多い．

低音型

- 伝音難聴で低音域の低下がみられれば滲出性中耳炎などの中耳貯留液が最も疑われ，感音難聴なら急性低音障害型感音難聴が疑われる．

高音漸傾型

- 伝音難聴でこのタイプは少ないが，感音難聴では突発性難聴などでよくみられる．

水平型

- 伝音難聴なら耳小骨離断でよくみられ，感音難聴ではやはり突発性難聴でみられる．

その他

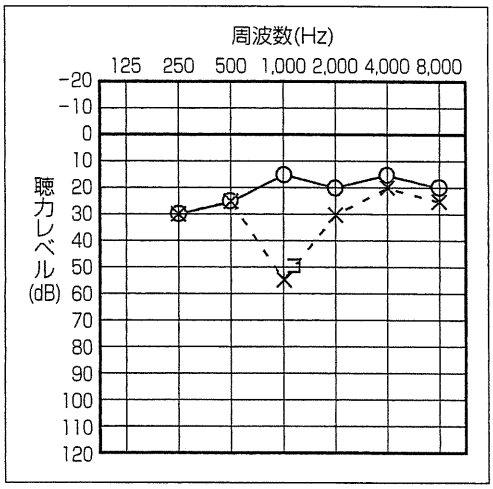
- 急性難聴にはあらゆる聴力型がありうるが，時に聴神経腫瘍の初期に耳閉感のみが主訴で，周波数はさまざまであるが dip 型の難聴を示すことがあり注意を要する(❷)．

ティンパノグラム（❸）

A 型★1

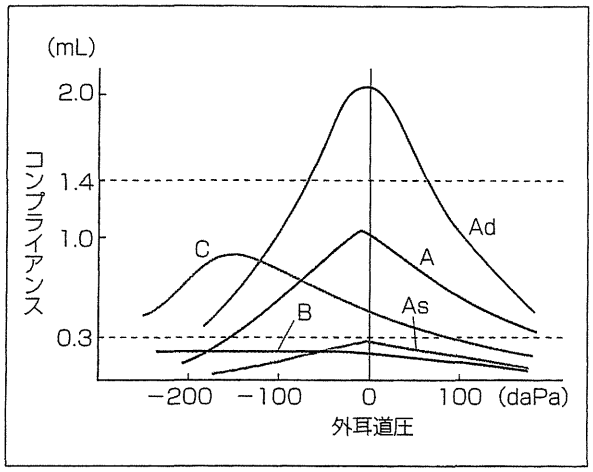
- 伝音連鎖の正常パターンであるが，ピークの低い As 型が中耳伝音連鎖の固着，ピークの高い Ad 型が離断とされている[1]．
- しかし，その診断的価値（感受性）は高くなく，次のアブミ骨筋反射と組み合わせて初めて診断的価値が高まる．

★1
As 型は外耳道容積がおよそ 0.3 mL 以下，Ad 型は外耳道容積がおよそ 1.4 mL 以上．

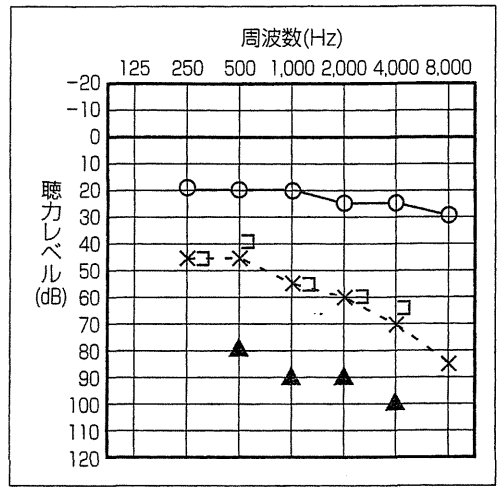


❷左聴神経腫瘍（47 歳，男性）の初診時聴力像
主訴は左耳閉感のみで症状に変動がみられたため，MRI 検査を行ったところ，左内耳道底に約 3 mm の腫瘍陰影を認めた．

聴覚系検査から鑑別する ⚲35



❸ティンパノグラムの型分類



❹左突発性難聴（56歳，男性）の聴力像と左耳の同側音刺激によるアブミ骨筋反射閾値（▲）
左耳の最小可聴閾値は45～85 dBで中等度難聴を示すが，アブミ骨筋反射閾値は正常耳と同等の80～100 dBであり，補充現象が陽性である．

B型

- 急性難聴で中耳貯留液や滲出性中耳炎は少ないが皆無ではなく，あわてて受診するケースもある．
- さらに鼓膜が肥厚していると貯留液が透見できず，突発性難聴と誤診する場合がある．

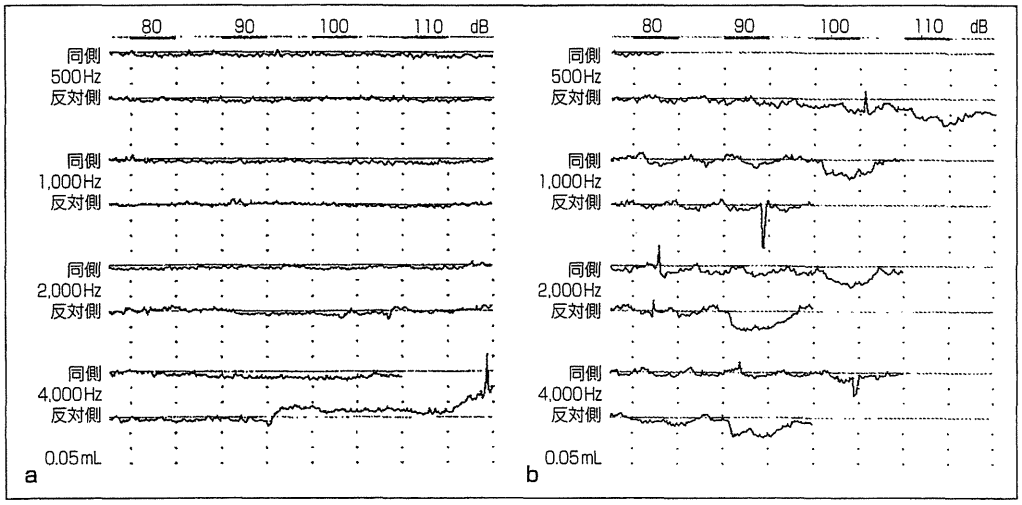
C型

- 中耳陰圧を示すが，C_2型★2では中耳貯留液がある可能性は低くはなく[2]，急性難聴の原因にもなりうる．

★2 C_2型
−200 daPaより高度の陰圧．

アブミ骨筋反射（SR）検査

- アブミ骨筋反射（stapedial reflex：SR）検査は，一般には反射の有無による中耳伝音連鎖の異常が診断できることが成書にも記されているが，感音難聴の場合に反射閾値も非常に重要であることを強調したい．
- 感音難聴には内耳性と後迷路性があるが，内耳性では補充現象（recruitment phenomenon）があるため，反射閾値は正常聴力耳と大差なく，80～100 dBの音刺激で発生する（メッツテスト〈Metz test〉，❹）[3]．一方，後迷路性では補充現象がないので最小可聴閾値からSRが生じる閾値との差は80～100 dBあり，軽度難聴以外では110 dBまでの音刺激では反射は生じないことが多い．
- 補充現象の検査として，SISI（short increment sensitivity index）検査，Jerger自記オージオメトリーなどがあるが，いずれも自覚的検査であり確実性を欠くが，SRは他覚的検査であるため，被検者の主観に左右されないという大きな利点がある．



❺ティンパノグラムC型（中耳陰圧）でのアブミ骨筋反射
外耳道圧を平圧にしてアブミ骨筋反射を測定すると検出されないが（a），外耳道圧を中耳圧と同じ圧（−150 daPa）にして測定すると正常に反射が検出される（b）．

ポイント
感音難聴でアブミ骨筋反射が正常耳と同等の閾値で検出されれば，ほぼ内耳性感音難聴と診断できる．

さらに鑑別が必要な場合に加える検査

歪成分耳音響放射検査（DPOAE）

歪成分耳音響放射検査（distortion product otoacoustic emission：DPOAE）は，内耳外有毛細胞の機能を反映する検査で，これが低下していれば内耳

Advice　SR検査のコツ

①ティンパノグラムC型のとき
➡ 中耳圧と同じ外耳道圧にして測定
SR検査を行う際に，中耳貯留液があってティンパノグラムがB型を示すときには反応が検出されないことはよく知られているが，C型やAd型の場合も検出できないことがある．
通常SRは外耳道内が平圧の状態で測定するが，C型では中耳が陰圧なので鼓膜の可動性が悪く，SRによる微妙なコンプライアンスの低下が波形に反映されないことがある．最近は自動的に外耳道圧を中耳圧と同じ圧に設定してSR検査を行う機器も増えているが，そうでない場合は手動で外耳道圧を設定できる機器では外耳道圧を中耳圧に近づけるように設定するとSRを検出できることがある（❺）．

②ティンパノグラムAd型のとき
➡ 中耳圧と少しずらせた外耳道圧で測定
またAd型の場合は逆で，ピーク圧付近でコンプライアンスが急激に変化することを示しており，SR測定中に脈拍や呼吸などのわずかな中耳圧変化で基線が変動するためにうまく検出できないことがある．その場合には，やはり可能なら手動で外耳道圧を中耳圧のピークから少しずらせて設定すれば，基線が安定してSRを検出できることがある．

性難聴の可能性が高い.

- 詳細は他書に委ねるが, auditory neuropathy では DPOAE が正常で, 次に述べる ABR が検出できない.
- 本検査は耳垢や中耳貯留液などの外耳, 中耳の状態に結果が左右されることが欠点である.

聴性脳幹反応（ABR）

- 聴性脳幹反応（auditory brainstem response：ABR）は, 4 kHz 付近の高さのクリックの音刺激に対する脳波を検出することで聴力を評価する検査で, これも客観的検査である.
- 後迷路性難聴では, 反応の欠如, 病巣より中枢側の波形が欠如, I-V 波の間隔の延長, などの所見がみられ, そのほか, 自覚的検査で難聴がみられても ABR の反応閾値が正常であれば機能性難聴(心因性難聴, 詐聴)の診断に有用である.

聴性定常反応（ASSR）

- 聴性定常反応（auditory steady-state response：ASSR）は, ABR と同様の聴性誘発反応による聴力検査である.
- ABR での I～VII 波のように反応波形は出ないので, 難聴の部位診断など神経学的診断には適さない.
- しかし音の周波数ごとに反応閾値が検出できるのが最大の利点で, 幼小児などの他覚的聴力検査に応用される.

実際の検査・診断手順

- 上記の検査を用いて実際に「鼓膜に明らかな異常がない急性難聴」の患者さんの検査・診断手順は❻のようになる.

①まずは純音聴力検査を行い, 難聴の種類(伝音, 感音, 混合)を確かめる.

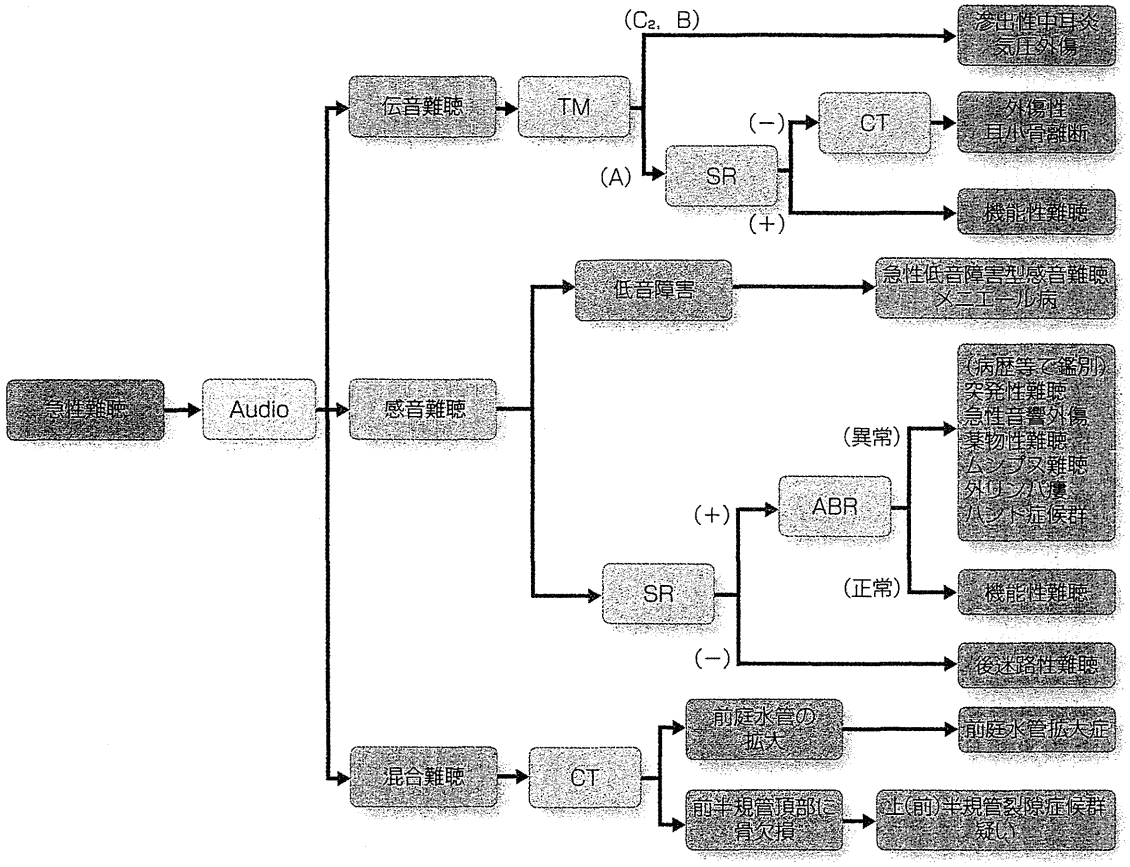
②伝音難聴の場合, 次にティンパノメトリーを行う. もし C_2 ないしは B 型であれば中耳貯留液の可能性が高く, 滲出性中耳炎や病歴によっては気圧外傷が考えられる.

③A 型の場合には SR 検査を行う. SR が検出されない場合は急性難聴としては耳小骨離断が考えやすく, CT 検査が必要となる. 正常閾値で検出される場合は機能性難聴が疑われる.

④感音難聴の場合, まず低音障害型を示せば急性低音障害型感音難聴, めまい, ふらつきを伴えばメニエール（Ménière）病が考えられる.

Topics　低音障害型感音難聴を示す遺伝性難聴

九州などでは遺伝性難聴で低音障害型感音難聴を示すものがあり, これはめまい・ふらつきを伴わず慢性に経過する. *WFS1* 遺伝子異常といわれており, 一般に薬物治療は奏効しない.



⑱難聴診断のためのフローチャート
Audio：純音聴力検査，SR：アブミ骨筋反射検査，TM：ティンパノメトリー．

⑤低音障害型以外の感音難聴ではSR検査を行う．SRが検出できなければ後迷路性難聴の可能性があるので，随伴症状の観察やMRIなどの中枢の検査が必要となる．

⑥SRが正常閾値で検出できれば内耳性難聴か機能性難聴と考えられるので，ABRを行う必要がある．いうまでもなく，ABRが正常なら機能性難聴で，検出されないなどの異常があれば内耳性感音難聴が考えられる．

⑦内耳性感音難聴には数多くの疾患があるが，それらを鑑別する聴覚的検査はほとんどなく，特徴的病歴などで鑑別を行う．

⑧まれではあるが混合難聴の場合には，前庭水管拡大症や上（前）半規管裂隙症候群であることがあるので，CTを撮る必要がある．

（髙橋晴雄）

引用文献

1) 泰地秀信．4．ティンパノメトリ．耳鼻咽喉科・頭頸部外科2003；75：32-7.
2) 本庄　巖編著．滲出性中耳炎の正しい取り扱い．改訂第2版．東京：金原出版；1999．p.45-6.
3) Metz O. Threshold of reflex contraction of muscles of middle ear and recruitment of loudness. Arch Otolaryngol 1952；55：536-43.

Annals of Otology, Rhinology & Laryngology 120(8):499-504.

Observation of Cortical Activity During Speech Stimulation in Prelingually Deafened Adults With Cochlear Implantation by Positron Emission Tomography–Computed Tomography

Haruo Yoshida, MD; Yukihiko Kanda, MD; Haruo Takahashi, MD; Izumi Miyamoto, PhD; Kenya Chiba, MD

Objectives: We evaluated the cortical activity of 2 successful prelingually deafened adult cochlear implant (CI) users who have been trained by auditory-verbal/oral communication since childhood.

Methods: Changes in regional cerebral blood flow were measured by positron emission tomography using ^{18}F-fluorodeoxyglucose while the subjects were receiving auditory language stimuli by listening to a story. Ten normal-hearing volunteers were observed as age-matched control subjects.

Results: In both cases, the auditory-related regions, when compared to same regions in the control subjects, showed hypermetabolism in the left dorsolateral prefrontal cortex and the left precentral gyrus — similar to that in successful CI users who are prelingually deafened children or postlingually deafened adults. Both subjects had the ability to activate these areas, and this ability might be one of the reasons that accounts for such exceptionally good performance in older prelingually deaf CI users. As for the visual-related regions, hypometabolism was observed in Brodmann areas 18 and 19, and this finding might be related to the intensive auditory-verbal/oral education that the subjects had received since childhood.

Conclusions: Despite the limits imposed by the small sample size and the spatial resolution of positron emission tomography, this study yielded insights into the nature of the brain plasticity in prelingually deafened adults who are successful CI users.

Key Words: auditory cortex, auditory-verbal/oral education, positron emission tomography, regional cerebral blood flow.

INTRODUCTION

Although cochlear implantation is recognized as an effective treatment for patients with severe to profound sensorineural hearing loss (SNHL),[1-3] prelingually deaf adolescents and adults have achieved only limited postimplantation improvement, and hence have not been considered good candidates for implantation.[4-7] In previous reports, age at implantation and duration of deafness were pointed out as the most important factors in influencing postimplantation performance.[2,8]

On the other hand, there has been some literature reporting good performance in language perception even in prelingually deaf adults.[9-12] We reported that cochlear implantation can be recommended to some prelingually deafened adults if they receive good habilitation with consistent auditory-verbal/oral training using well-fitted hearing aids (HAs).[13] The clinical reasons for such exceptionally good performances in these implantees are considered to be related to the recently improved quality of cochlear implants (CIs)[14-16] and/or use of an aurally based educational program.[9] However, there have been few studies on functional neuroimaging of cortical activity in successful prelingually deaf adults with CIs. The aim of this study was to evaluate the brain metabolic activity of prelingually deaf adults who are successful users of CIs and have been educated with auditory-verbal/oral communication since early childhood.

MATERIALS AND METHODS

Subjects. The subjects were 2 prelingually deafened adults who constituted 0.7% of the total of 279 patients who underwent cochlear implantation at Nagasaki University Hospital from 1997 to 2010. Details of their clinical information are shown in Table 1. Both of them showed 90 dB or worse hear-

From the Department of Otolaryngology–Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences (Yoshida, Kanda, Takahashi), Nagasaki Bell Hearing Center (Kanda), and the Departments of Radiology (Miyamoto) and Orthopedic Surgery (Chiba), Nishiisahaya Hospital, Nagasaki, and the Department of Otolaryngology–Head and Neck Surgery, Ureshino Medical Center, Saga (Yoshida), Japan.

Correspondence: Haruo Yoshida, MD, Dept of Otolaryngology–Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

TABLE 1. CLINICAL INFORMATION

	Subject 1	*Subject 2*
Age at CI	34 y	29 y
Sex	Female	Male
Implanted ear	Left	Right
Time since CI	70 mo	24 mo
Age at receipt of HA	18 mo	18 mo
Education	Deaf and ordinary school	Deaf school
Cause of deafness	Unknown	Unknown
Family history of HL	Yes (son)	Yes (father and brother)

CI — cochlear implantation; HA — hearing aid; HL — hearing loss.

ing loss on auditory brain stem response testing before the age of 2 years, and thus received a diagnosis of severe to profound SNHL. Thus, both diagnoses were of prelingual deafness rather than progressive hearing loss.

Subject 1 received a diagnosis of severe hearing loss at the age of 1 year, and high-power box HAs were fitted in both ears at the age of 1½ years. She attended an ordinary elementary school in which she received habilitation by auditory-verbal/oral communication until high school. She underwent cochlear implantation at 34 years of age, and positron emission tomography (PET) superimposed with brain computed tomography images (PET-CT) was performed 70 months later, by which time her articulation was slightly distorted but her communication abilities with the CI were excellent, leading to improvements in the quality of her life. Her use of the CI is the longest and most successful among prelingually deafened adult users of CIs in our institute. The cause of her hearing loss is uncertain, as genetic testing has not been performed, but her son also has severe congenital hearing loss (Table 1).

Subject 2 received a diagnosis of severe hearing loss at the age of 1 year. He used high-power box HAs in both ears after the age of 1½ years, and attended an elementary school for deaf children in which he received habilitation by auditory-verbal/oral communication until high school. He underwent cochlear implantation at 29 years of age, and underwent our PET-CT study 24 months later, by which time his communication skills with the CI were excellent.

Ten right-handed adult volunteers (mean age, 27.1 years; age range, 22 to 34 years; 6 male and 4 female) with normal hearing (pure tone air conduction thresholds of less than 20 dB hearing level at 0.5, 1.0, and 2.0 kHz) and without any evidence of

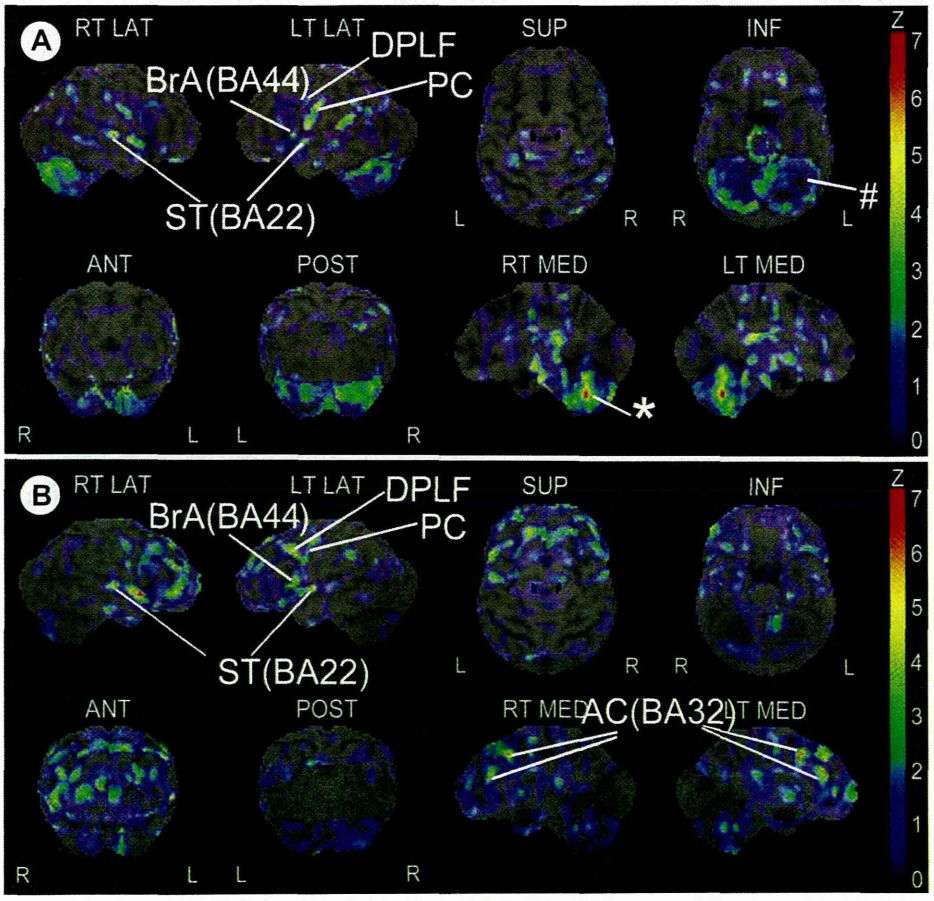


Fig 1. Z-score map computed by iSSP (Interface Stereotactic Surface Projection) application (iNEUROSTAT+) shows increased ^{18}F-fluorodeoxyglucose uptake areas examined by positron emission tomography–computed tomography. **A)** Subject 1. **B)** Subject 2. Cortical activity is shown as grading image of more-deviant regions in red (*) and less-deviant regions in purple (#) by pixel. R, RT — right; L, LT — left; LAT — lateral; SUP — superior; INF — inferior; ANT — anterior; POST — posterior; MED — medial; BA — Brodmann area; ST — superior temporal gyrus; DPLF — dorsolateral prefrontal cortex; PC — precentral gyrus; AC — anterior cingulate gyrus.

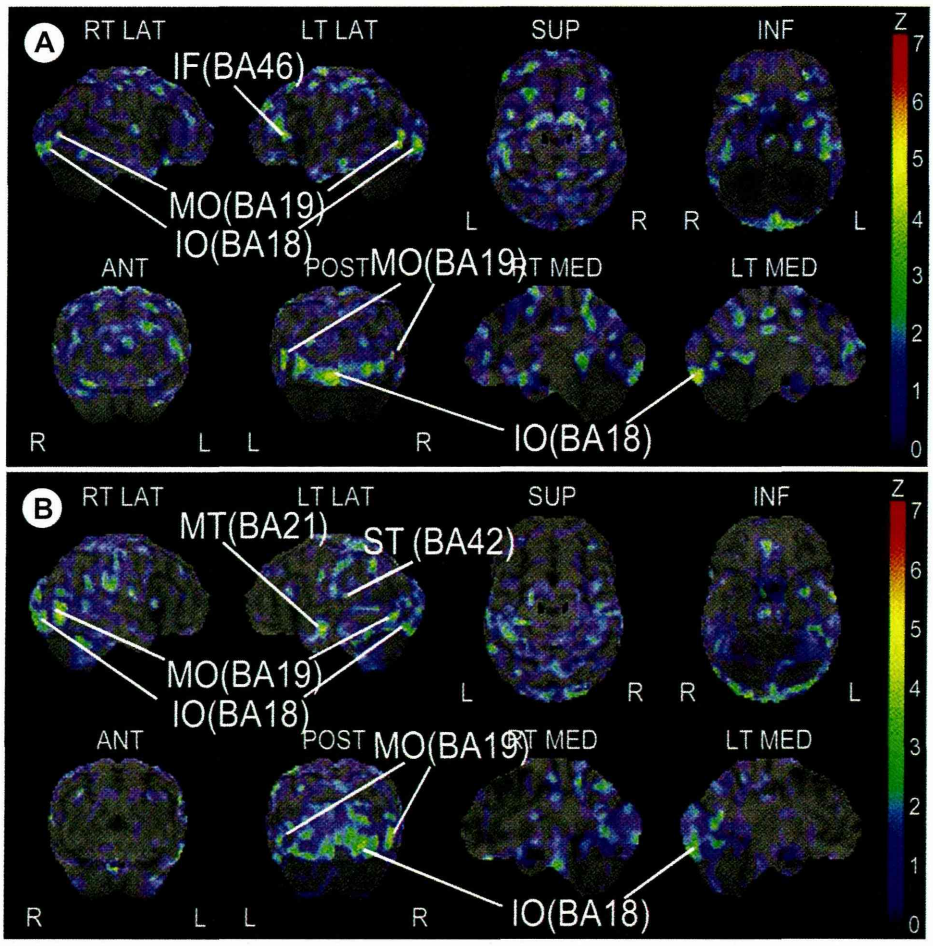


Fig 2. Decreased ^{18}F-fluorodeoxyglucose uptake areas examined by positron emission tomography–computed tomography. **A)** Subject 1. **B)** Subject 2. BA — Brodmann area; IF — inferior frontal gyrus; MO — middle occipital gyrus; IO — inferior occipital gyrus; MT — middle temporal gyrus; ST — superior temporal gyrus.

ear disease, history of noise exposure, previous ear surgery, or severe head injury were observed as control subjects who underwent the PET-CT study in the same manner as the 2 study subjects. All of the subjects gave written informed consent before participating in the study, which was approved by the ethical committee of our institute (approval number 08043067).

Scans. We injected 4 MBq/kg of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) intravenously 72 seconds before the PET scan of the brain. All of the subjects were instructed to listen to a 40-minute story that was read aloud by one speaker located out of sight of the subjects. Afterward, a video recording of the session was reviewed to ensure that the participants had been listening carefully throughout, and several questions were posed on the contents of the task story to exclude those subjects from the study who were unable to correctly answer 70% of the questions. The ^{18}F-FDG–PET scans were performed with a Discovery ST PET scanner (GE Medical Systems, Milwaukee, Wisconsin).

Analysis of Scans. The original ^{18}F-FDG–PET image data were transformed into a binary format and then into a stereotactic standard Talairach space by use of the 3-dimensional Stereotactic Surface Projection (3D-SSP) application of the iNEUROSTAT+ program,[17] and the cortical radioactivity of the 2 CI users was compared with that of the group of normal-hearing adults. The usefulness of this program as compared with Statistical Parametric Mapping (SPM) has been reported.[17-19] Stereotactic coordinates and anatomic regions, including Brodmann areas (BAs), were automatically computed. The resulting images are shown as a Z-score map, which was computed by each study subject's score derived from the mean score of the standard deviation of the control subjects, and are shown as graded images from more-deviant regions in red to less-deviant regions in purple by pixel (Figs 1 and 2).

RESULTS

Table 2 shows the preoperative hearing level, the aided hearing level with HAs, the preoperative and postoperative speech discrimination scores, and the speech perception rates with CIs of the 2 study subjects. Their mean preoperative hearing levels were greater than 100.0 dB, and their aided hearing levels were 52.5 dB and 61.3 dB, respectively. After co-

TABLE 2. AUDIOLOGICAL OUTCOMES

	Subject 1	*Subject 2*
Before implantation		
Mean hearing level right ear	105.0 dB	105.0 dB
Mean hearing level left ear	105.0 dB	105.0 dB
Mean aided hearing level	52.5 dB	61.3 dB
SDS (auditory and visual)	43%	23%
SDS (auditory)	10%	0%
After implantation		
Mean hearing level with implant	28.7 dB	28.8 dB
SDS (auditory and visual)	73%	53%
SDS (auditory)	47%	37%
Speech perception rates*	90%	85%

SDS — speech discrimination score.
*Only open-set sentences without hearing aids.

chlear implantation, their hearing levels improved to 28.7 dB and 28.8 dB, respectively. Their speech discrimination scores, with auditory stimulation only, also improved, from 10% to 47% and from 0% to 37%, respectively. Their postoperative speech perception rates, which were tested by open-set sentences, were as good as 90% and 85%, respectively.

Regions showing significant increase and decrease in ^{18}F-FDG uptake compared to the control subjects are displayed in Fig 1 and Fig 2, respectively. As for the auditory-related regions, the ^{18}F-FDG uptake was increased in the left dorsolateral prefrontal cortex, the left precentral gyrus, and the superior temporal gyrus (BA22) in both subjects (Fig 1). Only in subject 2 was hypermetabolism observed bilaterally in the anterior cingulate gyrus (BA32; Fig 1B).

On the other hand, hypometabolism was observed in the left inferior frontal gyrus (BA46) of subject 1 and in the left middle temporal gyrus (BA21) of subject 2 (Fig 2). As for the visual-related regions, hypometabolism was observed bilaterally in the occipital gyrus (BA19 and BA18) in both subjects.

DISCUSSION

In many of the previous reports about prelingually deafened CI users, the results of deaf children were compared with those of adult control subjects.[20-24] However, the glucose metabolism in the brain changes with age, and this may have had an influence on the interpretation of brain activity results.[22,25] Therefore, in this study, we sought to compare prelingually deafened adults with age-matched normal-hearing adults in order to avoid age-related errors in interpreting the results and identifying neurophysiological factors that might determine the outcome of cochlear implantation. The brain metabolic activity of prelingually deaf adult CI users was evaluated by auditory stimulation only, in order to avoid visual-related effects such as lipreading.

Both subjects showed hyperactivity in the left dorsolateral prefrontal cortex. Functionally, the left dorsolateral prefrontal cortex is generally recognized as participating in higher cognitive functions such as reasoning, control of attention, and working memory.[26,27] In postlingually deafened adult subjects who showed good performance in language perception with a CI, this area was reported to be activated while the subjects were listening to voices.[28] In prelingually deaf children with a CI, postoperative speech scores were associated with enhanced metabolic activity in this area, and subjects in whom this region becomes active during spontaneous brain activity are believed to have an advantage in acquisition of auditory language.[29] The left precentral gyrus was also hypermetabolic in both of our subjects. According to the previous report, these regions are crucial for language processing and are particularly implicated in processing of speech with a CI, and deaf subjects who engage these regions tended to have better performance.[29] According to those results, the ability of our subjects to activate these areas might have been related to their exceptionally good performance with CIs.

The ^{18}F-FDG uptake was increased bilaterally, especially in the left superior temporal gyrus (BA22), in both subjects. Lee et al[29] reported that the age at implantation was positively correlated with increased activity in the right superior temporal gyrus, and their results seem compatible with our present results.

Only in subject 2, hypermetabolism was observed bilaterally in the anterior cingulate gyrus (BA32), and this area is believed to be involved in attention and arousal processes.[30,31] Although both subjects were successful CI users by the standards of prelingually deafened adults, subject 2, who is a more recent user of CIs and has less developed speech perception skills with CIs than does subject 1, often needs to pay more attention when communicating with CIs than does subject 1. In other words, subject 1 does not need to make as much of an effort when communicating with CIs in daily life.

As for the visual-related regions, the integration of audiovisual inputs in auditory speech perception was reported to be crucial for successful speech perception in subjects with CIs in a series of neuroimaging studies.[28,32] The brain activity of children with early-onset deafness was greater in the medial visual cortex and bilateral occipitoparietal junctions after cochlear implantation, and these findings suggest that speech learning resulted in a greater demand