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ORIGINAL ARTICLE

Vestibular function of patients with profound deafness related to *GJB2* mutation

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Abstract

Conclusion: GJB2 mutations are responsible not only for deafness but also for the occurrence of vestibular dysfunction. However, vestibular dysfunction tends to be unilateral and less severe in comparison with that of bilateral deafness. *Objectives:* The correlation between the cochlear and vestibular end-organs suggests that some children with congenital deafness may have vestibular impairments. On the other hand, *GJB2* gene mutations are the most common cause of nonsyndromic deafness. The vestibular function of patients with congenital deafness (CD), which is related to *GJB2* gene mutation, remains to be elucidated. The purpose of this study was to analyze the relationship between *GJB2* gene mutation and vestibular dysfunction in adults with CD. *Methods:* A total of 31 subjects, including 10 healthy volunteers and 21 patients with CD, were enrolled in the study. A hearing test and genetic analysis were performed. The vestibular evoked myogenic potentials (VEMPs) were measured and a caloric test was performed to assess the vestibular function. The percentage of vestibular dysfunction was then statistically analyzed. *Results:* The hearing level of all CD patients demonstrated a severe to profound impairment. In seven CD patients, their hearing impairment was related to *GJB2* mutation. Five of the seven patients with CD related to *GJB2* mutation demonstrated abnormalities in one or both of the two tests. The percentage of vestibular dysfunction of the patients with CD related to *GJB2* mutation was statistically higher than in patients with CD unrelated to *GJB2* mutation and in healthy controls.

Keywords: *Vestibular evoked myogenic potentials, caloric test*

Introduction

Since a correlation between the peripheral auditory and vestibular systems has been identified both anatomically and phylogenetically, a subgroup of children with congenital deafness (CD) may be associated with vestibular and balance impairments [1–3]. Interestingly, the vestibular disturbance in these children gradually disappears as they grow up, probably because of a compensatory mechanism of the central nervous system. However, there have been only a few reports that conducted a detailed analysis of the vestibular function in adults with CD.

CD has been reported in approximately one child per 1000 births [1]. In more than half of these cases, the disease is caused by gene mutation. In particular, mutation in the *GJB2* gene, which encodes Cx26 in the gap junction, is known to be a most common cause (up to 50% of such cases) [2,3]. Gap junction channels enable the neighboring cells to exchange small signaling molecules. Immunohistochemical studies have revealed that Cx26 exists not only in the cochlea but also in the vestibular organs [4]. K^+ cycling involving gap junction protein Cx26 in the vestibular labyrinth, which is similar to that in the cochlea, is thought to play a fundamental role in the endolymph homeostasis and sensory transduction [5]. These findings suggest that mutations in the *GJB2* gene may thus cause vestibular dysfunction.

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In this study, the relationship between *GJB2* gene mutation and vestibular dysfunction in adults with CD was investigated to confirm whether or not there are any abnormalities associated with the vestibular function.

Material and methods

Subjects

The subjects in this prospective study included 21 patients with CD and 10 healthy volunteers. The patients were excluded from the study if they were being treated with ototoxic drugs or if they had a cytomegalovirus infection, bacterial meningitis, external and middle ear pathological findings, or other risk factors for inner ear damage. No participants had syndromic deafness due to pigmentary retinopathy, nephropathy, goiter, or any other diseases. Patients with vestibular dysfunction due to head trauma, brain tumor, Meniere's disease, or other conditions were also excluded from the study. All subjects underwent an otoscopic examination and were found to have a normal tympanic membrane. Audiometric testing was performed in a double-walled, sound-treated booth. All patients gave their informed consent in writing and the study was approved by the Ethics Committee of Juntendo University School of Medicine.

Genetic analysis

DNA was extracted from peripheral blood leukocytes of the subjects. The coding region of *GJB2* was amplified by PCR using the primers *GJB2*-2F 5′-GTGTGCATTCGTCTTTTCCAG-3′ and *GJB2*-2R 5′-GCGACTGAGCCTTGACA-3′. The PCR products were sequenced using the PCR primers and sequence primers *GJB2*-A 5′-CCACGC-CAGCGCTCCTAGTG-3′ and *GJB2*-B 5′-GAA-GATGCTGCTGCTTGTGTAGG-3′. These were visualized using an ABI Prism 310 Analyzer (PE Applied Biosystems, Tokyo, Japan).

Vestibular evoked myogenic potentials

The vestibular evoked myogenic potentials (VEMPs) were measured as described in a previous report [6]. Both sound stimuli of clicks (0.1 ms, 95 dBnHL) and short tone burst (500 Hz; rise/fall time, 1 ms, 95 dBnHL) were presented to each side of the ear through the headphones using a Neuropack evoked-potential recorder (Nihon Kohden Co. Ltd, Tokyo, Japan). The surface electromyographic activity was recorded with the patient in the supine position from symmetrical sites over the upper half of each sternocleidomastoid (SCM) muscle with a reference electrode on the lateral end of the upper sternum. During recording, the subjects were instructed to lift their head up or to turn the contralateral side to induce hypertonicity of the SCM. Thereafter, the electromyographic signals from the stimulated side of the SCM muscle were amplified.

Caloric test

The caloric test in the current study was performed as described elsewhere [7]. Briefly, 2 ml of ice-water (at 4°C) was irrigated in the external auditory meatus to induce a thermal gradient across the horizontal semicircular canal of one ear. The duration of horizontal and vertical nystagmus was recorded. The results were compared between the right and left ears.

Statistical analysis

The data are expressed as the mean ± SD. Statistical analyses were conducted using a non-repeated measures analysis of variance (ANOVA). Significant effects were further analyzed by post hoc multiple comparison tests using the Student-Newman-Keuls test. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Hearing test

The pure-tone averages of 0.5, 1.0, and 2.0 kHz are shown in Table I. The hearing impairments of CD patients ranged from severe (71–95 dB) to profound (>95 dB). The hearing levels of all controls were at the normal level (<30 dB; data not shown).

Genetic analysis

GJB2 mutations were found in nine CD patients (Table I). All three mutations have been described previously in association with deafness. Among these mutations, 235delC mutation was found in eight patients. One nonsense mutation (Y136X) and one frameshift mutation (176-191del) were also identified. In six patients with a homozygous *GJB2* mutation and one patient with a compound heterozygous

Table I. Results of hearing level, genetic analysis, and vestibular function of subjects with congenital deafness (CD)

Case no.	Hearing level (dB) Left	Right	Sex	Age (years)	Mutation in *GJB2*	VEMPs	Caloric test
Patients with *GJB2*-related CD							
1	86	98	M	26	Homo 235delC	Right decreased	Left CP
2	106	108	M	25	Homo 235delC	Right decreased	Normal
3	108	106	M	28	Homo 235delC	Right decreased	Normal
4	108	106	M	37	Homo 235delC	Normal	Right CP
5	100	106	M	32	Homo 235delC	Normal	Right poor/left CP
6	80	91	M	25	Homo 235delC	Normal	Normal
7	115	108	M	25	Y136X/235delC	Normal	Normal
Patients without *GJB2*-related CD							
8	98	98	F	24		Left decreased	Bilateral CP
9	98	115	M	26		Normal	Bilateral CP
10	97	97	M	20		Normal	Normal
11	111	108	M	31		Normal	Normal
12	100	104	F	34		Normal	Normal
13	98	95	M	21		Normal	Normal
14	91	91	M	24		Normal	Normal
15	99	101	F	26		Normal	Normal
16	99	95	F	23		Normal	Normal
17	80	68	M	27		Normal	Normal
18	96	95	M	27		Normal	Normal
19	85	73	M	23		Normal	Normal
Patients with heterozygous *GJB2* mutation							
20	73	100	M	25	Hetero 235delC	Normal	Normal
21	97	98	M	25	Hetero 176-191del16	Normal	Normal

CP, canal paresis; Poor, nystagmus was obviously weak.

mutation (case nos 1–7); their profound deafness was thought to be caused by a *GJB2* mutation. No *GJB2* mutation was identified in any of the controls.

Vestibular function

No patients or controls had any subjective symptoms of vertigo. Table I shows the results of the vestibular function in all CD patients. Abnormal responses of VEMPs and the caloric test in CD with a *GJB2*-related mutation were observed in three patients each (case nos 1–5). Three patients with a homozygous *GJB2* mutation showed asymmetrical responses in VEMPs (case nos 1–3). Three patients with a homozygous *GJB2* mutation showed asymmetrical responses in the caloric test (case nos 1, 4, and 5). One of them showed both VEMPs and the caloric test asymmetrical responses (case no. 1). One patient with a homozygous *GJB2* mutation and one patient with compound heterozygous *GJB2* mutation showed normal responses in both VEMPs and the caloric test (case nos 6 and 7). It is notable that five of the six patients with a homozygous 235delC mutation showed no abnormalities in either test. Two heterozygous patients (case nos 20 and 21) showed normal responses in both tests.

Two CD patients with no *GJB2* mutation exhibited abnormal findings for the vestibular tests (case nos. 8 and 9). One patient showed a unilateral reduction in VEMPs and bilateral canal paresis (case no. 8). Bilateral canal paresis was also observed in another patient (case no. 9).

All the controls with normal hearing showed normal responses in both the VEMPs and the caloric test (data not shown).

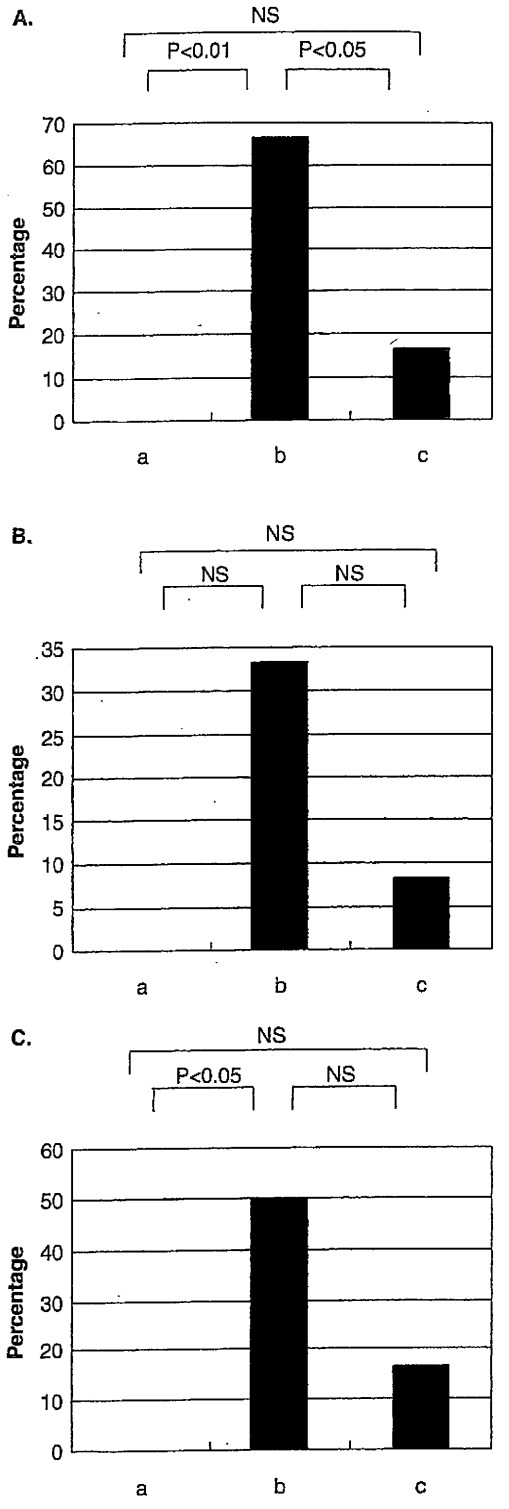

Figure 1. Comparison of the incidence of abnormality in the vestibular tests among the three groups. (A) Percentage showing abnormality in VEMPS and/or caloric test. (B) Percentage showing abnormality in VEMPs. (C) Percentage showing abnormality in the caloric test. a, Controls; b, *GJB2*-related CD subjects; c, CD subjects without *GJB2* mutations.

Statistical analysis of vestibular function in the three groups

Figure 1 shows a comparison of the controls, patients with CD related to a *GJB2* mutation, and those with CD without a *GJB2* mutation. The CD patients with *GJB2* heterozygous mutation were excluded from this statistical analysis, since their symptoms of hearing impairment are not necessarily caused by the *GJB2* mutation alone. Vestibular dysfunction showing an abnormality in VEMP and/or the caloric test significantly increased in patients with *GJB2*-related CD in comparison with those with CD without *GJB2* mutation ($p < 0.05$) and the controls ($p < 0.01$), whereas no difference was observed between CD without a *GJB2* mutation and the controls (Figure 1A). No differences in the incidence of abnormality in VEMPs were observed among the three groups (Figure 1B). The incidence of abnormalities in the caloric test in patients with *GJB2*-related CD differed significantly from that in the controls, but the other two comparisons were not significant (Figure 1C).

Discussion

In this study, vestibular tests were performed in CD patients with or without a *GJB2* mutation by measuring the VEMPs and using the caloric test. Only one report has previously investigated the vestibular function of patients with *GJB2*-related CD [8]. The authors noted that five of the seven patients showed no VEMP responses bilaterally and that only one case had a unilateral pathological response in the caloric test, which led to the conclusion that CD with a *GJB2* mutation is associated with severe saccular dysfunction. However, in the present study, there were no patients showing the absence of both VEMP and a caloric response. Todt et al. [8] showed the existence of *GJB2* mutations that do not cause CD (polymorphisms), thus suggesting a considerable bias. Furthermore, patients with low-grade hearing loss were included in their study. In contrast, all of the *GJB2* mutations detected in the present study are known to cause CD in the Asian population [9]. In addition, the present study included only patients with severe to profound hearing loss, which would therefore clarify the correlation between CD and *GJB2* mutations. Among the seven patients with *GJB2*-related CD, five (71.4%) showed abnormal responses in either or both tests. The incidence was apparently and significantly higher than that in patients with CD without a *GJB2* mutation (2/13: 15.4%). Moreover, the incidence in the controls significantly differed from that in patients with CD related to a *GJB2*

mutation but not in those with CD without *GJB2* mutation. Therefore, these findings support the hypothesis that *GJB2* mutations play a critical role in the disturbance of the vestibular function.

GJB2 mutations cause profound deafness and the associated mechanism has been discussed in several studies [10,11]. A recent study showed that *GJB2* is indispensable in the normal development of the organ of Corti and normal hearing on the basis of the study in *Gjb2* dominant-negative mutant mice [12]. Despite the widespread expression of Cx26 in both the cochlear and vestibular organs [4], the vestibular function impairment of the patients with a *GJB2* mutation is not as severe as the hearing dysfunction observed in the present study. Two hypotheses have been proposed to explain this inconsistency between hearing and balance function. One hypothesis is based on the fact that two temporal bone studies performed in patients with *GJB2*-related hearing impairment in the previous study revealed that one patient had mild vestibular hydrops and saccular degeneration, while another patient had a dysplastic neuroepithelium of the saccule [13,14]. This suggests that a *GJB2* mutation can cause morphological dysplasia in not an entire organ, but in part of the vestibular organs. This is contrast to the cochlea of these patients, which showed nearly total dysplasia of the organ of Corti. These histopathological studies support the results of the vestibular dysfunction of patients with *GJB2*-related CD in the present study. The other hypothesis is based on the presence of several connexins such as Cx26, Cx30 (encoded by *GJB6*), Cx31 (encoded by *GJB3*), and Cx32 (encoded by *GJB1*) in the inner ear. A previous study showed all of these connexins to be distributed in the vestibular organs [15]. Cx30 gene knockout mice had hair cell loss in the saccule, which was restored by the over-expression of the Cx26 gene [16]. Therefore, the specific loss of Cx30 causes vestibular dysfunction, which can be compensated by other types of connexins. The present clinical study in which a complete defect of Cx26 resulted in a definitive but partial dysfunction of vestibular end organs can be explained by the compensation of other connexins normally expressed in the vestibule. Further studies are required to clarify the relationship between connexins and the vestibular function.

Although there was a statistically significant difference in the objective examination of the vestibular function among patients with *GJB2*-related CD, those with CD without a *GJB2* mutation, and healthy controls, none of these subjects had any vestibular symptoms regardless of the presence or absence of a *GJB2* mutation. The peripheral vestibular dysfunction predicted in individuals with the *GJB2* mutation may be compensated by the central vestibular system in young patients with deafness, as shown in the present study. However, aging is known to affect both the peripheral and central vestibular system [17]. In patients with a *GJB2* mutation, the vestibular symptoms may progress with aging. Another problematic point regarding patients with CD related to *GJB2* mutations is cochlear implantation, which has been reported to cause vestibular dysfunction, such as a reduction of the caloric responses [18] and a decrease in the VEMP responses [19]. It is thought that the mechanical damage caused by the insertion of the electrode may induce vestibular dysfunction [20]. In the present study, four patients with *GJB2*-related deafness showed unilateral vestibular dysfunction, while only one of them had bilateral dysfunction. Therefore, it should be emphasized that the assessment of the vestibular function in patients with *GJB2*-related CD is important to determine which side of the ear should be selected to insert the cochlear implant.

Conclusions

A *GJB2* mutation is responsible not only for deafness but also for vestibular dysfunction. However, such vestibular dysfunction is likely to be unilateral and less severe in patients with a *GJB2* mutation than in those with bilateral deafness.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Vestibular dysfunction in a Japanese patient with a mutation in the gene *OPA1*

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ABSTRACT

OPA1 mutations are known to cause autosomal dominant optic atrophy (ADOA), and some types of *OPA1* mutations also cause auditory neuropathy. In the present study, we evaluated the vestibular dysfunction that accompanied auditory neuropathy in a patient with an *OPA1* mutation. A caloric test failed to elicit nystagmus or dizziness in either ear. Vestibular evoked myogenic potentials (VEMPs) in the right ear were characterized by a normal biphasic waveform. In contrast, no VEMPs were evoked in the left ear. Model building suggested that the *OPA1* mutation, p.R445H, indirectly distorts the catalytic structure of the GTPase reaction center and decreases GTPase activity. The patient complained of instability while walking or moving but thought these symptoms were caused by visual dysfunction. This is the first report of a detailed evaluation of vestibular dysfunction in a patient with an *OPA1* mutation. This case suggests that vestibular dysfunction may be involved in motor instability in patients with an *OPA1* mutation, even when patients do not complain of vestibular symptoms. Based on this case, we suggest that vestibular evaluation should be performed in auditory neuropathy patients carrying an *OPA1* mutation, even if the patients are free of symptoms of vestibular dysfunction.

1. Introduction

Autosomal dominant optic atrophy (ADOA; OMIM #165500) is a dominantly inherited optic neuropathy resulting in progressive loss of visual acuity, color vision deficits, a centrocecal scotoma, and optic nerve pallor [1]. ADOA is the most common form of optic atrophy, with an estimated prevalence of 1 in 50,000 individuals [2]. Although several types of loci are known to cause ADOA, it has been reported that as many as 89% of cases may be associated with a mutation in the gene *OPA1* (3q28-29) [3]. *OPA1* encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space and plays a key role in controlling the balance of mitochondrial fusion and fission. In most cases, ADOA occurs without additional neurological symptoms. However, there are several known cases of optic atrophy associated with sensorineural hearing loss, and the Arg445His (p.R445H) mutation of *OPA1* has been reported in patients with ADOA and moderate progressive hearing loss [4]. In patients having the p.R445H mutation, progressive hearing impairment begins in childhood, and audiological examinations show features of auditory neuropathy, for which the primary lesion is located in the inner hair cells, the auditory nerve, or the synapses between them [4,5]. Recently, a detailed analysis of OPA1 protein expression in the inner ear was reported in rat, and OPA1 protein was detected in the inner hair cells, outer hair cells, and spiral ganglia in the cochlea, as well as the hair cells and ganglia in the vestibular organ [6]. Although there have been several reports of auditory function in patients with this *OPA1* mutation, the analysis of vestibular function has not yet been reported in any *OPA1* mutation. In this paper, we report the results of examinations for auditory and vestibular function in a patient who presented with both hearing impairment and vestibular dysfunction due to an *OPA1* mutation that leads to distortion of the catalytic structure of the OPA1 protein.

2. Materials and methods

2.1. Auditory function tests

2.1.1. Audiometric tests

The patient underwent standard pure-tone air- and bone-conducted audiometry (125–8000 Hz) and speech discrimination testing using an audiometer (AA-75, Rion Co., Tokyo, Japan) and the 67-S Japanese word list.

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2.1.2. DPOAEs

DPOAES were recorded and analyzed using the ILO-92 system (Otodynamics Ltd, Herts, UK). DPOAE primary tones f1 and f2 were presented at 70 dB SPL. The f2:f1 ratio was kept at 1.22, and the frequency of f2 was changed in one-third octave steps from 708 to 6299 Hz. The levels of 2f1–f2 DPOAE were recorded. DPOAE values were plotted on a DP-gram, which expresses the emission level as a function of the f2 frequency.

2.1.3. Auditory brainstem responses (ABRs)

ABRs were recorded using the Neuropack system (Nihon Kohden, Tokyo, Japan) with an electrode montage of vertex (CZ) to the ipsilateral (stimulated) ear lobe and ground to forehead (Fz). The amplifier band pass was 100–1000 Hz. Alternating-polarity click stimuli were presented monaurally at a rate of 20 Hz at 100 dB nHL. Average responses to 1024 clicks were collected in each of two experiments.

2.2. Vestibular function tests

2.2.1. Electronystagmography

The patient underwent an electronystagmography test battery consisting of spontaneous, optokinetic, positional, postural, and caloric-induced nystagmus recordings. Nystagmus was recorded using an electronystagmograph recorder (Rion, Tokyo, Japan). Caloric testing using 20 °C and ice-cold water (5 cm^3, 5 s) was used to irrigate the external auditory meatus to induce a thermal gradient across the lateral semicircular canal.

2.2.2. Vestibular evoked myogenic potentials (VEMPs)

The sternocleidomastoid (SCM) muscle was chosen as the target to record VEMPs using the Neuropack system (Nihon Kohden, Tokyo, Japan). Surface electromyographic activity was recorded from symmetrical sites over the upper half of each SCM, with a reference electrode over the sternal attachment site of the contralateral SCM. The patient was laid supine on a bed and asked to raise and orient his head contralateral to the tested ear to maximally activate the SCM ipsilateral to the stimulation. Responses to 200 short-tone bursts (105 dB nHL, 500 Hz) were recorded at 100-ms intervals over a band pass of 500–1500 Hz.

2.3. Neuroimaging studies

2.3.1. High-resolution computed tomography (HRCT)

The protocol for HRCT included scanning with a multi-slice computed tomography scanner (Sensation 64; Siemens Medical Solutions, Inc., Malvern, PA, USA). Images were acquired with direct axial sequences using a spiral scan procedure with a 1.0-mm collimation. Data were reconstructed with a slice thickness of 1.0 mm using a bone algorithm.

2.3.2. Magnetic resonance imaging (MRI)

The patient was scanned on a 1.5-T MRI machine (Signa EXITE 1.5T, General Electric, Fairfield, CT, USA) with surface and head coil. Axial three-dimensional fast imaging employing steady-state acquisition (FIESTA, repetition time, 9.3 ms/echo time, 3.3 ms; scan thickness 1.0 mm) was performed. The axial images were reconstructed in the oblique sagittal plane traversing the internal auditory canal (IAC), producing cross-sectional images that visualize the neural structures of the IAC.

2.4. Homology modeling of OPA1and ligand fitting

The crystal structure of the GTPase domain of rat dynamin 1 (PDB ID: 2AKA) was used as a template in homology modeling because the GTPase domain of rat dynamin 1 is closely related to that of OPA1 in both function and structure (32% amino acid sequence identity). A program package for protein engineering and drug design, BIOCES[E] (NEC Corp., Tokyo, Japan) [7], was used for a series of molecular modeling. This package runs on an OCATANE2 (Silicon Graphics Inc., Fremont, CA, USA). The GTP molecule of Ras-GTP (PDB ID: 5P21) was fitted into the corresponding active site of the OPA1 model using DALI (http://ekhidna.biocenter.helsinki.fi/dali_server/) [8]. The p.R445H mutation structure was superimposed on the native structure (backbone atoms only) and displayed using UCSF Chimera (http://www.cgl.ucsf.edu/chimera/) [9].

3. Case report

The patient is a 28-year-old man who first presented with sudden optic atrophy at the age of 17 years. Clinical history of vision disorder and the result of genetic test have been reported [10]. In brief, he received a detailed examination for visual function at age 21. His best corrected visual acuity was 20/200 in both eyes. He had atrophy of the optic disks, central scotoma, and generalized bilateral dyschromatopsia. As a result, the patient was diagnosed with ADOA, and a genetic examination revealed a heterozygous G-to-A substitution in the second nucleotide of codon 445 in *OPA1*, resulting in an Arg-to-His amino acid substitution (p.R445H). He had no apparent family history of either optic atrophy or hearing impairment. At that time, he was also found to have a slight bilateral hearing impairment. The patient

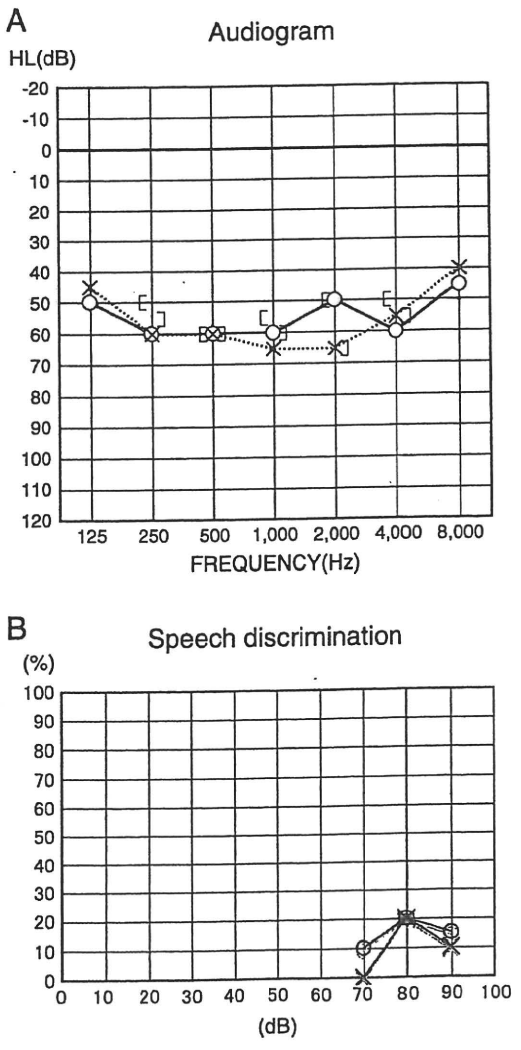

Fig. 1. Pure-tone (A) and speech (B) audiograms of a patient with an *OPA1* mutation. O = right air conduction hearing level; X = left air conduction hearing level; [=right bone conduction hearing level;] = left bone conduction hearing level.

developed progressive hearing impairment, and had particular difficulty understanding speech. He came to our department for a hearing evaluation at age 28. Although he did not initially complain of balance disorders, he stopped riding a bicycle at age 17 years because of difficulty controlling balance and also started to feel unsteady walking at that time. He thought the unsteadiness resulted from his visual dysfunction.

4. Results

4.1. Auditory function test results

Direct otoscopic observation revealed normal findings in both ears. A bilateral sensorineural hearing loss of approximately 60 dB was shown by pure-tone audiometry (Fig. 1A). The maximum speech discrimination scores were 20% in both ears (Fig. 1B), which were significantly worse than expected based on the results of pure-tone audiometry. Although no differences were observed between left and right ears, the patient reported better hearing discrimination in the right ear (Fig. 1). ABRs were absent bilaterally even at 100 dB nHL (Fig. 2A), but high-amplitude DPOAEs were present at all frequencies tested in both ears (Fig. 2B).

4.2. Vestibular function test results

No spontaneous, positioning, or pressure-induced nystagmus was found by electronystagmography. Neither 20 °C nor ice-water caloric stimulation of the labyrinth elicited nystagmus or dizziness in either ear (Fig. 3A). Short-tone burst-evoked VEMP analysis revealed a biphasic VEMP waveform in the right ear; however, the latency of n23, which is the second wave of VEMP, was delayed. No VEMPs were evoked in the left ear (Fig. 3B).

4.3. Neuroimaging studies

There were no abnormal findings by HRCT. In particular, no inner ear malformation or internal auditory canal stenosis was observed (Fig. 4A, D). By MRI, both the cochlear nerves and vestibular nerves were detected from brainstem to the inner ear in both ears in axial FIESTA slices (Fig. 4B, E). However, the diameter of the right cochlear nerve was 0.82 mm whereas that of the left cochlear nerve was 0.69 mm, and the diameter of the right facial nerve was 1.06 mm whereas that of the left facial nerve was 1.02 mm in oblique sagittal reconstructions through the IAC (Fig. 4C, F). Thus, the cochlear nerves on both sides are considered hypoplasia according to reported criteria [11].

4.4. OPA1 predicted structure

The distance between Cα of R445 of OPA1 and the GTP binding pocket is 18 Å (Fig. 5). The electric field around R445 is negatively charged due to its proximity to D450, D442, and E444. Under physiological conditions, positively charged R445 is structurally stable, and thus the mutation p.R445H reduces the electrostatic stability and indirectly distorts the structure of the GTPase catalytic

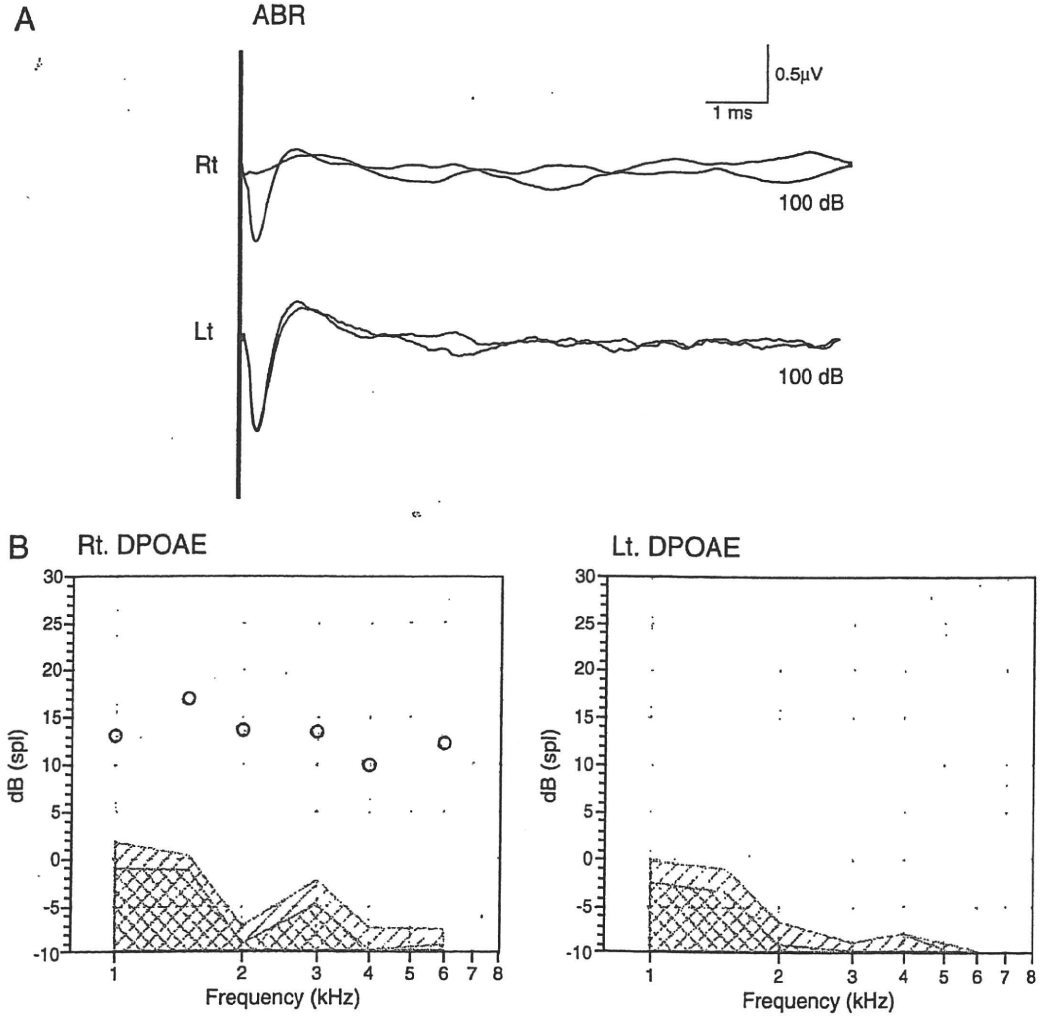

Fig. 2. (A) ABR tests revealed no ABR waveforms in this patient. (B) DPOAE recordings were normal for this patient. Residual noise levels are shown by the shaded area.

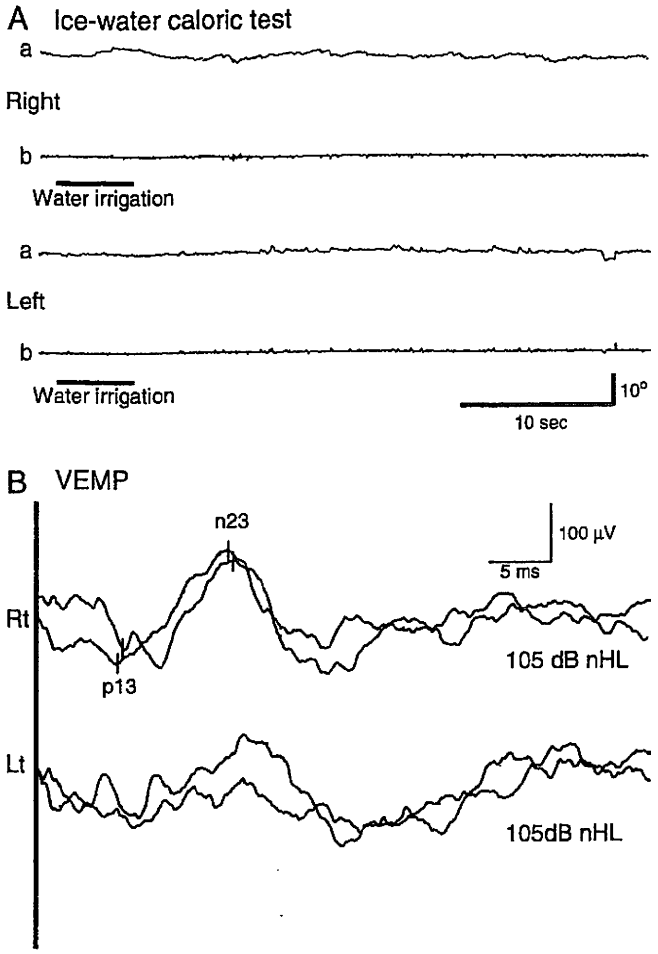

Fig. 3. (A) Horizontal record of electronystagmograph on ice-water caloric test. Time constants: a, 3.0 s; b, 0.03 s. No nystagmus were elicited in both side of ears. (B) Air-conducted VEMPs. Electromyographic responses of the right (Rt) and left (Lt) SCM to right ear stimulation. A biphasic VEMP waveform was revealed in the right ear; however, a latency of n23 was delayed. In contrast, no VEMPs were evoked in the left ear.

domain. In addition, salt bridges between R445 and D450 in the α3-helix and strong electrostatic interactions between R445 and D442/E444 are observed. The α3-helix is a key structure that constructs the common wire frame of the G-protein core fold [7,9]. Thus, the p.R445H mutation indirectly distorts the catalytic structure of the GTPase reaction center and decreases GTPase activity.

5. Discussion

Several reports have described hearing impairments associated with an *OPA1* mutation [4,12–16]. As with the case we present here, these hearing impairments were reported to result from auditory neuropathy. Common features in these patients include moderate hearing threshold elevation and a severe speech discrimination disability. No vestibular symptoms or function test results have yet been reported. To our knowledge, this is the first report of a detailed vestibular analysis in a patient with an *OPA1* mutation. Moreover, inner ear neuroimaging studies, including HRCT or 3-D MRI, have not yet been reported in patients with *OPA1* mutations. This report provides the first evidence of cochlear nerve atrophy in the IAC in a patient with an *OPA1* mutation.

OPA1 encodes a dynamin-related GTPase that is located in the mitochondrial intermembrane space and plays a key role in controlling the balance of mitochondrial fusion and fission [17]. Furthermore, release of cytochrome *c* from mitochondria and caspase-dependent activation of the apoptosis cascade have been observed in the down-regulation model of expression by RNA interference in HeLa cells [17]. The *OPA1* p.R445H mutation is reportedly associated with various neurological disturbances, including ataxia, peripheral neuropathy, ptosis, and cognitive impairment [18]. In cases involving the heterozygous p.R445H mutation, ADOAs associated with deafness have been reported [4], and these sensorineural hearing losses show audiological features compatible with auditory neuropathy. In normal rats, expression of OPA1 protein is seen in the inner hair cells, outer hair cells, and spiral ganglia in the cochlea, and in the vestibular hair cells and ganglia [6]. OPA1 protein expression has also been observed in membranous or submembranous compartments of vestibular ganglion cells and at the level of the calyx synapse, which typically envelopes type 1 hair cells in the vestibular epithelium [6]. Bilateral vestibular dysfunction in our present patient is probably caused by dysfunction of these parts of the vestibular organs.

An abnormality in the OPA1 protein may cause mitochondrial dysfunction, leading to insufficient energy production. Homozygous mutant mice are not viable and show impaired development as early E8.5. [19]. This study also reported that heterozygous mutants show a reduction in OPA1 protein level (about 50% compared with wild-type littermates) due to rapid degradation of the mutant polypeptide [19]. Skin fibroblasts obtained from patients carrying the heterozygous *OPA1* p.R445H mutation show hyperfragmentation of the mitochondrial network, decreased mitochondrial membrane potential, and an ATP synthesis defect [4]. Our three-dimensional structure study suggests that the p.R445H mutation reduces the electrostatic interactions and therefore the stability of the protein and indirectly distorts the structure of the GTPase catalytic center, thereby decreasing GTPase activity. According to these findings, we suggest that the OPA1 p.R445H mutation leads to severely insufficient energy production by decreasing GTPase activity in the mitochondria. This deficiency could, in turn, affect critical energy-dependent functions such as axoplasmic transport in both cochlear and vestibular nerve fibers as well as optic nerve fibers.

This patient had almost normal VEMP results in the right ear but no response in the left ear. Although the mechanisms underlying these different responses are unclear, asymmetrical hearing impairments have been reported in patients with the *OPA1* p.R445H mutation [12,13]. There was no response to caloric stimulation in either ear. The VEMP consists of myogenic potentials obtained as a response to tone-burst stimuli and is used to test the saccule and inferior vestibular nerve of the vestibular system. The caloric test, on the other hand, is used to evaluate the function of the lateral semicircular canals and the superior vestibular nerve [20]. In the right ear, there was no response in the caloric test but fare VEMPs. *OPA1* is expressed in sensory epithelia in both the saccule and the lateral semicircular canal [6]. Atrophy of the superior vestibular nerve was not detected by MRI scan. The mechanisms underlying different responses for the caloric test and VEMPs in the right ear are uncertain. In the present case, the patient reported slightly better hearing in the ear that also had good VEMP responses (the right ear). It is well established that ADOA is a progressive atrophy disease. If the main mechanism for nerve atrophy in ADOA is the same in both the eye and the inner ear, we speculate that nerve atrophy in the inner ear may develop gradually from the superior vestibular nerve to the inferior vestibular nerve in patients with the *OPA1* mutation. It has been reported that VEMPs are less affected than horizontal semicircular canal function during caloric testing in bilateral vestibulopathy [21]. We found only two reports with results of both caloric testing and VEMP analysis in auditory neuropathy patients with causes other than an *OPA1* mutation [20,22], and these revealed normal caloric responses and abnormal VEMPs in all patients ($n=4$) with auditory neuropathy. We revealed a different profile in a patient with auditory neuropathy due to an *OPA1* mutation. We speculate that the vestibule is also an organ that is sensitive to the mitochondrial dysfunction associated with the *OPA1* mutation.

In conclusion, we have presented a case of vestibular dysfunction accompanied with auditory neuropathy in a patient with an *OPA1*

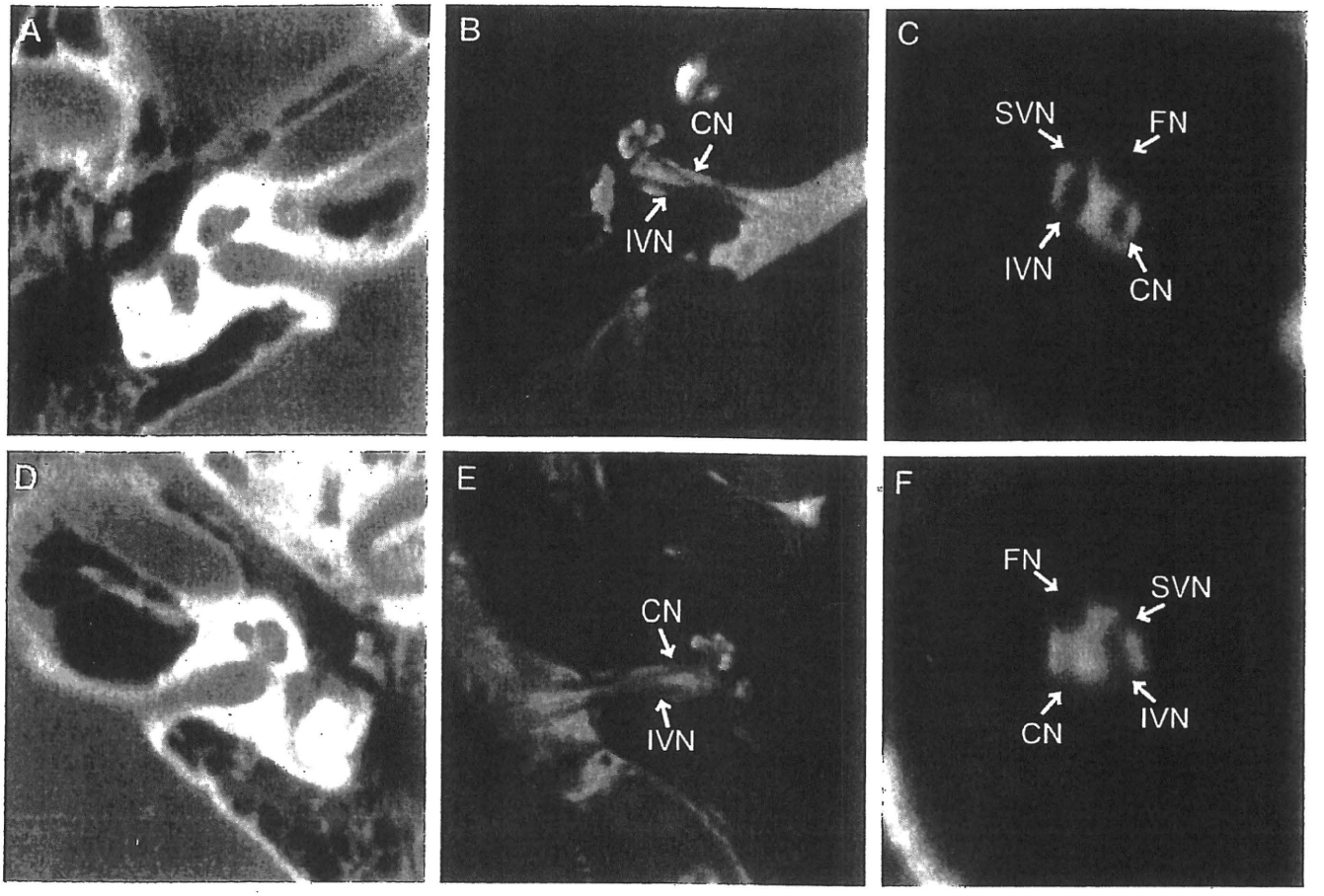

Fig. 4. Images showing the HRCT (A, D), axial MRI (FIESTA; B, E), and oblique sagittal reconstructions (C, F). The facial nerve (FN), cochlear nerve (CN), superior vestibular nerve (SVN), and inferior vestibular nerve (IVN) can be recognized in both sides of the internal auditory canal. However, the cochlear nerves in both ears were narrower than the vestibular nerves in axial FIESTA slices. Moreover, the cochlear nerves on both sides were smaller than the adjacent facial nerves in oblique sagittal reconstructions.

mutation. In a standard evaluation, this patient's balance disorder could easily have been overlooked because he attributed it to his visual dysfunction. Based on this case, we suggest that vestibular evaluation should be performed in auditory neuropathy patients carrying an *OPA1* mutation, even if the patients do not complain of balance dysfunction.

Acknowledgements

The authors give thanks to Ms. Reiko Yakushimaru and Ms. Akemi Hori for their excellent technical assistance in the audiometric and vestibular tests.

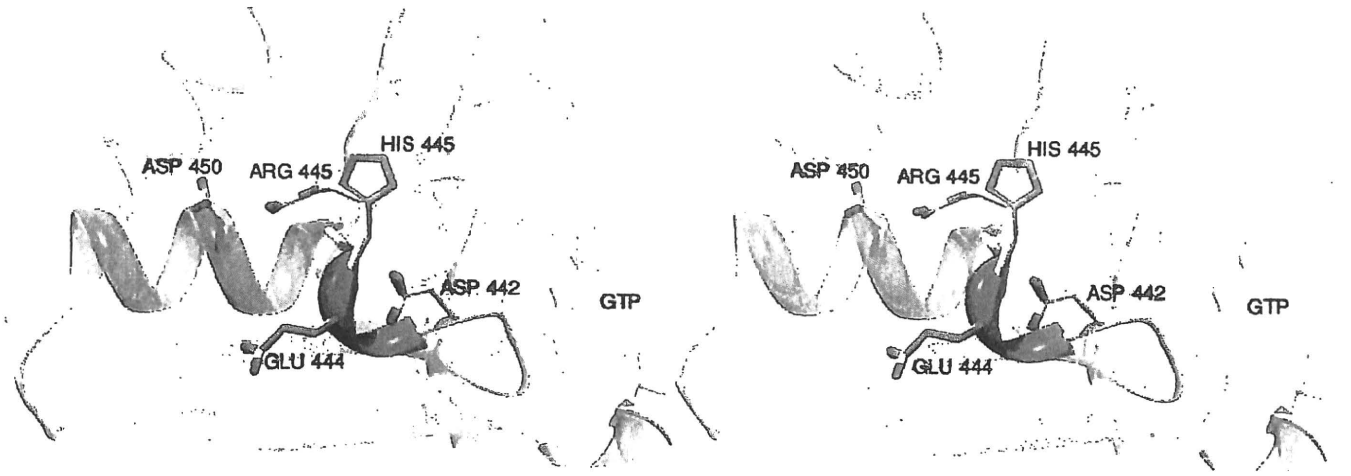

Fig. 5. Stereo view of the GTPase domain of predicted structure of human OPA1 with arginine at position 445 replaced by histidine. The electric field around R445 is negatively charged due to the proximity of D450, D442, and E444. Positively charged R445, under a physiological environment, is structurally stabilized, and thus the mutation p.R445H reduces the electrostatic stability and indirectly distorts the GTPase catalytic structure. Image produced using the UCSF Chimera package supported by NIH P41 RR-01081.

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特集 障害を持つ子どもたちが通う病院と施設

5 聴覚障害

国立病院機構東京医療センター・臨床研究（感覚器）センター長，
東京大学名誉教授 加我君孝（かがきみたか）

はじめに

筆者は幼小児の難聴と言語障害の外来を東京医療センターをはじめとして埼玉，東京，川崎市にある病院や療育センターで行なっています。東京医療センターの「幼小児難聴・言語障害クリニック」（http://www.ntmc.go.jp/nancho/index.htm）は，開いてわずか2年半でインターネットのヒット数がGoogle, Goo, Yahoo！のいずれでも第1位となっております。私の外来には聴覚障害のお子さんを持つ保護者が，新生児聴覚スクリーニングで難聴を疑われると，インターネットで調べて受診，今井絵理子さんの本「ココロノウタ」（祥伝社）（この本の中で私と今井絵理子さんの対談が掲載されております）を読んで受診します。同時に，日本聾話学校，難聴児通園施設の富士見台聴こえとことばの教室，神奈川県のろう学校や療育センターなどから紹介されて受診されます。難聴は検査をしないと診断できません。私がこの問題に本格的に取り組んで20年以上になりますが，今もなお耳鼻科や小児科の先生方の知識が乏しいために発見が遅れたり，間違ったお話しを両親にするために混乱が生じています。検査データの判定を正しくできない耳鼻科や新生児科や産科の先生が多いという「不都合な現実」があります。ここでは正しい受診の仕方をわかりやすく解説します。

新生児聴覚スクリーニングとはなんですか？

コンピューターを使った聴力検査に聴性脳幹反応（Auditory Brainstem Response：ABR）があります。これは専門家の操作によって行なわれ正確に難聴の重さや脳幹の発達を評価できるのですが，1例につき約1時間かかります。これを短時間（約10分程度）でだれでも簡単に操作できる難聴のスクリーニング検査の代表的なものが自動ABR（Automatic ABR：AABR）です。ただし結果は詳細には表れず，pass（合格），refer（要精密聴力検査）として表示されます。もう一つの検査法は耳音響放射（Otoacoustic emission：OAE）といい，過渡的耳音響放射（Transient OAE）と歪成分耳音響放射（Distortion Product OAE：DPOAE）の二つがあります。ここで注意が必要なのはスクリーニングでの正常と異常を二分する音圧レベルです。AABRは35 dBに設定され，TOAEもDPOAEも20～30 dB以上の難聴があると無反応になるような小さな値であるため，少しでも中耳や内耳に異常があると「要精密聴力検査」と出てしまうことです。

わが国では2000年より厚生省

著者プロフィール 1971年東京大学医学部卒業。帝京大学耳鼻咽喉科助教授，東京大学耳鼻咽喉科教授などを経て，現在は国立病院機構東京医療センター・臨床研究（感覚器）センター長。ほかに，東京大学名誉教授，獨協医科大学特任教授，目白大学客員教授。専門は耳科学，聴覚医学，めまい・平衡医学，小児耳鼻咽喉科学。関連著書・文献に，「加我君孝，編：新生児聴覚スクリーニング 早期発見・早期教育のすべて．金原出版，2005」「Kaga K：Central Auditory Pathway Disorders. Springer Verlag 2009」などがある。

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(現・厚生労働省) の主導で 2007 年まで検査に援助がありましたが，現在は地方自治体の責任となっています。

難聴が疑われたときの受診の経路

先天性難聴を想定すると三つの経路があります。

1）耳鼻咽喉科の受診

大きな病院の耳鼻咽喉科の受診を勧めます。耳鼻咽喉科の先生は開業医や病院医師，大学の教室の先生などですが，専門が耳や聴覚とは限りません。鼻や頭頸部の癌や音声を専門とする場合，必ずしも難聴について詳しくないことが多いのです。とくに幼小児の難聴について詳しい先生は極めて少ないのです。そのため，「しばらく様子をみましょう」と言われ発見が遅れることが少なくありません。大きい病院の耳鼻科には，コンピューターを利用した聴力検査装置の ABR や耳音響放射装置などが備えられており，難聴の有無を判定できます。日本耳鼻咽喉科学会では，全国精密聴力検査機関として 164 の数の病院をホームページに紹介しています。近くにこのリストに掲載されている病院があれば受診を勧めます。

2）小児科の受診

小児科の先生は，難聴による言語の発達の遅れについては詳しいとはいえません。「この年齢では聴こえは検査できないし，喃語があるので難聴はないでしょうから，半年後に来るように」と言われたりすることがありますが，これは正しくはありません。

3）保健所

保健所では小児科医が 3〜4 か月から 3 歳に至るまで定期健診をしますが，面接あるいはアンケートのみで検査をすることがない難聴の発見は困難です。そのため保健所でも様子をみることを勧めるか，耳鼻科受診を勧めます。

耳鼻咽喉科ではどのようにして難聴の診断をするのですか？

小児の聴覚障害を専門とする病院では，次のような検査で最終診断をします。

1）行動反応聴力検査

音に対する身体の反応を，音の大きさを変えて調べ，その反応するもっとも小さな反応を“閾値”といい目安とします。検査方法には Behavioral Observation Audiometry (BOA) と Conditioned orientation Reflex Audiometry (COR) があります。

2）他覚的聴力検査

聴性脳幹反応 (ABR)，耳音響放射聴力検査 (TOAE, DPOAE)，聴性定常反応聴力検査 (Auditory Steady-State Response：ASSR)，Tympanometry があります。

以上のどの検査も長所と欠点があります。それを考慮しながら総合的に診断します。成長とともに改善したり，逆に悪化することがあるので注意深くフォローアップして確定診断をします。

難聴が診断されたあとはどのような経路をたどるのでしょうか？（就学前教育）

難聴が診断されると，資格のある耳鼻科の先生によって身体障害者診断書（聴覚）を発行します。難聴の重症度別に 6 級から 2 級の認定をし，最後に役所に届けて身体障害者手帳が発行されます。そのあと補聴器意見交付書によって，ベビー型や耳掛型か箱型などの補聴器の種類を決めて役所に申請します。難聴児は

表 1　修学前の教育施設

	1．聴覚口話法	2．日本語対応手話＋聴覚口話法
先天性難聴児 中途失聴児	難聴児通園施設（25） 公立療育センター（多数，ただし不明） 私立ろう学校（1） 国立ろう学校（1）	公立ろう学校（100） 私立明晴学園（1）日本手話
難聴に他障害合併	同上	同上
盲ろう児（2 重障害）	盲ろう児施設（全国にあるが数は少ない）	

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表2 難聴児の発達・療育・教育についての7つの誤解

1．先天性難聴児には喃語がない。したがって喃語があれば難聴はない。
　間違いである。先天性難聴児も初期の喃語は健聴児と同様に活発にある。
2．難聴児通園施設はスパルタ式の怖いところである。
　間違いである。母親も子どもも楽しみにして通園し，将来の希望がある。大学への進学率が60%に近い。
3．ろう学校は手話教育しかしない。
　間違いである。私立日本聾話学校と国立筑波大学附属聴覚特別支援学校（筑波大学附属聾学校）は聴覚口話に手話を併用している。公立ろう学校は聴覚口話と手話を併用する。
4．人工内耳はメスを使っているので危険である。
　間違いである。素人がメスを振り回せば危険であるが，耳の外科医が使う限り安全で，病気を治すことができる。外科手術をすでに500年の歴史がある。
　メスを使って治療しなければ治すことができない病気はたくさんある。
5．人工内耳は将来手術をやり直さなければならない。スピーチプロセッサーも新型に変えなければならない。そのときにまた100万円もの費用がかかる。
　間違いである。事故で人工内耳が故障した場合は特定医療材料費という援助する仕組みがある。1996年に保険に適用されて以来，14年が過ぎたが，自然な故障は100件中数件にすぎない。スピーチプロセッサーの破損は病院で健康保険の特定医療材料費という制度により保険の範囲で供給される。
6．難聴児は大学へ行く者がまれである。
　間違いである。東京の難聴児通園施設に通った補聴器装用で成長した青年の60%，私立ろう学校では50%が大学へ進学している。カナダのモントリオールの聴覚口話学校は人工内耳と補聴器で育った80%が大学へ進学しているほど進学率が高い。
7．聴覚口話の教育施設は手話を絶対に使用させない偏ったところである。
　間違いである。日本人の母語は日本語である。その日本語も最初に正しく聴いて話し，書く力は聴覚口話で脳の可塑性の豊かな乳幼児期には習得して，日本語が確立してから手話を学ぶことが勧められる。その方が成人して社会で活躍するときに有用である。手話には助詞や接続詞がないため，手話だけの教育を受けると助詞がうまく使えないことがあり，誤解されることが多い。

両耳に補聴器を装用し，以下のところで就学前の教育を受けます（表1）。

①聴児通園施設（全国で27ある。児童福祉法によるもので厚生労働省管轄）
②地域の身障センター・療育センターなどが（全国に多数ある。地域の地方自治体管轄）
③ろう学校（全国に102ある。学校教育法によるもので，文部科学省の管轄）
　a．私立日本聾話学校(聴覚口話)
　b．国立筑波大学附属聴覚特別支援学校(筑波大学附属聾学校)(文部科学省管轄。聴覚口話)
　c．公立ろう学校（都道府県立，市立。聴覚口話・日本語対応手話併用）
　d．私立明晴学園（日本手話）

どこでも初めは補聴下に教育を受けますが，難聴が重度の場合は，1歳半以降に人工内耳手術を受けて聴覚口話法教育を受けます。

小学・中学の義務教育期間はどこで教育を受けますか？

①普通小・中学校（私立・公立）
②難聴児学級を併設する普通小・中学校（公立）
③ろう学校
　a．私立日本聾話学校
　b．国立筑波大学附属聴覚特別支援学校(筑波大学附属聾学校)
　c．公立ろう学校

高校教育はどこで教育を受けますか？

①普通高校（私立・公立）
②ろう学校高等部

大学教育はどこで教育を受けますか？

①一般の大学
②筑波技術大学

社会に出るときに会社の方の配慮がありますか？

企業の障害者枠を利用して入社する場合があります。

おわりに

先天性難聴児の場合，早期発見・早期教育がわが国でも定着し，補聴器だけでなく人工内耳もあり，大いに希望の持てる時代となりました。それにもかかわらずここで述べたことが理解されていないために本来受けるべき早期のサービスや教育が手遅れとなる「不都合な現実」があります。教育方法が異なると，まるで宗教間の対立に類似した現実があり，これを７つの誤解として表２にまとめましたのでご参照ください。

成長してから教育をやり直すことはできません。言語の習得は，脳の可塑性（かそせい）の時期がすぎると手遅れになります。自分の歩んだ道を肯定的に考えるほかなくなるのです。

●文献●
1) 加我君孝，編：新生児聴覚スクリーニング 早期発見・早期教育のすべて．金原出版，2005
2) 大沼直紀：日本における障害教育の展望と課題．韓国聴覚口話教育 100 周年記念誌．pp77-93，2009

☆☆☆☆☆ ☆☆☆☆☆

特集 発達という視点〜さまざまな能力の発達について〜

② 聞く・話す力の発達

東京医療センター・臨床研究（感覚器）センター
加我君孝（かがきみたか），新正由紀子（しんじょうゆきこ），竹腰英樹（たけごしひでき），内山 勉（うちやまつとむ）

はじめに〜思考の道具としての言語〜

聞く力の発達は話す力の発達にそのままつながります。話す力とは，言葉で考えて相手に伝えたい内容を音声で伝える力です。ここに「言語は思考の道具である」といわれる本質があります。道具というと即物的に聞こえますが，私たちの日常生活は道具を使って営まれています。箸を使って食べる，自転車や電車，飛行機を使って移動するのもその例です。パソコンのように道具によって便利な現代の生活を行なっています。思考の道具としては，聞く・読む・書く・話す・計算するに分けています。見る力は読む・書くとつながっています。このなかで聞く・話す力の発達は小児の言語の発達の最初に発達し，話す・書く力へとつながるもっとも重要なものです（表1）。

音と聴覚と脳

空気があって聴覚と言語があります。音は空気の振動であり，脳の指令による声帯の振動によって音声が産出され，耳はその振動をキャッチし，脳が分析して内容を理解します。私たちのまわりは無数の音で満ちています。音に対する脳の代表的な5つの作用を表2に示します。幼児にとって音に対する反応は，反射，定位，一般的注意，選択的注意や記憶へと生後1年あまりのうちに発達します。このような脳の働きも言葉がまわりにあって言語獲得へつながります。言語の獲得によって考える力，すなわち論理操作へと発展します。言葉はlogosといい，logicやlanguageと表現され，ヨーロッパ言語では，言葉は論理と直結した表現がされてきました。同時に感情も伝えることができます。

脊椎動物と聞く・話す力の進化

私たちは音を聴き音声で話します。音は空気の振動であり，振動は周波数と強さと時間で表わされま

表1 思考の道具（リテラシー）としての言語

1．聞く
2．話す
3．読む
4．書く
5．計算する

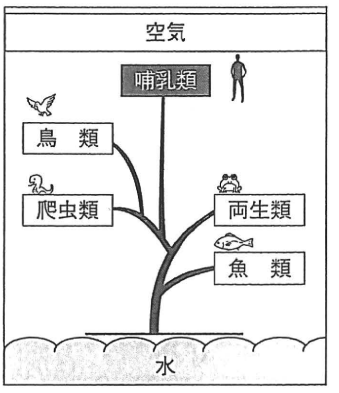
表2 脳の5大聴覚作用

単耳聴でも両耳聴でも生じる
1．Reflex（反射）……驚愕反射
2．General attention（一般的注意）……暗騒音
3．Selective attention（選択的注意）……判断と選択
4．Integration（統合）……聞いて見る，行動する，ほか
5．Memory（記憶）……言葉，音楽，環境音

著者プロフィール 1971年東京大学医学部卒業，同耳鼻咽喉科学教室へ入局。帝京大学講師，同助教授，東京大学耳鼻咽喉科学教室教授を経て，現在は東京大学名誉教授，東京医療センター・臨床研究（感覚器）センター名誉センター長，獨協医科大学特任教授，目白大学客員教授。2010年日本医学教育学会牛場賞を受賞。

1344-3151/10/¥50/頁/JCOPY

す。地球にははじめから空気があったわけではありません。地球が誕生して空気ができるまでには長い歴史があります。生物は，水ができ，植物の光合成によって空気が生まれて初めて発生します。脊椎動物の進化は魚類，両生類，爬虫類，鳥類，哺乳類の順をたどることができます(図 1)。この順に聞く力と話す力の進化を解剖学的にみると，魚類から両生類，爬虫類では音を検知する器官の発達はきわめて悪く，聞き取る周波数は低周波から 1～2 kHz 程度で，蝸牛管はなく，前庭器官の球形嚢で聞いています(図 2)。発声器官も特殊で，声帯はありません。複雑な発声はできていないと考えられます。しかし鳥類になると声によるコミュニケーションが豊かになります。親から子の音声の学習や求愛行動をはじめとする音声の認識の仕組みが研究されています。聴覚の器官は蝸牛管でそのなかに感覚細胞があります。聞くことのできる周波数は低周波より 6 kHz と幅が広くなっています。ただし声帯はなく，音声は鳴管という気道の特殊な管を共鳴させて発声しています。鳥は空を自由に飛ぶことができるため至るところで音声を発しコミュニケーションすることができます。魚類・両生類・爬虫類も鳥と同様に声帯はなく，気管や気管支に袋のようなものがあり，これを振動させて音を出しています。



＊進化の古い順に
1. 魚 (水)
2. 両生類 (水と空気)
3. 爬虫類 (空気)
4. 鳥 (空気)
5. 哺乳類 (空気)

脊椎動物の系統図

図 1 水と空気と動物の耳の進化

〔1) 安藤唯一：人間の随意運動―生理学的心理学的解説―．体育の科学社，1960〕

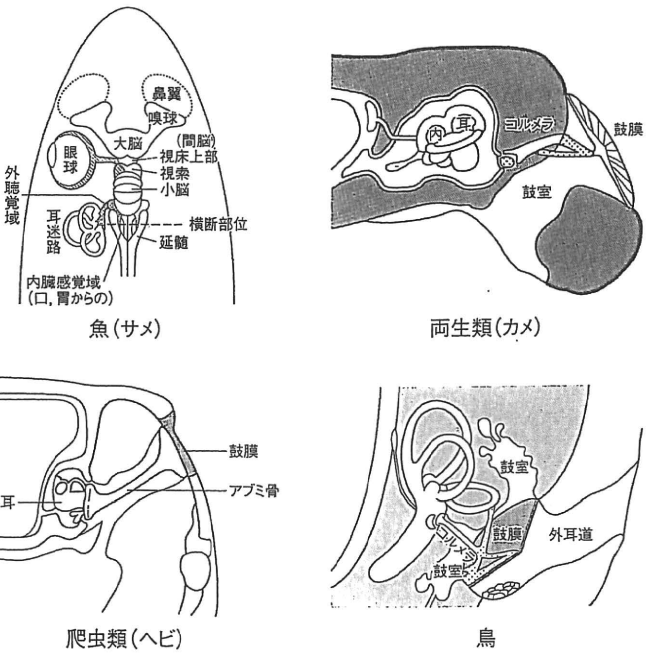


図 2 聴器の進化

哺乳類は地上生活のため鳥ほど行動は自由ではありません。聞く器官はラセンを巻きコンパクトなラセン構造の中に，低周波数から高い周波数まで検知できます。同時にマウスのような小動物から馬のような大型動物まで声帯があり，自由に周波数を変えて発声できます。脳は発達し

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a 過渡的喃語
健聴児13：4か月時の「アーアーアー」の
発声のサウンドスペクトログラフ

b 標準的喃語
健聴児10：8か月時の「マンマンマン」の
発声のサウンドスペクトログラフ

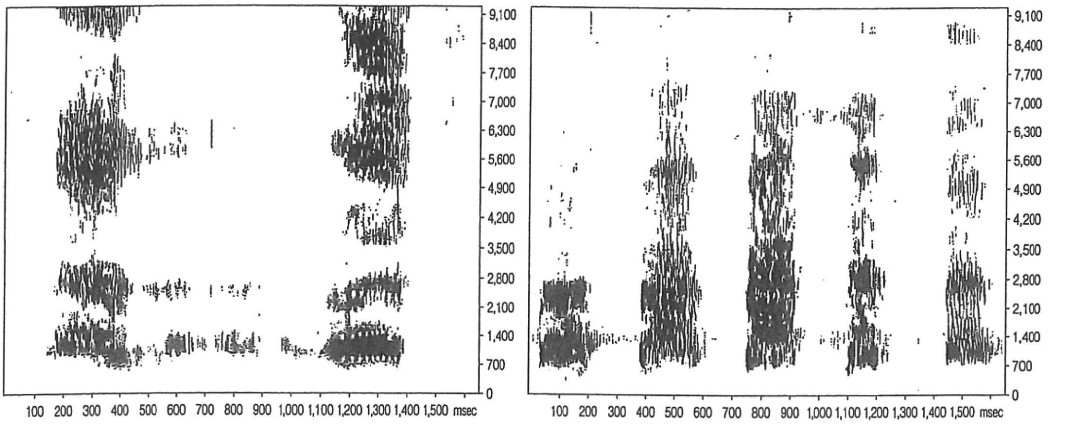

図3 喃語の音響分析

ヒトでは言語脳を持つようになります。自由に思考し，高度なコミュニケーションの活動ができ，現代の文明をつくるに至っています。脳と蝸牛と声帯が一体となったものがコミュニケーションの力そのものといえます。

聞く力と喃語と発声する力 ～前言語期～

言葉を話し始めるまでの生後約1年間は前言語期と呼ばれます。この間では何が起きるのでしょうか。

1）原始的喃語期の声

難聴があってもなくても生後は喃語があります。原始的喃語期あるいは泣いて表現するため叫声期ともいいます。新生児期には蝸牛も声帯も完成し，脳幹の聴覚伝導路もほぼ完成しています。しかし大脳の聴皮質への髄鞘化には約12か月，ブローカ中枢，ウェイルニッケ中枢の髄鞘化には約1年半ぐらい必要です。すなわち認知レベルの髄鞘化はゆっくり発達します。原始的喃語はまだ周囲のことばのシャワーの影響が少ない時期と思われます。音響分析をするとまだフォルマント構造は認められません（図3-a）。

2）標準的喃語期

健聴で健康な幼児は，1歳頃より片言の日本語を話し始めます。これは前言語期の後半の標準的喃語期に日本語のシャワーを毎日浴びることで発達するものです。音響分析をするとフォルマント構造が認められます（図3-b）。他の国の言葉の環境であればその国の言葉を話し始めます。脳の可塑性と言語脳の発達によって自由に習得できます。しかし先天性の難聴児で，もし補聴されていないとこのようには進みません。言葉のシャワーが耳に届いていないからです。一方，発声・発語の解剖学的構造は聴覚に依存せず発達します。

聞く力と発語する力 ～言語脳の発達初期～

喃語の前言語期を経て，正常幼児は1歳前後に言語期に至ります。話す言語は単語，2語文，3語文と発達します。「あれとって」「あれ何？」と初めて論理操作を使うようになります。1歳までには脳の言語中枢やウェルニッケ中枢とブローカ中枢が働き始めます。私たちのMRIによる言語中枢の髄鞘化の研究でも，1歳半には髄鞘化が完成していることを示しています（図4）。

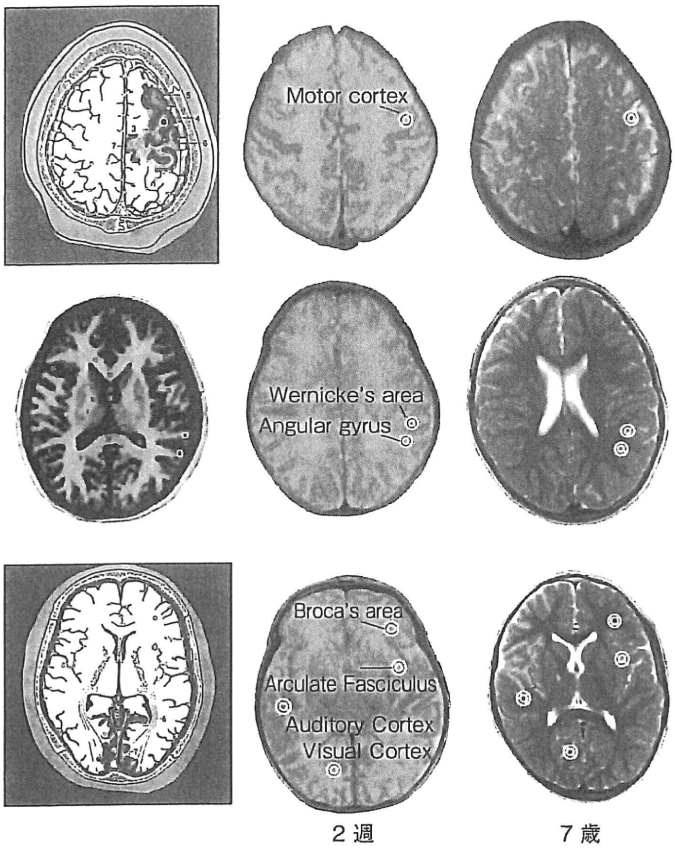

図4 MRIによる言語中枢の髄鞘化

髄鞘化が完成すると，神経信号の速度は徒歩から新幹線の速度並みに速くなり，脳活動は著しく活発になります（表3）。

後言語期～論理的言語期～

1歳を過ぎると，健聴の幼児は道具としての言葉の操作法を身につけるようになります。対人関係が母親との一対一から一対多数に変化します。単語のみから2語文，3語文と聞き取った言葉を組み合わせて自分の要望を伝えます。絵本を読んでもらって聴いて楽しんだり，音楽に合わせて踊ったり，歌を歌ったり，楽器で遊ぶようになります。2歳になると，動物の絵を見てゾウ，ウサギ，キリン，パンダなどとはっきり言い，色を見て赤，青，白，黒などと言えるようになり，物の名称が記憶に残ります。このようにして言語活動は爆発的に進みます。3歳児になると，体系だった幼児教育のなかで言語のリテラシーを身につけるようになります。言語で感情を豊かに表現します。

表3 髄鞘化と神経信号の速度

×髄鞘化なし……時速3～5 km
●髄鞘化あり ……時速50～400 km

〔2）文部科学省特定領域研究：「統合脳」5領域．2010〕

難聴疾患による聞く力への影響と治療と教育

小児の難聴には先天性と後天性があります。

1）先天性難聴

中耳の疾患による伝音難聴も，蝸牛の疾患による感音難聴でも音の伝達は制限され，聞く力と話す力にさまざまな影響があり，一様ではありません。しかし早期（1歳以内）に発見し，補聴下の聴覚口話法の教育で良好な聞く力・話す力を身につけることができます。

a．伝音難聴と補聴器

両側外耳道閉鎖や中耳奇形では，もっとも重い難聴でも60～70 dB程度の伝音難聴で，前者では骨導補聴器，後者では気導補聴器を用います（図5）。40 dB前後の中等度難聴児でも補聴器を使用しています。伝音難聴は聴力改善手術を就学前後で行ない，改善可能です。

b．感音難聴と補聴器

音のセンサーであるコルチ器にある感覚細胞の先天性の障害で生じます。現在ではその半数近くは難聴の