Table 3. The patients with mutations in two different genes.

Sample	Genes with two pathogenic mutations	Gene with one heterozygous mutation	Nucleotide change	Amino acid change	control	SIFT score	PolyPhen score	Referense
5	*MYO7A*	*CDH23*	c.C719T	p.P240L*	0.26	0.06	0.999	Wagatsuma et al. (2007)
8	*MYO7A*	*CDH23*	c.2568C>G	p.Ile856Met	0	0.08	1	This study
15	*CDH15*	*USH1C*	c.2437T>G	p.Tyr813Asp	0	0.19	0.932	This study
3	*PCDH15*	*USH1G*	c.28C>T	p.Arg10Trp	0	0.19	1	This study

*homozygotes.

doi:10.1371/journal.pone.0090688.t003

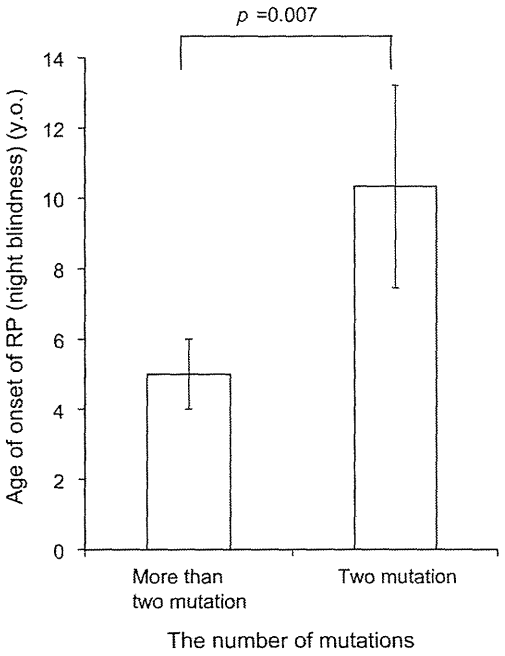

Figure 1. The number of mutations and the age of RP onset in Usher syndrome type 1 patients. The age of RP onset is earlier in the patients with more than two pathogenic mutations. RP: retinitis pigmentosa.

doi:10.1371/journal.pone.0090688.g001

99°C for 15 sec and 60°C for 4 min, ending with a holding period at 10°C in a PCR thermal cycler (Takara, Shiga, Japan). After the Multiplex PCR amplification, amplified DNA samples were digested with FuPa enzyme at 50°C for 10 min and 55°C for 10 min and the enzyme was successively inactivated for 60°C for 20 min incubation. After digestion, diluted barcode adapter mix including Ion Xpress Barcode Adapter and Ion P1 adaptor were ligated to the end of the digested amplicons with ligase in the kit for 30 min at 22°C and the ligase was successively inactivated at 60°C for 20 min incubation. Adaptor ligated amplicon libraries were purified with the Agencourt AMPure XP system (Beckman Coulter Genomics, Danvers, MA). The amplicon libraries were quantified by using Ion Library Quantitation Kit (Applied Biosystems, Life Technologies) and the StepOne plus realtime PCR system (Applied Biosystems, Life Technologies) according to the manufacturers' procedures. After quantification, each amplicon library was diluted to 20 pM and the same amount of the 12 libraries for 12 patients were pooled for one sequence reaction.

Emulsion PCR and Sequencing

The emulsion PCR was carried out with the Ion OneTouch System and Ion OneTouch 200 Template Kit v2 (Life Technologies) according to the manufacturer's procedure (Publication Part Number 4478371 Rev. B Revision Date 13 June 2012). After the emulsion PCR, template-positive Ion Sphere Particles were enriched with the Dynabeads MyOne Streptavidin C1 Beads (Life Technologies) and washed with Ion OneTouch Wash Solution in the kit. This process were performed using an Ion OneTouch ES system (Life Technologies).

After the Ion Sphere Particle preparation, MPS was performed with an Ion Torrent Personal Genome Machine (PGM) system

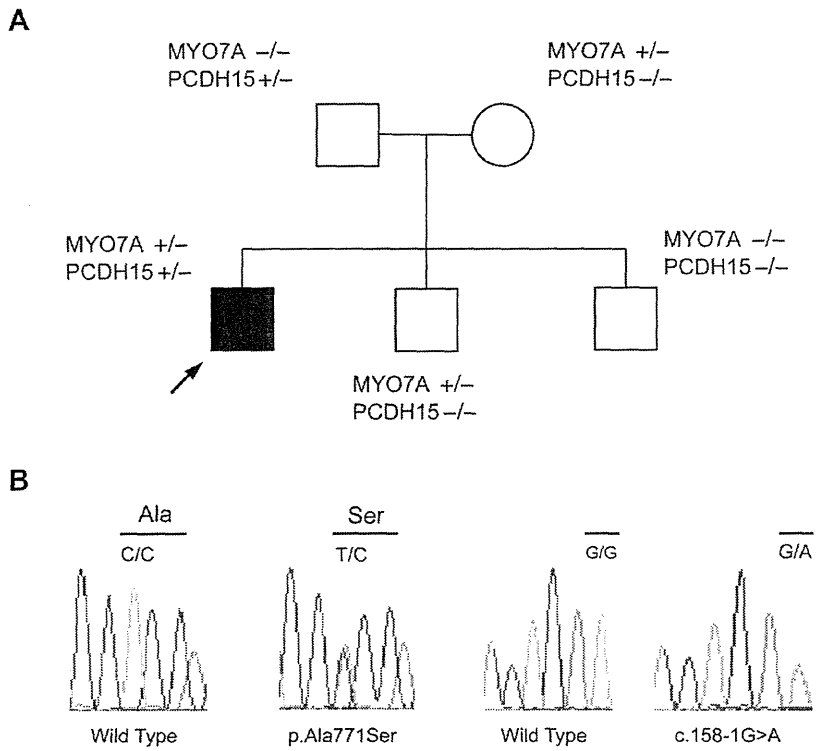

Figure 2. Pedigree and sequence chromatograms of the patient with the p.Ala771Ser in *MYO7A* and c.158-1G>A in *PCDH15* mutations. (A) The pedigree and sequence results of the proband and family. (B) Sequence chromatograms from wild-type and mutations. The proband, his mothor and one brother carried a heterozygous 2311G>T transition in exon 20, which results in an alanine to a serine (Ala771Ser) in *MYO7A*. Another variation, 158-1G>A in intron 3 of *PCDH15*, was derived from the proband and his father. Another brother had no variants.
doi:10.1371/journal.pone.0090688.g002

using the Ion PGM 200 Sequencing Kit and Ion 318 Chip (Life Technologies) according to the manufacturer's procedures.

Base Call and Data Analysis

The sequence data were processed with standard Ion Torrent Suite Software and Torrent Server successively mapped to human genome sequence (build GRCh37/hg19) with Torrent Mapping Alignment Program optimized to Ion Torrent data. The average of 562.33 Mb sequences with about 4,300,000 reads was obtained by one Ion 318 chip. The 98.0% sequences were mapped to the human genome and 94% of them were on the target region. Average coverage of depth in the target region was 314.2 and 93.8% of them were over 20 coverage.

After the sequence mapping, the DNA variant regions were piled up with Torrent Variant Caller plug-in software. Selected variant candidates were filtered with the average base QV (minimum average base quality 25), variant frequency (40–60% for heterozygous mutations and 80–100% for homozygous mutations) and coverage of depth (minimum coverage of depth 10). After the filtrations, variant effects were analyzed with the wANNOVAR web site [25,26] (http://wannovar.usc.edu) including the functional prediction software for missense variants: Sorting Intolerant from Tolerant (SIFT; http://sift.jcvi.org/), and Polymorphism Phenotyping (PolyPhen2; http://genetics.bwh.harvard.edu/pph2/). The sequencing data was available in the DNA databank of Japan (Accession number: DRA001273).

Algorithm

Missense, nonsense, and splicing variants were selected among the identified variants. Variants were further selected as less than 1% of: 1) the 1000 genome database (http://www.1000genomes.org/), 2) the 5400 exome variants (http://evs.gs.washington.edu/EVS/), and 3) the in-house control. Candidate mutations were confirmed by Sanger sequencing and the responsible mutations were identified by segregation analysis using samples from family members of the patients. In addition, the cases with heterozygous or no causative mutation were fully sequenced by Sanger sequencing for USH1 genes in order to verify the MPS results.

Direct Sequence Analysis

Primers were designed with the Primer 3 plus web server (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi). Each genomic DNA sample (40 ng) was amplified using Ampli Taq Gold (Life Technologies) for 5 min at 94°C, followed by 30 three-step cycles of 94°C for 30 sec, 60°C for 30 sec, and 72°C for 30 sec, with a final extension at 72°C for 5 min, ending with a holding period at 4°C in a PCR thermal cycler (Takara, Shiga, Japan). The PCR products were treated with ExoSAP-IT (GE Healthcare Bio, Buckinghamshire, UK) and by incubation at 37°C for 60 min, and inactivation at 80°C for 15 min. After the products were purified, we performed standard cycle sequencing reaction with ABI Big Dye terminators in an ABI 3130xl sequencer (Life Technologies).

Accession numbers

MYO7A, [NM_000260.3]; *USH1C*, [NM_ 153676.3]; *CDH23*, [NM_ 022124.5]; *PCDH15*, [NM_ 033056.3]; *USH1G*, [NM_ 173477.2]; *USH2A*, [NM_206933.2]; *GPR98*, [NM_ 032119.3]; *DFNB31*, [NM_ 015404.3]; *CLRN1*, [NM_ 174878.2]; *PDZD7*, [NM_ 001195263.1].

Acknowledgments

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Author Contributions

Conceived and designed the experiments: HY SI SN SU. Performed the experiments: HY SN. Analyzed the data: HY SN SU. Contributed reagents/materials/analysis tools: HY SI SN KK TT YK HS KN KI TI YN KF CO TK HN SU. Wrote the paper: HY SN SU.

References

1. Kimberling WJ, Hildebrand MS, Shearer AE, Jensen ML, Halder JA, et al. (2010) Frequency of Usher syndrome in two pediatric populations: Implications for genetic screening of deaf and hard of hearing children. Genet Med 12: 512–516.
2. Yan D, Liu XZ (2010) Genetics and pathological mechanisms of Usher syndrome. J Hum Genet 55: 327–335.
3. Jaworek TJ, Bhatti R, Latief N, Khan SN, Riazuddin S, et al. (2012) USH1K, a novel locus for type I Usher syndrome, maps to chromosome 10p11.21-q21.1. J Hum Genet 57: 633–637.
4. Riazuddin S, Belyantseva IA, Giese AP, Lee K, Indzhykulian AA, et al. (2012) Alterations of the CIB2 calcium- and integrin-binding protein cause Usher syndrome type 1J and nonsyndromic deafness DFNB48. Nat Genet 44: 1265–1271.
5. Weil D, Blanchard S, Kaplan J, Guilford P, Gibson F, et al. (1995) Defective myosin VIIA gene responsible for Usher syndrome type 1B. Nature 374: 60–61.
6. Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, et al. (2001) Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. Am J Hum Genet 68: 26–37.
7. Ahmed ZM, Riazuddin S, Bernstein SL, Ahmed Z, Khan S, et al. (2001) Mutations of the protocadherin gene PCDH15 cause Usher syndrome type 1F. Am J Hum Genet 69: 25–34.
8. Verpy E, Leibovici M, Zwaenepoel I, Liu XZ, Gal A, et al. (2000) A defect in harmonin, a PDZ domain-containing protein expressed in the inner ear sensory hair cells, underlies Usher syndrome type 1C. Nat Genet 26: 51–55.
9. Mustapha M, Chouery E, Torchard-Pagnez D, Nouaille S, Khrais A, et al. (2002) A novel locus for Usher syndrome type I, USH1G, maps to chromosome 17q24-25. Hum Genet 110: 348–350.
10. Ouyang XM, Yan D, Du LL, Hejtmancik JF, Jacobson SG, et al. (2005) Characterization of Usher syndrome type I gene mutations in an Usher syndrome patient population. Hum Genet 116: 292–299.
11. Bonnet C, Grati M, Marlin S, Levilliers J, Hardelin JP, et al. (2011) Complete exon sequencing of all known Usher syndrome genes greatly improves molecular diagnosis. Orphanet J Rare Dis 6: 21.
12. Le Quesne Stabej P, Saihan Z, Rangesh N, Steele-Stallard HB, Ambrose J, et al. (2012) Comprehensive sequence analysis of nine Usher syndrome genes in the UK National Collaborative Usher Study. J Med Genet 49: 27–36.
13. Nakanishi H, Ohtsubo M, Iwasaki S, Hotta Y, Takizawa Y, et al. (2010) Mutation analysis of the MYO7A and CDH23 genes in Japanese patients with Usher syndrome type 1. J Hum Genet 55: 796–800.
14. Eudy JD, Yao S, Weston MD, Ma-Edmonds M, Talmadge CB, et al. (1998) Isolation of a gene encoding a novel member of the nuclear receptor superfamily from the critical region of Usher syndrome type IIa at 1q41. Genomics 50: 382–384.
15. Weston MD, Luijendijk MW, Humphrey KD, Moller C, Kimberling WJ (2004) Mutations in the VLGR1 gene implicate G-protein signaling in the pathogenesis of Usher syndrome type II. Am J Hum Genet 74: 357–366.
16. Aller E, Jaijo T, van Wijk E, Ebermann I, Kersten F, et al. (2010) Sequence variants of the DFNB31 gene among Usher syndrome patients of diverse origin. Mol Vis 16: 495–500.
17. Joensuu T, Hamalainen R, Yuan B, Johnson C, Tegelberg S, et al. (2001) Mutations in a novel gene with transmembrane domains underlie Usher syndrome type 3. Am J Hum Genet 69: 673–684.
18. Nakanishi H, Ohtsubo M, Iwasaki S, Hotta Y, Usami S, et al. (2011) Novel USH2A mutations in Japanese Usher syndrome type 2 patients: marked differences in the mutation spectrum between the Japanese and other populations. J Hum Genet 56: 484–490.
19. Miyagawa M, Nishio SY, Ikeda T, Fukushima K, Usami S (2013) Massively parallel DNA sequencing successfully identifies new causative mutations in deafness genes in patients with cochlear implantation and EAS. PLoS One.
20. Ebermann I, Phillips JB, Liebau MC, Koenekoop RK, Schermer B, et al. (2010) PDZD7 is a modifier of retinal disease and a contributor to digenic Usher syndrome. J Clin Invest 120: 1812–1823.
21. Senften M, Schwander M, Kazmierczak P, Lillo C, Shin JB, et al. (2006) Physical and functional interaction between protocadherin 15 and myosin VIIa in mechanosensory hair cells. J Neurosci 26: 2060–2071.
22. Loman NJ, Misra RV, Dallman TJ, Constantinidou C, Gharbia SE, et al. (2012) Performance comparison of benchtop high-throughput sequencing platforms. Nat Biotechnol 30: 434–439.
23. Ben-Yosef T, Ness SL, Madeo AC, Bar-Lev A, Wolfman JH, et al. (2003) A mutation of PCDH15 among Ashkenazi Jews with the type 1 Usher syndrome. N Engl J Med 348: 1664–1670.
24. Usami S, Wagatsuma M, Fukuoka H, Suzuki H, Tsukada K, et al. (2008) The responsible genes in Japanese deafness patients and clinical application using Invader assay. Acta Otolaryngol 128: 446–454.
25. Wang K, Li M, Hakonarson H (2010) ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res 38: e164.
26. Chang X, Wang K (2012) wANNOVAR: annotating genetic variants for personal genomes via the web. J Med Genet 49: 433–436.

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ORIGINAL ARTICLE

Clinical features of rapidly progressive bilateral sensorineural hearing loss

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Abstract

Conclusion: Rapidly progressive bilateral sensorineural hearing loss (SNHL) often develops as a symptom of intracranial diseases or systemic vasculitis. For early diagnosis and treatment of these potentially fatal diseases, a history of hearing deterioration within 2 months and associated symptoms may be important. *Objectives:* To reveal clinical features and causative diseases for rapidly progressive bilateral SNHL. *Methods:* The inclusion criterion was patients with bilateral progressive SNHL, who had experienced difficulty in daily conversation within 4 days to 1 year after the onset of hearing loss awareness. This study was a retrospective evaluation of 12 patients with rapidly progressive bilateral SNHL who visited our hospital between 2007 and 2011. *Results:* The causative disease for hearing loss was identified in 11 of 12 patients; intracranial lesions including nonbacterial meningitis, meningeal metastasis of lymphoma, and superficial siderosis in 4 patients, systemic vasculitis in 2, auditory neuropathy spectrum disorder in 1, and an isolated inner ear disorder in 4. Relatively rapid hearing deterioration within 2 months showed a significant association in six patients with an intracranial lesion or systemic vasculitis. Moreover, all these six patients complained of dizziness and/or non-cochleovestibular symptoms such as fever, headache, and/or altered mental state in addition to hearing loss.

Keywords: *Auditory perception, intracranial disease, systemic vasculitis, magnetic resonance imaging, hearing threshold*

Introduction

Sensorineural hearing loss (SNHL) is caused by various disorders, including sudden deafness, presbycusis, hereditary hearing loss, drug-induced hearing loss, and Meniere's disease. Various clinical data are used to diagnose the cause of SNHL, of which the time course of hearing deterioration may be particularly important for estimating the nature of the disorder. For example, sudden deafness has an onset period of < 72 h [1], while presbycusis deteriorates by 1–2.5 dB per year over a long period of time. We also encounter patients with bilateral SNHL whose hearing deteriorates more slowly than that in sudden deafness but more quickly than that in presbycusis. Such patients often have serious complicating diseases, although only a few studies have examined this type of hearing loss. In this study, we report 12 cases of rapidly progressive bilateral SNHL and analyze the clinical features and causative diseases for hearing loss.

Material and methods

The study was a retrospective review of medical records. Of the 908 patients diagnosed with bilateral SNHL who visited the Department of Otolaryngology at Kobe City Medical Center General Hospital from

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Table I. Characteristics of 12 patients with rapidly progressive bilateral sensorineural hearing loss.

Case no.	Onset (age in years)	Time from onset to difficulty in daily life (days)	Gender	Causative disorder	Category of causative disorder	Worst hearing (dB)		Hearing after treatment (dB)		Clinical symptoms
						R	L	R	L	
1	33	4	M	Cryptococcal meningitis	Intracranial lesion	115	115	68.3	25	Fever, headache, altered mentation, dizziness
2	45	60	M	Chronic herpes meningitis + labyrinthitis		115	108.3	No improvement		Fever, tinnitus
3	60	6	M	Meningial metastasis of lymphoma		75	50	45	48.3	Fever, dizziness
4	79	30	F	Superficial siderosis		65	61.7	No improvement		Dizziness, tinnitus
5	73	45	F	Cogan's syndrome	Systemic vasculitis	115	115	No improvement		Fever, headache, dizziness
6	44	4	F	Vasculitis syndrome		93.3	81.7	51.7	38.3	Fever, headache, altered mentation
7	26	7	F	Auditory neuropathy	ANSD	115	113.3	No improvement		Tinnitus
8	63	120	F	Isolated inner ear disorders	Isolated inner ear disorder	65	56.7	No improvement		Tinnitus
9	67	90	M	Isolated inner ear disorders		103.3	103.3	No improvement		Tinnitus
10	69	360	M	Isolated inner ear disorders		95	115	No improvement		Tinnitus
11	69	360	F	Isolated inner ear disorders		80	73.3	No improvement		Tinnitus
12	61	14	F	Undefined disorder	Undefined	53.3	55	41.7	41.7	Fever, backache

January 2007 to December 2011, 12 (1.3%, 5 males and 7 females; Table I) who met the following criteria for rapidly progressive bilateral SNHL were selected: (1) pure-tone audiometry data showing bilateral SNHL and average hearing thresholds at 500, 1000, and 2000 Hz of ≥ 50 dB; (2) difficulty in daily conversation without lip-reading or sign language within 4 days to 1 year after the onset of hearing loss awareness; and (3) exclusion of cases with bilateral Meniere's disease or functional hearing loss. Wegener's granulomatosis [2], Churg-Strauss syndrome [3], and eosinophilic otitis media [4], are also known to induce progressive hearing loss, but were excluded from this study because these diseases lead to mixed hearing loss rather than SNHL. The median age at onset of hearing loss was 62 years (range 26–79 years). The precise deterioration speed of the patients' pure-tone audiometric thresholds could not be calculated because most of them came to our hospital after having moderate or severe SNHL and their initial pure-tone audiometry thresholds before the onset of hearing loss had not been tested. Therefore, we defined progressive bilateral SNHL on the basis of subjective time course of deterioration in auditory perception.

The diagnoses of causative diseases of rapidly progressive bilateral SNHL were based on medical interviews, physical findings, and examinations by otologists, internal medicine specialists, and radiologists. The examinations included blood autoantibody tests, microbiological culture tests, radiographic examinations (CT and MRI), and cerebrospinal fluid (CSF) tests, as well as conventional otological examinations including pure-tone audiometry, distortion product otoacoustic emissions (DPOAEs), and auditory brainstem response (ABR). The causative diseases were categorized into five groups: (1) an intracranial lesion for which CT, MRI, and/or CSF tests revealed an abnormality in the central nervous system; (2) systemic vasculitis, diagnosed by positive blood tests for autoantibodies and systemic inflammation and vasculitis-specific skin lesion, retinal vasculitis, or non-syphilitic interstitial keratitis; (3) auditory neuropathy spectrum disorder (ANSD), diagnosed on the basis of good responses in DPOAE and a lack of obvious responses in ABR; (4) isolated inner ear disorder, with no abnormality on CT or MRI scans and no symptoms other than cochleovestibular symptoms; and (5) an undefined disorder with symptoms other than cochleovestibular symptoms.

The time course of hearing deterioration was evaluated using subjective manifestations. The time course was defined as the time period from the onset of hearing loss awareness to the onset of difficulty in understanding speech in daily life, and it was classified as follows: (1) 4 days to 1 week, (2) 1 week to 1 month, (3) 1–6 months, and (4) 6 months to 1 year. We also focused on clinical manifestations other than hearing loss, which were divided into cochleovestibular symptoms including tinnitus and dizziness and noncochleovestibular symptoms including fever, headache, and altered mental state.

Results

Clinical manifestations

The time course of hearing deterioration was from 4 days to 1 week in four patients, from 1 week to 1 month in two patients, from 1 to 6 months in four patients, and from 6 months to 1 year in two patients. The median hearing level (i.e. the worst value for each patient) of the 12 patients was 94 dB for the right ear and 93 dB for the left ear (Table I). With respect to manifestations related to noncochleovestibular disorders, fever was the leading symptom and was observed in six patients (50%). Among these patients with fever, three also complained of severe headache and two of these further suffered from altered mental state. Tinnitus was observed in seven patients including all six patients without noncochleovestibular symptoms. Dizziness was reported in four patients and three of these were also associated with a noncochleovestibular symptom, but the other complained of only tinnitus and dizziness (Table I).

MRI findings

Brain MRI was performed in nine patients including all six with a noncochleovestibular symptom, one with both tinnitus and dizziness, and two with tinnitus. Association of noncochleovestibular symptoms and dizziness with bilateral SNHL suggests the presence of systemic or intracranial lesions in the former and a retrocochlear or unusual inner ear disease in the latter. In fact, the diagnosis of an intracranial lesion or systemic vasculitis was confirmed or supported by MRI in five of seven patients with a noncochleovestibular symptom or dizziness (Figure 1). In case 4, T2-weighted MRI revealed superficial hypointensity on the surface of the brainstem and cerebellum, which was diagnosed as superficial siderosis. In the other four patients, gadolinium-enhanced T1-weighted MRI showed abnormal enhancement in the inner ear or internal auditory canal. In five cases complaining solely of tinnitus in addition to hearing loss, only two underwent brain MRI. In the other three cases, results of neurological examinations implied that the lesion was restricted in the cochleae and, therefore, careful follow-up of pure-tone audiometry, ABR,

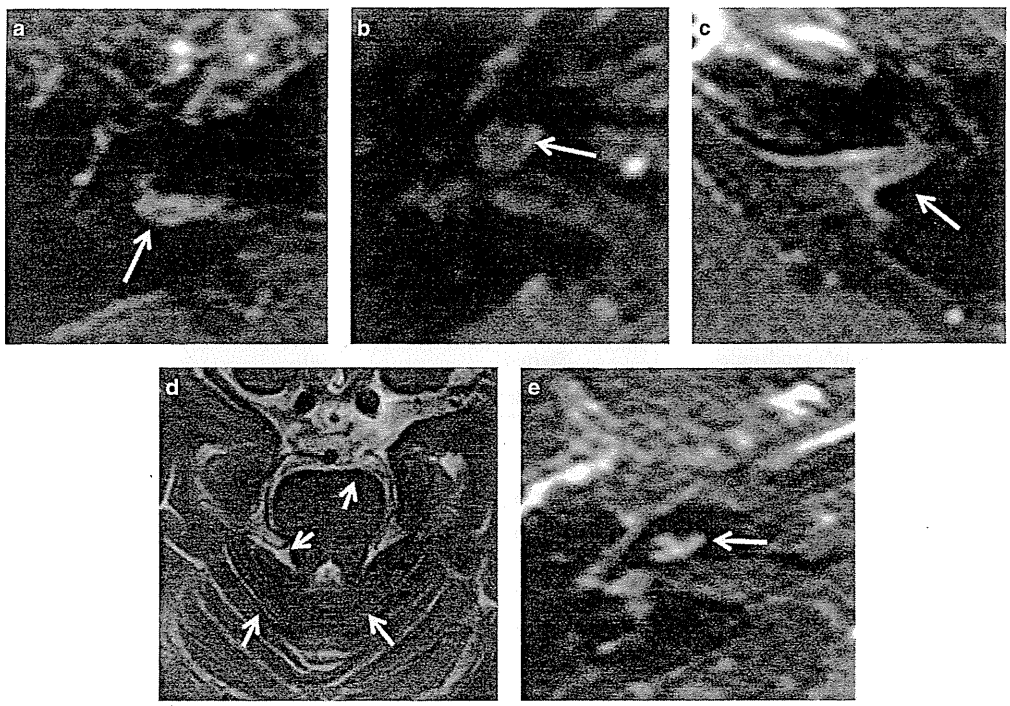

Figure 1. (a) Case no. 1. Cryptococcus meningitis with enhancement of bilateral internal auditory canal (IAC) on gadolinium-enhanced MRI. The enhanced right IAC is shown. (b) Case no. 2. Chronic viral meningitis plus labyrinthitis with enhancement of bilateral cochlea on gadolinium-enhanced MRI. The enhanced basal turn of the right cochlea is shown. (c) Case no. 3. Meningeal metastasis of lymphoma with enhancement of bilateral IAC on gadolinium-enhanced MRI. Enhanced left IAC is shown. (d) Case no. 4. Superficial siderosis with hypointensity along the brainstem and cerebellum on T2-weighted MRI. (e) Case no. 5. Cogan's syndrome with enhancement of bilateral cochlea on gadolinium-enhanced MRI. The right whole cochlea is enhanced.

DPOAE, and/or blood tests for autoimmune antibodies rather than brain MRI were conducted to evaluate cochlear disorders.

Categories of causative diseases

The causative diseases for hearing loss are shown in Table I. Systemic evaluation showed abnormalities restricted to the inner ear in four patients (isolated inner ear disorder). Intracranial lesions were detected in four patients and systemic vasculitis in two, with these disorders diagnosed as the causes of bilateral SNHL. The intracranial lesions included Cryptococcus meningitis, chronic meningitis due to herpes simplex virus, meningeal metastasis of lymphoma, and superficial siderosis. The two patients with systemic vasculitis were diagnosed with Cogan's syndrome and Sjögren syndrome with aseptic meningitis, retinal vasculitis, and skin lesions.

Relationship between category of causative diseases and clinical manifestations

The time course for deterioration in auditory perception was ≤ 60 days in the six patients with an

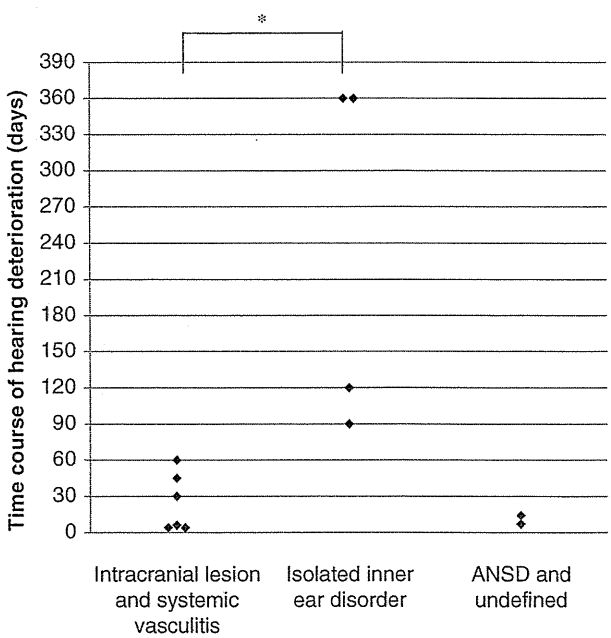

Figure 2. Time course of hearing deterioration in different categories of causative disorders. There was a significant difference between patients with intracranial lesion and systemic vasculitis, and those with an isolated inner ear disorder.
*: $p < 0.05$

Table II. Characteristics of six patients with an intracranial lesion or systemic vasculitis.

Case no.	Diagnosis	Treatment	Time before treatment (days)	Hearing improvement
1	Cryptococcal meningitis	Antifungal drug	3	Improved
2	Chronic herpes meningitis + labyrinthitis	Steroid and anti-HSV agents	Unknown	Not improved
3	Meningial metastasis of lymphoma	Steroid and anticancer drug	6	Improved
4	Superficial siderosis	No treatment		Not improved
5	Cogan's syndrome	Steroid	90	Not improved
6	Sjögren syndrome	Steroid	4	Improved

intracranial lesion or systemic vasculitis and ≥ 90 days in the four patients with an isolated inner ear disorder. The Mann–Whitney U test showed a significant difference ($p < 0.05$) between these groups (Figure 2). As shown in Table I, all patients with an intracranial lesion or systemic vasculitis complained of dizziness and/or noncochleovestibular symptoms in addition to hearing loss. Four of these six patients had dizziness and five of them had fever, headache, or altered mental state. These symptoms were not observed in patients with ANSD or an isolated inner ear disorder, who had only tinnitus as an associated symptom.

Hearing improvement after treatment for the causative diseases

The causative disease was treated in five patients with an intracranial lesion or systemic vasculitis, except in case 4 who had superficial siderosis (Table II). Hearing improved in three patients, who did not require hearing aids in daily life. The delay from the onset of hearing loss awareness to the beginning of treatment was within 1 week in cases 1, 3, and 6, who showed an improvement in hearing. However, it took as long as 90 days in case 5, who showed no change in hearing threshold after treatments. In case 4, the origin of bleeding that caused hemosiderosis was not determined despite radiographic evaluations, including brain and spinal MRI, and the patient showed no improvement in hearing at follow-up. Improvement in hearing loss did not occur in any of the patients with ANSD or an isolated inner ear disorder, despite systemic administration of steroids and/or circulation activators.

Discussion

This study was performed as a retrospective review of 12 cases with progressive bilateral SNHL who complained of difficulty in daily conversation within 4 days to 1 year after the onset of hearing loss awareness. The patients with bilateral SNHL presenting this time course of deterioration were relatively rare and accounted for only 1.3% of those with bilateral SNHL in this study. However, retrospectively, distinguishing this type of SNHL from others was meaningful because 6 of these 12 patients (50%) developed SNHL from an intracranial lesion or systemic vasculitis, which can be fatal without appropriate treatment. It is also noteworthy that all three patients with an intracranial lesion or systemic vasculitis, who showed improvement in hearing, underwent early treatment of the causative diseases, suggesting that accurate diagnosis and appropriate treatments for the causative disease at its early stage may be important to restore hearing as well as to lower the mortality. In the present study, the rapidly progressive SNHL was also caused by ANSD or an isolated inner ear disorder, but clinical manifestations of intracranial lesions and systemic vasculitis were different from those observed in other categories of causative diseases. Our study showed that in patients with intracranial lesions and systemic vasculitis, the time from onset of hearing loss to difficulty in daily life was within 2 months and significantly shorter than that in patients with an isolated inner ear disorder. In addition to the rapidly progressing hearing loss, noncochleovestibular symptoms and/or dizziness were always associated with intracranial lesions and systemic vasculitis, while all five patients with an isolated inner ear disorder or ANSD complained of only tinnitus. Among noncochleovestibular symptoms, fever was the leading symptom (6 of 12 patients), followed by headache and an altered mental state. In all cases with fever, the origin of fever was difficult to identify at first and systemic inflammation or intracranial infection was identified later based on systemic evaluations by otologists, internal medicine specialists, and radiologists. The presence of headache and an altered mental state also suggests that lesions may

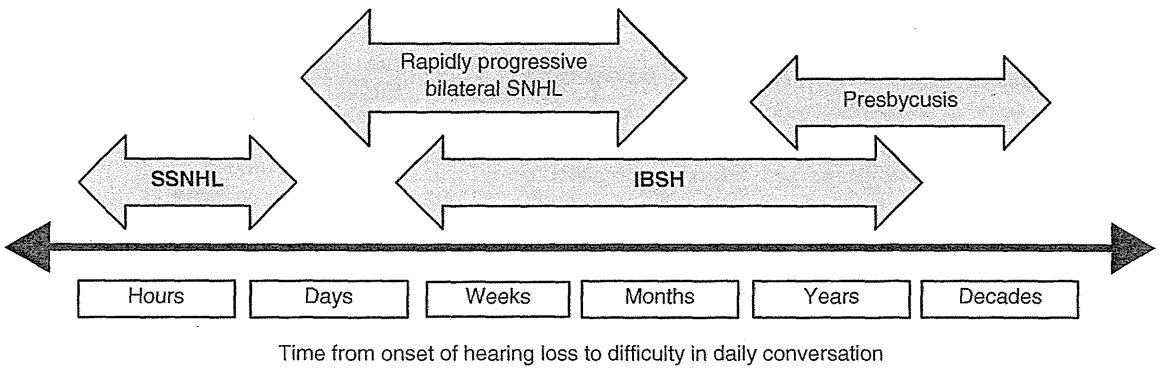

Figure 3. The time course in various types of bilateral sensorineural hearing loss (SNHL). IBSH, idiopathic bilateral SNHL; SSNHL, sudden SNHL.

involve other areas of the central nervous system in addition to the auditory neural pathway. Interestingly, obvious vestibular dysfunction was not observed in patients with an isolated inner ear disease, although four of the six patients with an intracranial lesion or systemic vasculitis had dizziness. The inner ear lesions in the present series may have been limited to the cochlea, with central compensation possibly making the vestibular symptoms less prominent despite the presence of some vestibular involvement.

We performed brain MRI in nine patients including all seven with a noncochleovestibular symptom or dizziness. Headache, altered mental state or other abnormal neurological findings in addition to the eighth cranial nerve dysfunction suggests the presence of an intracranial lesion. In this situation, brain MRI is necessary to evaluate intracranial diseases. Even though the neurological disorders were limited to the eighth cranial nerve, association of dizziness with SNHL might be caused by labyrinthitis or lesions in internal auditory canals and brain MRI may be recommended. Prolonged unknown origin of fever associated with bilateral SNHL is also an indication for brain MRI to evaluate labyrinthitis and nonbacterial meningitis.

In the present study, pure-tone hearing thresholds were improved in case 1 with Cryptococcus meningitis and case 3 with meningeal metastasis of lymphoma after the intracranial administration of antifungal and anticancer drugs, respectively. Hearing recovery is usually difficult in patients with Cryptococcus meningitis [5], although a patient with this disease was reported to show partial recovery of hearing after treatment [5]. Hearing improvement after treatment has also been reported in patients with bacterial and viral meningitis [6,7]. Vasculitis causes SNHL in patients with connective tissue diseases such as systemic lupus erythematosus and polyarteritis nodosa [8], with this type of hearing loss reported to improve following plasmapheresis or immunosuppressive therapy using steroids or cyclophosphamide [2,9]. In our study, case 6, who had Sjögren syndrome, showed hearing improvement after steroid treatment. In contrast, hearing loss in case 5, who had Cogan's syndrome, was not improved by steroids. Although hearing improvement has been described in a patient with Cogan's syndrome [10], it is often difficult to improve hearing loss in such patients.

Previous case reports indicate that the etiology of bilateral SNHL, which deteriorates more slowly than sudden deafness and more quickly than presbycusis, also includes meningeal carcinomatosis [11], metastasis of carcinoma in the bilateral internal auditory canal [12], mitochondrial neurogastrointestinal encephalopathy (MINGIE) [13], and polyarteritis nodosa [14]. These diseases were not found in the present study due to the small size of the study. The rapidly progressive bilateral SNHL can be induced by various types of diseases with different etiologies described above and, moreover, within each type of a disease, severity of symptoms may vary widely between patients. Therefore, further study investigating more patients with rapidly progressive bilateral SNHL is needed to lead to definite conclusions about the importance of clinical manifestations and indications for MRI for diagnosis of the causative diseases.

The definition of rapidly progressive SNHL in previous reports varies, including SNHL deteriorating in days [15] or in weeks to months [14,16–18]. However, the disease entity described in these reports is almost identical, which is the SNHL that progresses more slowly than sudden deafness and more rapidly than presbycusis. Thus, in line with those previous reports, we defined rapidly progressive SNHL as the one that deteriorates in days to months. The time course of rapidly progressive bilateral SNHL compared with that of other types of common bilateral SNHL is illustrated in Figure 3. Idiopathic bilateral SNHL (IBSH) is a progressive bilateral SNHL of unknown etiology and

was proposed as a clinical entity in 1976. In IBSH, hearing loss usually progresses over several years; therefore, deterioration in hearing loss is slower than that observed in the current patients [19], suggesting different etiologies. In the current study, the four patients with isolated inner ear disorders showed a significantly slower deterioration in hearing loss compared with the other patients. IBSH sometimes shows rapid progression of hearing loss within several days or weeks; therefore, patients with similar pathology to that observed in IBSH could meet our criteria for rapidly progressive bilateral SNHL if they visit a hospital in the rapid phase of the disease.

A noteworthy aspect of the patients reported in this study was that early treatment of intracranial lesions and systemic vasculitis improved hearing loss, suggesting the importance of early diagnosis of the causative disease, although further investigation of large numbers of patients is necessary to prove the effectiveness of early treatment. Early diagnosis is also important because the causative diseases for rapidly progressive bilateral SNHL include fatal conditions such as meningitis or malignant diseases, or diseases that may result in irreversible neurological deficits such as superficial siderosis. In patients with superficial siderosis, decreasing the risk for a poor outcome requires early diagnosis of the disease and identification and ablation of the bleeding source [20].

Conclusion

Rapidly progressive bilateral SNHL is rare, but it often develops as a symptom of intracranial disease or systemic vasculitis, both of which are potentially fatal. Hearing may recover in patients who undergo treatment at an early stage of the causative disease. This indicates that early diagnosis followed by appropriate treatment of the causative disease is critical for the management of these patients.

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References

[1] Plaza G, Durio E, Herraiz C, Rivera T, Garcia-Berrocal JR, Asociacion Madrilena de ORL. [Consensus on diagnosis and treatment of sudden hearing loss. Asociacion Madrilena de ORL.] Acta Otorrinolaringol Esp2011;62: 144–57 (in Spanish).

[2] Yamazaki H, Fujiwara K, Shinohara S, Kikuchi M, Kanazawa Y, Kurihara R . Reversible cochlear disorders with normal vestibular functions in three cases with Wegener's granulomatosis. Auris Nasus Larynx 2012;39: 236–40.

[3] Ishiyama A, Canalis RF. Otological manifestations of Churg-Strauss syndrome. Laryngoscope 2001;111: 1619–24.

[4] Iino Y. Eosinophilic otitis media: a new middle ear disease entity. Curr Allergy Asthma Rep 2008;8:525–30.

[5] Matos JO, Arruda AM, Tomita S, Araujo Pde P, Madeira FB, Sarmento Junior KM. Cryptococcus meningitis and reversible hearing loss. Braz J Otorhinolaryngol 2006;72:849.

[6] Richardson MP, Reid A, Tarlow MJ, Rudd PT. Hearing loss during bacterial meningitis. Arch. Dis. Child. 1997;76: 134–8.

[7] Miyashita T, Kobayashi Z, Numasawa Y, Akaza M, Ishihara S, Shintani S. Epstein-Barr virus-associated meningitis presenting with hearing impairment. Intern Med 1755; 51:1755–7.

[8] Kikuchi T, Yokoe I, Masuyama A, Maniwa K, Tsuruta S, Hatanaka Y . Behçet's disease initially presenting with meningitis and sudden hearing loss. Intern. Med. 2010;49: 483–6.

[9] Kobayashi S, Fujishiro N, Sugiyama K. Systemic lupus erythematosus with sensorineural hearing loss and improvement after plasmapheresis using the double filtration method. Intern. Med. 1992;31:778–81.

[10] Migliori G, Battisti E, Pari M, Vitelli N, Cingolani C. A shifty diagnosis: Cogan's syndrome. A case report and review of the literature. Acta Otorhinolaryngol Ital 2009;29:108–13.

[11] Shen TY, Young YH. Meningeal carcinomatosis manifested as bilateral progressive sensorineural hearing loss. Am J Otol 2000;21:510–12.

[12] Yamakami I, Oishi H, Iwadate Y, Yamaura A. Isolated metastases of adenocarcinoma in the bilateral internal auditory meatuses mimicking neurofibromatosis type 2–case report. Neurol. Med. Chir. (Tokyo) 1999;39:756–61.

[13] Kaidar-Person O, Golz A, Netzer A, Goldsher D, Joachims HZ, Goldenberg D. Rapidly progressive bilateral sensory neural hearing loss as a presentation of mitochondrial neurogastrointestinal encephalomyopathy. Am J Otolaryngol 2003;24:128–30.

[14] Wolf M, Kronenberg J, Engelberg S, Leventon G. Rapidly progressive hearing loss as a symptom of polyarteritis nodosa. Am J Otolaryngol 1987;8:105–8.

[15] Terayama Y, Ishibe Y, Matsushima J. Rapidly progressive sensorineural hearing loss (rapid deafness). Acta Otolaryngol Suppl 1988;456:43–8.

[16] Harris JP, Sharp PA. Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. Laryngoscope 1990;100:516–24.

[17] Veldman JE, Hanada T, Meeuwsen F. Diagnostic and therapeutic dilemmas in rapidly progressive sensorineural hearing loss and sudden deafness. A reappraisal of immune reactivity in inner ear disorders. Acta Otolaryngol. 1993; 113:303–6.

[18] Gottschlich S, Billings PB, Keithley EM, Weisman MH, Harris JP. Assessment of serum antibodies in patients with rapidly progressive sensorineural hearing loss and Menière's disease. Laryngoscope 1995;105: 1347–52.

[19] Yagi M, Harada T, Yamasoba T, Kikuchi S. Clinical features of idiopathic bilateral sensorineural hearing loss. ORL J Otorhinolaryngol Relat Spec 1994;56:5–10.

[20] Moreira NC, Nylander R, Briaukait I, Velyvyte S, Gleiznien R, Monastyreckien E. Superficial siderosis: a case report. Medicina (Kaunas) 2011;47:320–2.

Notice of correction

The Early Online version of this article published online ahead of print on 21 Nov 2013 was missing information about the authors.
The corrected version is shown here.

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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

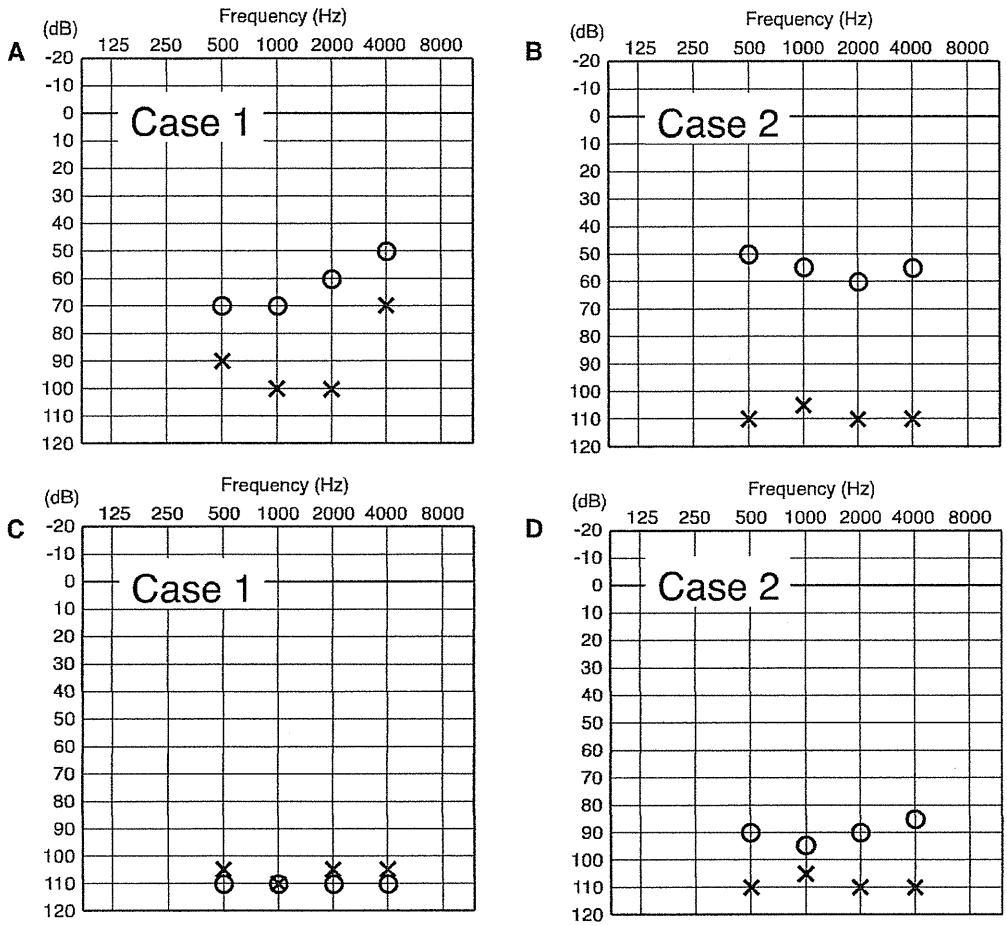

Fig. 1. (A) Case 1; a 5-year-old girl with asymptomatic congenital CMV infection (threshold using ASSR test). (B) Case 2; a 5-year-old girl with asymptomatic congenital CMV infection. These were results of first diagnosed with hearing loss. (C and D) Deterioration in hearing, for one month and for one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

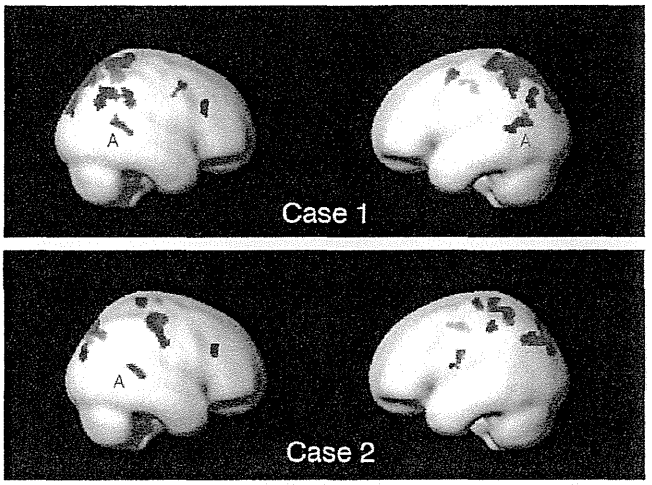

Fig. 2. Cortical activation by language-related visual stimuli in two profoundly deafened with congenital CMV infection cases. Case 1 and 2 showed significant activation in auditory association areas (A) (SPM2, $p < 0.001$, uncorrected).

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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References

[1] Y. Naito, I. Tateya, N. Fujiki, S. Hirano, K. Ishizu, Y. Nagahama, et al., Increased cortical activation during hearing of speech in cochlear implant users, Hear. Res. 143 (2000) 139–146.
[2] S. Hirano, Y. Naito, H. Kojima, I. Honjo, M. Inoue, K. Shoji, et al., Functional differentiation of the auditory association area in prelingually deaf subjects, Auris Nasus Larynx 27 (2000) 303–310.
[3] Y. Naito, S. Hirano, I. Honjo, H. Okazawa, K. Ishizu, H. Takahashi, et al., Sound-induced activation of auditory cortices in cochlear implant users with post- and prelingual deafness demonstrated by positron emission tomography, Acta Otolaryngol. 117 (1997) 490–496.
[4] Y. Naito, S. Hirano, H. Okazawa, H. Takahashi, K. Ishizu, N. Fujiki, et al., Central auditory processing of speech in cochlear implant users demonstrated by positron emission tomography, Adv. Otorhinolaryngol. 52 (1997) 19–23.
[5] T.A. Zwolan, C.M. Ashbaugh, A. Alarfaj, P.R. Kileny, H.A. Arts, H.K. El-Kashlan, et al., Pediatric cochlear implant patient performance as a function of age at implantation, Otol. Neurotol. 25 (2004) 112–120.
[6] B. May-Mederake, Early intervention and assessment of speech and language development in young children with cochlear implants, Int. J. Pediatr. Otorhinolaryngol. 76 (2012) 939–946.
[7] K. Fujiwara, Y. Naito, M. Senda, T. Mori, T. Manabe, S. Shinohara, et al., Brain metabolism of children with profound deafness: a visual language activation study by ^{18}F-fluorodeoxyglucose positron emission tomography, Acta Otolaryngol. 128 (2008) 393–397.
[8] W.E. Nance, B.G. Lim, M.K. Dodson, Importance of congenital cytomegalovirus infections as a cause for pre-lingual hearing loss, J. Clin. Virol. 35 (2006) 221–225.
[9] S. Iwasaki, M. Yamashita, M. Maeda, K. Misawa, H. Mineta, Audiological outcome of infants with congenital cytomegalovirus infection in a prospective study, Audiol. Neurootol. 12 (2007) 31–36.
[10] S.D. Grosse, D.S. Ross, C.S. Dollard, Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment, J. Clin. Virol. 41 (2008) 57–62.
[11] C.C. Morton, W.E. Nance, Newborn hearing screening – a silent revolution, N. Engl. J. Med. 354 (2006) 2151–2164.
[12] S. Furutate, S. Iwasaki, S.Y. Nishio, H. Moteki, S. Usami, Clinical profile of hearing loss in children with congenital cytomegalovirus (CMV) infection: CMV DNA diagnosis using preserved umbilical cord, Acta Otolaryngol. 131 (2011) 976–982.
[13] S.f.t.K.S.o.P.D., Test Shinpan K Shiki Hattatsu Kensahou 2001 Nenban, Nakanishi Shuppan, Kyoto, 2008.
[14] I. Foulon, A. Naessens, G. Faron, W. Foulon, A.C. Jansen, F. Gordts, Hearing thresholds in children with a congenital CMV infection: a prospective study, Int. J. Pediatr. Otorhinolaryngol. 76 (2012) 712–717.
[15] K. Fukushima, K. Sugata, N. Kasai, S. Fukuda, R. Nagayasu, N. Toida, et al., Better speech performance in cochlear implant patients with GJB2-related deafness, Int. J. Pediatr. Otorhinolaryngol. 62 (2002) 151–157.
[16] A. Kawasaki, K. Fukushima, Y. Kataoka, S. Fukuda, K. Nishizaki, Using assessment of higher brain functions of children with GJB2-associated deafness and cochlear implants as a procedure to evaluate language development, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 1343–1349.
[17] D.J. Lee, L. Lustig, M. Sampson, J. Chinnici, J.K. Niparko, Effects of cytomegalovirus (CMV) related deafness on pediatric cochlear implant outcomes, Otolaryngol. Head Neck Surg. 133 (2005) 900–905.
[18] A. Ciorba, R. Bovo, P. Trevisi, C. Bianchini, R. Arboretti, A. Martini, Rehabilitation and outcome of severe profound deafness in a group of 16 infants affected by congenital cytomegalovirus infection, Eur. Arch. Otorhinolaryngol. 266 (2009) 1539–1546.
[19] H. Yamazaki, R. Yamamoto, S. Moroto, T. Yamazaki, K. Fujiwara, M. Nakai, et al., Cochlear implantation in children with congenital cytomegalovirus infection accompanied by psycho-neurological disorders, Acta Otolaryngol. 132 (2012) 420–427.
[20] M. Viccaro, R. Filipo, E. Bosco, M. Nicastri, P. Mancini, Long-term follow-up of implanted children with cytomegalovirus-related deafness, Audiol. Neurootol. 17 (2012) 395–399.
[21] H. Nishimura, K. Doi, T. Iwaki, K. Hashikawa, N. Oku, T. Teratani, et al., Neural plasticity detected in short- and long-term cochlear implant users using PET, Neuroreport 11 (2000) 811–815.
[22] A.L. Giraud, E. Truy, R. Frackowiak, Imaging plasticity in cochlear implant patients, Audiol. Neurootol. 6 (2001) 381–393.
[23] H.J. Lee, E. Kang, S.H. Oh, H. Kang, D.S. Lee, M.C. Lee, et al., Preoperative differences of cerebral metabolism relate to the outcome of cochlear implants in congenitally deaf children, Hear. Res. 203 (2005) 2–9.

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シリーズ教育講座「難治性めまいへのアプローチ」

5．メニエール病の外科治療

土井　勝美

Surgical treatments of intractable Meniere's disease

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Meniere's disease is characterized by intermittent episodes of vertigo lasting from minutes to hours, with fluctuating sensorineural hearing loss, tinnitus, and aural pressure. The primary histopathological correlate is endolymphatic hydrops. Several medical and surgical treatments have been offered to patients with Meniere's disease. It has been confirmed that no one effective treatment is available for these patients. According to the severity of the patients' symptoms, appropriate therapeutic strategies should be selected. If medical therapies including lifestyle change, diuretics, and local/systemic steroids have failed, then surgical approaches such as intratympanic gentamicin perfusion (GM), pressure pulse treatment with Meniett®, endolymphatic sac surgery (ESS) and vestibular neurectomy (VN) should be considered. Most reviews have reported relative good (80–100%) vertigo control rates with either GM, Meniett®, ESS, or VN, however, recurrence of vertigo has been noticed in certain cases. A combination of medical and surgical strategies should be recommended and the treatment algorithm for Meniere's disease indicated in "2011 Clinical practice guidelines for Meniere's disease" must be adopted.

Key words: Meniere's disease, endolymphatic shunt surgery, intratympanic gentamycin treatment, middle ear pressure treatment, vestibular neurectomy

はじめに

メニエール病確実例では，発症後わずか１年でめまいの頻度は急速に減少，発症後10年以内にめまいの頻度はほぼ一定となり，その後も20–30年目にかけて徐々に減少していく。一方で，メニエール病に対するさまざまな薬物治療の再発率は約20–30％で，こうした難治性メニエール病症例の一部は手術的治療を選択することになる。手術的治療の中で，内リンパ嚢手術の再発率は短期で10–15％と良好であるが，長期では30％前後とされ，再手術や別の外科治療の適応となる症例がある。鼓室内 GM 治療や中耳加圧治療は，比較的侵襲が小さく EBM の蓄積が始まっているが，やはり20–30％の再発率が報告されている。前庭神経切断術と迷路破壊術の再発率は10％以下と極めて低率であるが，一方で，大きな侵襲を伴い，重篤な合併症や前庭代償不全の可能性が心配される。

めまいを反復する難治性メニエール病への対応に関して EBM に基づいて論ずるためには，メニエール病の薬物治療・手術的治療に関して，周期

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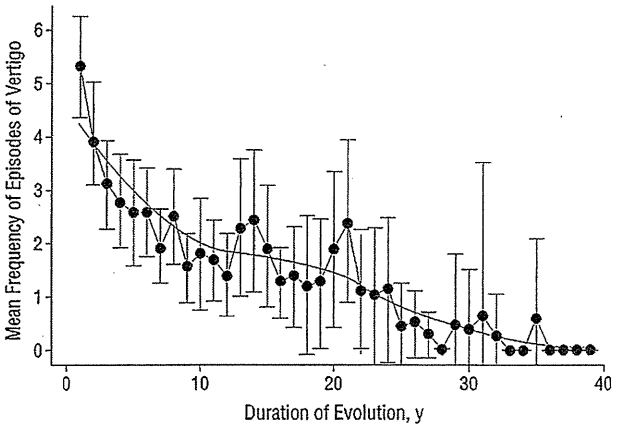

図１　メニエール病確実例における長期経過観察中のめまいの頻度（文献３）図１より改変）

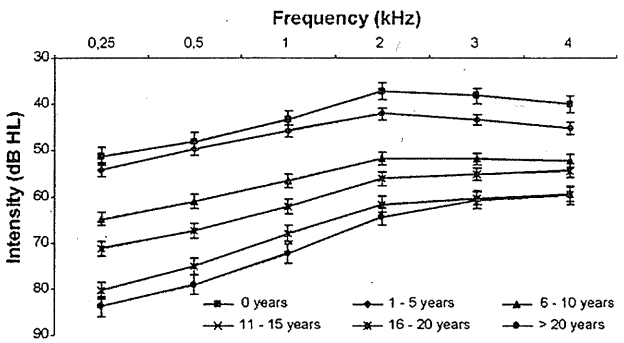

図２　一側性メニエール病確実例における長期経過観察中の聴力低下（文献７）図１より改変）

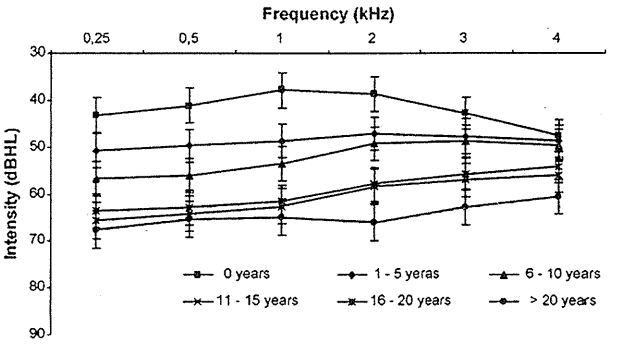

図３　両側性メニエール病確実例における長期経過観察中の聴力低下（文献７）図１より改変）

的な自然緩解やプラセボ効果にも十分に配慮がなされた良質の trial が推進される必要がある。

メニエール病のめまい

メニエール病は内リンパ水腫をその病態とし，めまい・難聴・耳鳴・耳閉感などの症状を反復する疾患である。メニエール病の発症後，病期の進行に従いめまい発作の頻度がどのように変化するかについては，徐々に減少する[1)~3)]，あまり変わらない[4)]とする両方の報告がある。米国 AAO-HNS の診断基準[5)]に基づいてメニエール病確実例と診断された510症例（手術的治療なし）を対象に，20分間以上続くめまい発作の頻度を長期間追跡した研究[3)]によれば，発症後わずか１年でめまいの頻度は急速に減少，さらに年数の経過とともにますます減少し，発症後10年以内にめまいの頻度はほぼ一定となり，その後も20-30年目にかけて徐々に減少していくことが明らかになった（図１）。薬物治療によりめまい発作が良好に制御される症例が大部分である一方で，薬物治療に抵抗性を示しめまいを反復する症例が存在し，それらの症例の一部には外科治療が選択される。上記論文では，510例中103例（20％）が最終的に手術的治療の適応となったとしている。

メニエール病の聴覚障害

病期の進行に伴い，難聴は徐々に増悪することが知られている。メニエール病では，発症初期には低音部の感音難聴が特徴的であり，めまい発作期に聴力変動を繰り返すが，病期の進行に従い中音～高音部にも聴力低下を来たし，徐々に固定した水平型の感音難聴を呈するようになる[6)]。加齢変化による高音部の感音難聴を補正した解析でも，一側性メニエール病では，低音部でより著明ではあるが，中音域から高音部も含め全ての周波数で進行性の聴力低下が確認されている（図２）[7)]。内科治療の継続あるいは定期的な経過観察（自然経過）の過程でめまいは良好に制御され，一方で大部分の症例では固定化した感音難聴を呈するようになる。Belinchon らは，加齢変化による高音部の感音難聴を補正した上で，235症例のメニエール病確実例の聴力変化を長期にわたって観察し，①一側性および両側性メニエール病ともに，罹病期間が長くなるにつれて感音難聴が進行，②一側性メニエール病では，両側性と比較して，より急速に感音難聴が進行，③一側性では0-25-1 kHz の低音部でより著明な聴力低下が進行，④両側メニエール病では，一側性と比較して，聴力はより良好で水平型が優位，などの特徴を報告した（図２，３）[7)]。

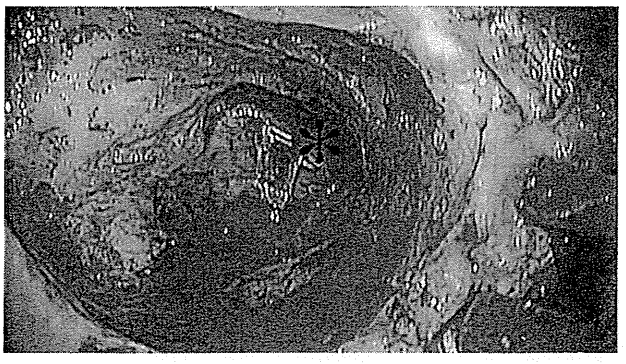

図4　右メニエール病に対する内リンパ嚢開放術
乳突洞削開，S状静脈洞～後頭蓋窩硬膜の減圧に続いて，内リンパ嚢開放（＊）を行い，ジェルフィルムの留置を行う。

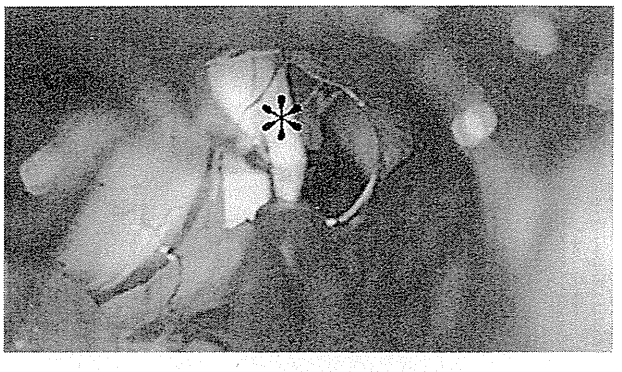

図5　左メニエール病に対する前庭神経切断術（後S状静脈洞法）
小脳橋角部で第8脳神経を同定，前庭神経と蝸牛神経を分離した後，前庭神経（＊）のみを選択的に切断する。

自然緩解とプラセボ効果

メニエール病は，回転性のめまい，難聴，耳鳴，耳閉感を主たる症状とし，周期的にメニエール病の発作と自然緩解を繰り返す疾患である。「自然緩解」と「治療によるメニエール病の治癒」との見極めには中長期的な経過観察が必要となる。前述の通り，メニエール病のstageが進むにつれて回転性めまいは軽快する[1)~3)]。すなわち，発作期に生じた難聴が緩解期には改善する「early fluctuant stage」ではめまいが頻発するのに対して，聴力レベルが水平型で約60 dBに固定する「late neural stage」ではめまい症状は軽快・消失していく。治療担当者が扱う症例がいずれのstageに多く属するかによって，自然緩解の割合や治療後の再発率に大きな差が生じる可能性がある[8)]。米国AAO-HNSの聴力レベルによるstagingでは，stage 1 & 2が「early fluctuant stage」，stage 3 & 4が「late neural stage」に相当すると考えても良い。一般的には，「early fluctuant stage」では主として薬物治療が選択され，「late neural stage」では手術的治療を選択する症例も含まれてくる。手術的治療を「early fluctuant stage」に適応とすることの是非については，今後の科学的な検討が求められよう。将来的には，遺伝子解析等によりいわゆる「予後不良群」と診断されたメニエール病症例に対して，「early fluctuant stage」での手術的治療を選択する時代が来るかもしれない。いずれにしても，治療効果の判定に際して，メニエール病の周期的な自然緩解とstage分類による治療成績の違いを十分に理解しておく必要がある。

メニエール病の治療成績を検討する際，もう一つ問題となるのはいわゆる「プラセボ効果」である。単なる乳突削開術を対照群として内リンパ嚢手術のプラセボ効果について報告したThomsen論文[9)]を除き，現在では無作用プラセボを対照群に使用することは倫理的に許されないことから，陽性プラセボを用いたrandomized，double-blind法の解析が基本になる。薬物治療の治療成績の優劣判定についてはこのような解析は可能であるが，手術的治療については陽性プラセボの設定自体が極めて困難であり，中耳加圧治療に関する検討があるものの，プラセボ効果を純粋に排除することは事実上不可能に近い。さらに，手術的治療に関しては，その施行には必ず何らかの麻酔操作を伴うことから，麻酔の影響の排除も治療効果の判定には必要となる。従って，以下に述べていく薬物治療・手術的治療の有効症例中にはプラセボ効果や治療自体とは別の要素によるものが一部含まれる可能性があることを認識して頂きたい。

外科治療によるめまい制御

薬物治療に反応しない難治性メニエール病の症例に対して，手術的治療が考慮されることになる。十分なインフォームドコンセントの後，最終的に手術的治療を決断する症例は，メニエール病症例の約20%とされている。手術的治療には以下に示す通りいくつかの選択肢があり，年齢，重症度，聴力レベル，対側耳の状態，社会的・経済的要素を検討した上で，どの治療を施行するかが決定される[8)10)]。

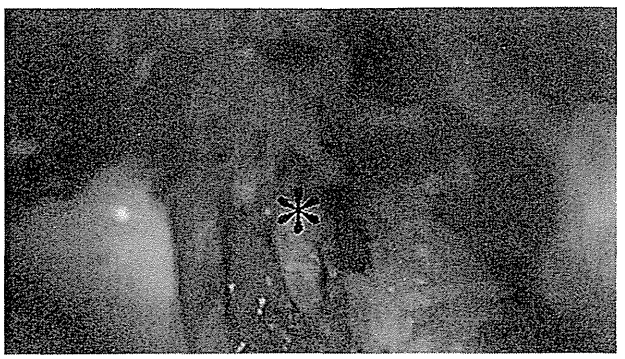

図6　右メニエール病に対する前庭神経切断術（経中頭蓋窩法）
中頭蓋窩で開頭，側頭葉を剥離・挙上，膝神経節より迷路部，そして内耳道まで顔面神経を追いかけることで内耳道を同定し，硬膜を開放した後，前庭神経（＊）のみを選択的に切断する。

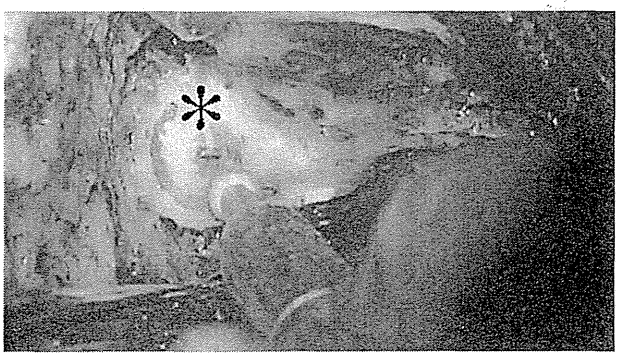

図7　右メニエール病に対する迷路破壊術
乳突削開の後，外側半規管，後半規管に続いて，前半規管（＊）の削開を行う。

米国ANS（American Neurotology Society）の会員300名へのアンケート調査[11]によれば，203名のANS会員より返答があり，保存的治療の後に最初に施行する手術的治療として50％が内リンパ嚢手術，38％が鼓室内GM治療，９％がMeniett®による中耳加圧治療で，前庭神経切断術は２％であった。Thomson論文の後も，内リンパ嚢手術の有効性を確認するいくつかの報告があり，現時点でも同手術が手術的治療の第一選択肢として最も多く支持されていることがわかる。英国耳鼻科医を対象とする同様の調査でも，52％の手術的治療担当医が内リンパ嚢手術，50％が中耳換気チューブの留置術を選択しており，また，２／３の医師が鼓室内GM治療についても考慮するとされている[12]。我国においても，破壊手術（前庭神経切断術および迷路破壊術）よりも，機能保存を目指す内リンパ嚢手術，GM治療，中耳加圧治療の中から，より低侵襲かつ有効な治療法を選択するという傾向にある。

１）内リンパ嚢手術

上述の通り，1926年にPortmannにより開始された内リンパ嚢手術は，現在も手術的治療の選択肢の一つとして支持されている（図４）。実際には，内リンパ腔の減圧と内リンパ液の排出を目的に内リンパ嚢を開放してdrainageを行う手術，内リンパ嚢と後頭蓋窩硬膜を減圧するのみの手術，内リンパ嚢を摘出する手術等，さまざまな改良が試みられている[8)10)]。Drainageに用いられるprosthesisもいろいろである。しかしながら，どの手術内容によっても治療成績に大きな差は見られず，短期成績では80–90％の症例でめまい発作は良好に制御され，より長期でのめまい制御率は60–70％前後に落ち着いていく[8)10)13)]。「メニエール病の再発」という意味では，短期成績で10–15％，長期成績では30–40％ということになる。初回治療として内リンパ嚢手術を施行された症例中で，追加の手術的治療（再手術を含む）を必要としたものは７–37％とされている[13)]。

内リンパ嚢（開放）再手術に関しては，いくつかの報告があり，概ね治療成績は初回手術とほぼ同等であるとされる[10)]。再手術後のめまい再発率としては５–17％の数字が報告されていて，それらの症例では前庭神経切断術，迷路破壊術等の別の手術的治療が追加されることになる[14)15)]。内リンパ嚢再手術時に観察された内リンパ嚢周辺の局所所見としては，①Ｓ状静脈洞～後頭蓋窩硬膜～内リンパ嚢での骨新生，②内リンパ嚢の線維化，③乳突洞の閉鎖，④内リンパ嚢周囲での肉芽増生，⑤留置したシリコン膜の変性等が観察されていて，メニエール病の発症機序および病態を考慮する上で興味深い。著者が担当した内リンパ嚢手術症例（51例）中でめまい発作の頻発により再手術を必要とした症例は１例のみである。後頭蓋窩硬膜上～内リンパ嚢に骨新生（再生）が観察されたが，内リンパ嚢の線維化や肉芽増生はなく，骨削開による再度のdecompressionと内リンパ嚢のdrainageを行った。再手術後の経過は良好で