eight-channel phased-array coil. 3D-FLAIR imaging was performed before and after the intravenous administration of a single dose of gadolinium diethylenetriaminepentaacetic acid *bis*-methyl amide (Gd-DTPA-BMA; Omniscan, Daiichi Pharmaceutical Co., Tokyo, Japan) at 0.1 mmol/kg. Heavily T2-weighted 3D constructive interference in the steady-state imaging was performed before the contrast material was administered, to delineate the anatomy of the CSF space. Contrast-enhanced 3D-FLAIR was initiated 7 min after the gadolinium was administered, so that the contrast 3D-FLAIR images were determined approximately 10 min after the administration of the gadolinium. Positive postcontrast imaging implies an increase of signal intensity after intravenous gadolinium administration. These methods have been described in detail in previous reports [3,4,11,12]. The mean period from the time of onset of symptoms to the MRI examination was 11.8 ± 11.4 days. All patients were also examined using T1-weighted MRI.

MR findings

The MRI findings for the inner ear or CSF in patients with facial nerve paralysis and idiopathic sudden sensorineural hearing loss were evaluated using the methods described in previous reports [12,13].

The MRI findings were ranked as follows: none (no signal in the affected inner ear or CSF) or high (the signals in the affected inner ear or CSF were as high as or higher than those of the cerebellar white matter).

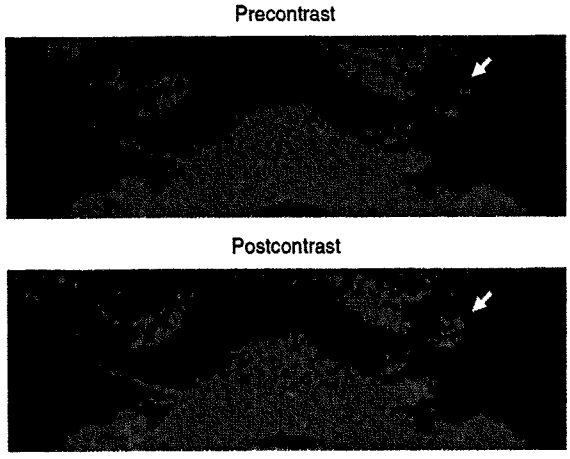


Figure 1. Patient no. 5, a case of atypical Bell's palsy (see Tables I and II). This patient had a mild hearing loss, tinnitus and dizziness with facial paralysis on his left side. He had no vesicle in his left ear. This patient showed high signals (arrow) in his left cochlea on both precontrast and postcontrast 3D-FLAIR.

These MRI findings were inspected by a neuroradiologist experienced in inner ear MRI, who was blinded to the clinical manifestations using the criteria as described above.

Statistics

We used a χ^2 test with Yates' correction for 2 × 2 tables to compare the differences in the high precontrast and postcontrast signals in the cochlea or vestibule between patients with facial nerve paralysis with and without audio-vestibular disorder. For all the above statistical analyses, a p value of <0.05 was considered significant.

Results

The characteristics of the 15 patients with facial nerve paralysis are summarized in Table I. 3D-FLAIR findings of the inner ear in these patients are summarized in Table II. Figure 1 shows an example of positive precontrast and postcontrast 3D-FLAIR images in the cochlea.

Five of the six patients with facial nerve paralysis with audio-vestibular disorder showed high signals in the inner ear on precontrast 3D-FLAIR. In contrast, only one of the nine patients without audio-vestibular disorder showed high signals in the inner ear on precontrast 3D-FLAIR ($p < 0.05$), while two patients with facial nerve paralysis with audio-vestibular disorder also showed gadolinium enhancement in the inner ear. Only one of the nine patients without audio-vestibular disorder showed gadolinium enhancement in the inner ear. The high-signal areas observed on 3D-FLAIR were not detected by T1- or heavily T2-weighted MRI in any of these patients. No patient had signals in the unaffected inner ear.

Six patients had hearing loss or vertigo, as shown in Table II. Of five patients with hearing loss, three had high signals in the cochlea. Of five patients with vertigo, two had high signals in the vestibule (Table II). After treatment, all patients recovered from facial nerve paralysis.

We tested 10 patients for paired antibody formations with a serological examination. The remaining five patients underwent serology only at their initial visit. VZV reactivation was indicated serologically in 60% of patients with Ramsay Hunt syndrome or atypical Bell's palsy by either anti-VZV IgM detection or a significant change (greater than twofold) in anti-VZV IgG response [14] while VZV reactivation was indicated serologically in none of five patients (0%) with Bell's palsy by the same criteria (Table I).

Table II. 3-D FLAIR findings of the inner ear in patients with facial nerve paralysis.

Patient no.	Hearing loss	Vertigo	Period from onset to MRI (days)	Precontrast	Postcontrast enhancement
1	Yes	Yes	7	CO	No
2	Yes	Yes	4	VE	No
3	Yes	No	7	No	No
4	Yes	Yes	6	CO, VE	CO, VE
5	Yes	Yes	7	CO	CO
6	No	Yes	6	CO	No
7	No	No	15	CO	No
8	No	No	8	No	CO
9	No	No	19	No	No
10	No	No	33	No	No
11	No	No	3	No	No
12	No	No	5	No	No
13	No	No	41	No	No
14	No	No	4	No	No
15	No	No	4	No	No

No, no finding with precontrast or postcontrast 3D-FLAIR images; CO, cochlea; VE, vestibule.

Discussion

Since the study by Daniels et al. in 1989 [15], many investigators have reported the enhancement on MRI of paralysed facial nerves after Gd-DTPA. Jonsson et al. reported that ipsilateral facial nerve contrast enhancement is frequently observed in cases of acute peripheral facial paralysis [1]. It has been reported that no difference in gadolinium enhancement of the facial nerves was observed between patients with Bell's palsy and those with Ramsay Hunt syndrome [1]. However, in some cases of Ramsay Hunt syndrome, the vestibular and cochlear nerves, the labyrinth and some parts of the internal and external ear canals are enhanced [1].

The present study revealed that high concentrations of protein in the inner ear are associated with hearing deterioration or dizziness in patients with facial nerve paralysis with audio-vestibular disorder. Precontrast high signals on 3D-FLAIR may reflect minor haemorrhage or an increased concentration of protein in the inner ear, which has passed through blood vessels with increased permeability or has originated in disrupted cells in the inner ear [4]. A patient with Ramsay Hunt syndrome examined with 3D-FLAIR, previously reported to have high signals in the affected ear [8], showed gadolinium enhancement in the affected inner ear on 3D-FLAIR. We demonstrate here that 3D-FLAIR is a useful tool with which to detect the precise abnormality in the inner ear.

In conclusion, 3D-FLAIR MRI revealed differences in the precontrast and postcontrast signals in the inner ear between facial nerve paralysis patients with audio-vestibular disorder, including Ramsay Hunt syndrome and atypical Bell's palsy, and those without audio-vestibular disorder, having Bell's palsy. This suggests an abnormal elevation of blood vessel permeability in this area in Ramsay Hunt syndrome and atypical Bell's palsy.

Acknowledgments

This study was supported by research grants from the Ministry of Health, Labour and Welfare in Japan.

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

References

[1] Jonsson L, Tien R, Engstrom M, Thuomas KA. Gd-DTPA enhanced MRI in Bell's palsy and herpes zoster oticus: an overview and implications for future studies. Acta Otolaryngol 1995;115:577–84.

[2] Naganawa S, Koshikawa T, Nakamura T, Fukatsu H, Ishigaki T, Aoki I. Comparison of flow artifacts between 2D-FLAIR and 3D-FLAIR sequences at 3 T. Eur Radiol 2004;14:1901–8.

[3] Sugiura M, Naganawa S, Teranishi M, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in patients with sudden sensorineural hearing loss. Laryngoscope 2006;116:1451–4.
[4] Yoshida T, Sugiura M, Naganawa S, Teranishi M, Nakata S, Nakashima T. Three dimensional FLAIR MRI findings and prognosis in sudden sensorineural hearing loss. Laryngoscope 2008;118:1433–7.
[5] Sugiura M, Naganawa S, Sone M, Yoshida T, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in a patient with cochlear otosclerosis. Auris Nasus Larynx 2008;35:269–72.
[6] Otake H, Sugiura M, Naganawa S, Nakashima T. 3D-FLAIR magnetic resonance imaging in the evaluation of mumps deafness. Int J Pediatr Otorhinolaryngol 2006;70:2115–17.
[7] Sone M, Mizuno T, Sugiura M, Naganawa S, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging investigation of inner ear disturbances in cases of middle ear cholesteatoma with labyrinthine fistula. Otol Neurotol 2007;28:1029–33.
[8] Sugiura M, Naganawa S, Nakata S, Kojima S, Nakashima T. 3D-FLAIR MRI findings in a patient with Ramsay Hunt syndrome. Acta Otolaryngol 2007;1270:547–9.
[9] Mattox DE. 2005. Clinical disorders of the facial nerve. In: Cummings CW, Flint PW, Harker LA, Haughey BH, Richardson MA, Robbins KT, et al., editors. Cummings otolaryngology head & neck surgery, vol. 2, 2nd edn. Philadelphia, PA: Elsevier Mosby. p 3333–40.
[10] House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg 1985;93:146–7.
[11] Naganawa S, Koshikawa T, Fukatsu H, Ishigaki T, Nakashima T, Ichinose N. Contrast-enhanced MR imaging of the endolymphatic sac in patients with sudden hearing loss. Eur Radiol 2002;12:1121–6.
[12] Naganawa S, Komada T, Fukatsu H, Ishigaki T, Takizawa O. Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol 2006;16:733–7.
[13] Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Nakashima T, Maruyama K. Prompt contrast enhancement of cerebrospinal fluid space in the fundus of the internal auditory canal: observation in patients with meningeal disease on 3D-FLAIR images at 3 Tesla. Magn Reson Med Sci 2006;5:151–5.
[14] Aizawa H, Ohtani F, Furuta Y, Sawa H, Fukuda S. Variable patterns of varicella-zoster virus reactivation in Ramsay Hunt syndrome. J Med Virol 2004;74:355–60.
[15] Daniels DL, Czervionke LF, Millen SJ, Haberkamp TJ, Meyer GA, Hendrix LE, et al. MR imaging of facial nerve enhancement in Bell palsy or after temporal bone surgery. Radiology 1989;171:807–9.

Acta Oto-Laryngologica, 2009; 129: 1169–1174

informa
healthcare

ORIGINAL ARTICLE

Endolymphatic space imaging in patients with delayed endolymphatic hydrops

SACHIO KASAI[1], MASAAKI TERANISHI[1], NAOMI KATAYAMA[1], MAKOTO SUGIURA[1], SEIICHI NAKATA[1], MICHIHIKO SONE[1], SHINJI NAGANAWA[2] & TSUTOMU NAKASHIMA[1]

[1]*Department of Otorhinolaryngology and* [2]*Department of Radiology, Nagoya University, Graduate School of Medicine, Nagoya, Japan*

Abstract

Conclusion: Magnetic resonance imaging (MRI) after intratympanic gadolinium injection can reveal endolymphatic hydrops (ELH) in patients with delayed ELH (DELH). Patients with contralateral DELH may have bilateral ELH. *Objective:* DELH has previously been diagnosed based on clinical history, hearing and vestibular examinations. DELH is classified into three types: ipsilateral, contralateral and bilateral indicate the side with the longstanding hearing loss. Ipsilateral DELH occurs in the ear with a profound hearing loss, contralateral DELH in the better hearing ear and bilateral DELH in both ears. Imaging diagnosis of the endolymphatic space may add a new dimension to the diagnosis and treatment of DELH. *Patients and methods:* Gadodiamide hydrate was diluted eightfold with saline. The diluted gadodiamide hydrate was injected intratympanically through the tympanic membrane in two patients with ipsilateral DELH and five patients with contralateral DELH. One day after the injection, 3 Tesla MRI was performed to evaluate the endolymphatic space. *Results:* ELH was observed in all patients. In three patients who underwent bilateral intratympanic injection of gadolinium and were diagnosed with contralateral DELH, ELH was observed bilaterally. In one of these three patients, ELH was observed in the cochlea on the left and in the vestibule on the right.

Keywords: *Endolymphatic hydrops, 3D-FLAIR MRI, inner ear*

Introduction

Delayed endolymphatic hydrops (DELH) is a clinical entity that can be differentiated from Ménière's disease and is typically observed in patients who suffer from longstanding unilateral profound inner ear hearing loss [1]. The disease is characterized by a profound sensorineural hearing loss in one ear, found to have been present in most cases from early childhood, due to an unknown cause, trauma or viral infection. ELH is probably the most important factor. After a prolonged period (usually many years) patients with DELH experience the onset of episodic vertigo from the deaf ear (ipsilateral DELH) or develop a fluctuating hearing loss and/or episodic vertigo in the opposite ear that previously had normal hearing (contralateral DELH). ELH is the most important underlying pathology that causes the hearing loss and the vestibular symptoms both in the better ear and in the ear with profound hearing loss [2]. When ipsilateral and contralateral hydrops exist simultaneously, this is called bilateral hydrops. In bilateral hydrops, it is often difficult to judge whether hydrops exists in the ear with profound hearing loss.

Recently, we have succeeded in visualizing ELH by injecting gadolinium enhancement intratympanically and taking three-dimensional (3D) FLAIR magnetic resonance (MR) images with a 3 T MR unit. The development of 3D real inversion recovery (IR) has improved the MRI of ELH. Using 3D real IR, ELH can be observed in all cochlear turns [3].

With this new imaging method, we attempted to visualize the endolymphatic space in patients clinically diagnosed with DELH.

Correspondence: Masaaki Teranishi MD PhD, Department of Otorhinolaryngology, Nagoya University, Graduate School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan. Tel: +81 52 744 2323. Fax: +81 52 744 2325. E-mail address: masaaki@med.nagoya-u.ac.jp

(Received 16 September 2008; accepted 13 December 2008)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016480802691143

Patients and methods

Patients

Seven patients were enrolled in this study. Age, sex, average hearing level at 500 Hz, 1 kHz and 2 kHz, the presence or absence of vertigo, the degree of hydrops scored by radiologists and the clinical diagnosis are presented in Table I. Two patients were diagnosed with ipsilateral DELH and five patients with contralateral DELH. All patients underwent 3 T MRI at 24 h after the intratympanic injection of gadolinium. The Ethics Review Committee of Nagoya University School of Medicine approved the protocol for the study. All patients gave their informed consent to participation in this study.

Intratympanic gadolinium injection

Gadodiamide hydrate (Omniscan Daiichi Pharmaceutical Co. Ltd, Tokyo, Japan) was diluted with saline (1:7 v/v). The diluted gadodiamide hydrate was injected intratympanically through the tympanic membrane using a 23 G needle and a 1 ml syringe after the patient was placed in the supine position with his/her head turned approximately 30° away from the sagittal line toward the uninjected ear. The gadolinium was injected until a backflow of fluid into the external ear was observed under a microscope. The amount of diluted gadolinium injected was 0.4–0.5 ml. After the injection, the patient remained in the supine position for 60 min with his/her head turned approximately 60° away from the sagittal line toward the uninjected ear. Four patients (cases 1–4) underwent intratympanic injection only in one ear. Three patients (cases 5–7) underwent intratympanic injection in both ears.

MRI

MRI scans were performed 24 h after intratympanic injection of gadolinium with a 3 T MR unit (Trio, Siemens, Erlangen, Germany) using a receive-only 12-channel phased-array coil. T1-weighted 3D fast low-angle shot imaging, heavily T2-weighted 3D constructive interference in steady state imaging and 3D fluid-attenuated inversion recovery (FLAIR) imaging were performed. For this study, we performed a second 3D-FLAIR with higher in-plane spatial resolution in addition to the methods described previously [4–6].

All MRIs were attached to the electronic medical record and reviewed independently on a liquid crystal display in the Department of Radiology and the Department of Otorhinolaryngology.

Image evaluation of endolymphatic space on MRI

The size of the endolymphatic space was scored by radiologists based on the MRI reports and using the following criteria. For the vestibule, a score of 2 indicates a noticeable enlargement of the endolymphatic space occupying more than half of the vestibule. A score of 1 indicates a moderate enlargement of the endolymphatic space occupying between

Table I. Details of the patients in the study.

Patient no.	Age (years)	Sex	HL		Vertigo (period after onset)	Ear injected with gadolinium	Gadolinium distribution	
			R	L			Cochlea	Vestibule
1	26	M	88.3	48.3	Yes (1 year)	R	2	2
2	66	F	56	55	No	L	2	0
3	56	M	81.7	103.3	No	L	1	2
4	24	F	10	101.7	Yes (1 year)	L	1	2
5	38	M	20	66.7	Yes (9 years)	Both	R1L2	R2L2
6	33	M	88.3	18.3	No	Both	R0L2	R2L0
7	66	M	18.3	103.3	No	Both	R1L1	R2L1

HL, average of hearing level of 500 Hz,1 kHz and 2 kHz (dB); M, male; F, female; R, right; L, left; Cochlea, hydrops in cochlea; Vestibule, hydrops in vestibule. The degree of hydrops determined by radiologists was: 0, none; 1, mild; 2, significant. Details of hearing level in each patient are as follows. Patient no. 1: severe hearing loss in the right ear was noticed from birth. Audiogram of the better hearing ear (left ear) showed no hearing change during our observation (ipsilateral type). Patient no. 2: fixed hearing loss was seen in the right ear, the timing of its occurrence is unknown. Fluctuation of hearing loss was observed in the left ear for 1.5 years (contralateral type). Patient no. 3: profound, fixed hearing loss was seen in the left ear after sudden deafness 14 years ago. Fluctuation of hearing loss was observed in the right ear for 2 months (contralateral type). Patient no. 4: profound, fixed hearing loss was seen in the left year since childhood. Right ear shows normal hearing (ipsilateral type). Patient no. 5: fixed hearing loss was observed in the left ear after sudden deafness 10 years ago. Fluctuation of hearing loss in the right ear with vertigo occurred 9 years ago (contralateral type). Patient no. 6: severe hearing loss was observed in the right ear after sudden deafness 8 years ago. Fluctuation of hearing loss was observed in the left ear for 1 month (contralateral type). Patient no. 7: profound hearing loss was observed in the left ear after sudden deafness 30 years ago. Fluctuation of hearing loss was observed in the right ear for 20 years (contralateral type).

one-third (33.3%) and 50% of the vestibule. A score of 0 indicates no or very mild, if any, enlargement of the endolymphatic space occupying less than one-third (33.3%) of the vestibule. For the cochlea, a score of 2 indicates a noticeable enlargement of the endolymphatic space to a size at least as large as the scala vestibuli. A score of 1 indicates a moderate enlargement of the endolymphatic space with Reissner's membrane bulging toward the scala vestibuli, although the endolymphatic space is smaller than the perilymphatic space of the scala vestibuli. A score of 0 indicates no or very mild, if any, enlargement of the endolymphatic space, with no bulging of Reissner's membrane or no endolymphatic space observed. These tentative criteria were established according to previous histological research in humans and animals [7,8].

Pure tone audiometry, DPOAE, VEMP

Functional tests such as pure tone audiometry (PTA), distortion product otoacoustic emission (DPOAE) and vestibular evoked myogenic potential (VEMP) were performed in all patients. DPOAE ($2f_1$-f_2) were collected bilaterally using Otodynamics ILO 92 version 2.04. VEMP was measured by surface myogenic potentials in the sternocleidomastoid muscle, which were added 150 times with a reference electrode over the sternum while clicks (105 dB) were presented to the ipsilateral ear and white noise (75 dB) was presented to the contralateral ear (Synax 2100, NEC Medical Systems, Tokyo, Japan). The ground electrode was on the forehead.

Results

Clinical and imaging results are summarized in Table I (7 cases, 10 ears). ELH was observed in all seven cases clinically diagnosed as DELH. The two patients with ipsilateral DELH showed ELH in both the cochlea and vestibule. They also experienced vertigo spells and exhibited remarkable ELH in the vestibule. Two MR images are presented (patient no. 1 in Figure 1, patient no. 5 in Figure 2). Patient no. 1, who had right profound perceptive deafness at birth and a moderate degree of left perceptive deafness, had suffered from rotatory vertigo for a year. Noticeable ELH was observed in the vestibule of the right ear with intratympanic administration of gadolinium. Patient no. 5 had a moderate degree of left perceptive deafness for 10 years and had suffered over that time from tinnitus and fluctuating hearing loss in the right ear and vertigo spells. A noticeable ELH was observed in the cochlea of the left ear and in the vestibules of both ears. Moderate ELH was revealed in the cochlea of the right ear.

Gadolinium injection into the asymptomatic ear with normal hearing is not approved by the Ethics Review Committee of our university. Therefore, we did not perform intratympanic injection of gadolinium in the right ear of patient no. 4. Because patient nos 1 and 2 were not hoping for the injection, we did not perform it on the left ear of patient no. 1 or the right ear of patient no. 2, both of which showed no hearing fluctuation and had moderate hearing loss. Patient no. 3 did not hope for the injection in the better hearing ear, so we did not perform it in the right ear in this patient. In patient no. 1, DPOAE responses were absent and VEMP responses were present in both ears. In patient no. 2, DPOAE response was present only at 1 kHz for the right ear and only at 3 kHz for the left ear. VEMP responses were within noise level for both ears. In patient no. 3, DPOAE responses were absent in both ears and VEMP response was present in the right ear and absent in the left ear. In patient no. 4, DPOAE showed normal response in the right ear and no response in the left ear, while VEMP responses were present in both ears.

Discussion

We have previously reported that intratympanically injected gadolinium moves quickly into the scala tympani of the basal turn of the cochlea and the perilymphatic space of the vestibule, and that 1 day after intratympanic administration of gadolinium, it appears in almost all parts of the perilymphatic space inside the inner ear. We also showed that with the use of 3 T 3D-FLAIR MRI, the size of the endolymphatic space can be clearly evaluated. In addition, with the use of 3D real IR MRI we can separately visualize endolymph, perilymph and bone, and in the cochlea can distinguish hydrops of the basal turn from hydrops of the upper turn.

This study included all clinically diagnosed cases (7 cases, 10 ears) of DELH. The most common cause of hearing loss preceding DELH is juvenile-onset unilateral profound deafness (early childhood unilateral profound sensorineural hearing loss of unknown aetiology), followed by labyrinthitis from various causes, and physical and acoustic traumas to the inner ear. Three types of DELH exist: 1) ipsilateral DELH in which the ear with profound hearing loss suffers progressive ELH; 2) contralateral DELH in which the formation of progressive ELH occurs in the ear opposite to the previously deafened ear; and 3) bilateral DELH in which both ipsilateral and contralateral DELH occurs simultaneously.

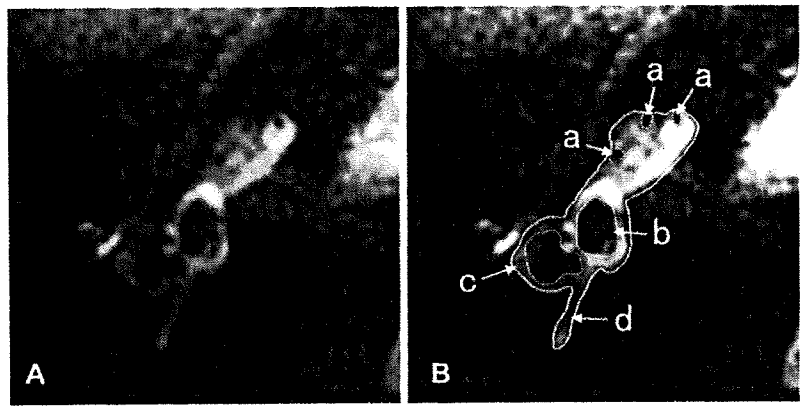


Figure 1. (A) Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MR image obtained 1 day after intratympanic injection of gadolinium (right ear of patient no. 1 in Table I). (B) Line diagram of (A). Arrows: (a) endolymphatic space in the cochlea; (b) endolymphatic space in the vestibule; (c) lateral semicircular canal; (d) posterior semicircular canal. Gadolinium is visible in all turns of the cochlea, vestibule and semicircular canals. The black area indicated by arrows (a, b) is surrounded by gadolinium-filled perilymph. Endolymphatic hydrops (ELH) in the vestibule (b) is prominent.

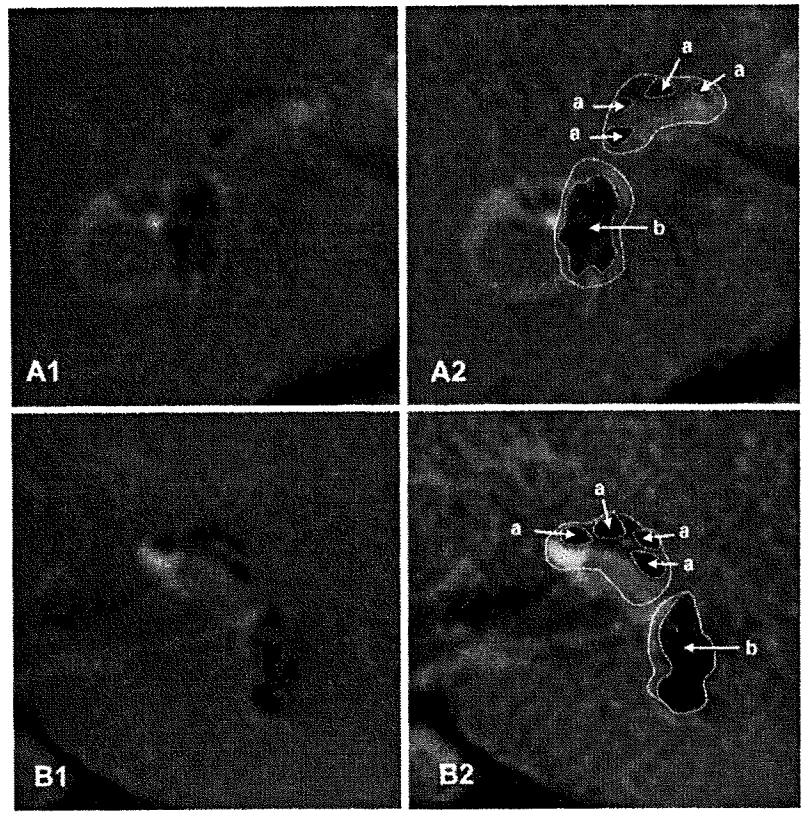


Figure 2. (A1) Three-dimensional inversion recovery utilizing real reconstruction (3D real IR) MRI obtained 1 day after intratympanic injection of gadolinium (right ear of patient no. 5 in Table I). (A2) Line diagram of (A1). Arrows: (a) endolymphatic space in the cochlea; (b) endolymphatic space in the vestibule. Gadolinium is visible in the cochlea, vestibule and semicircular canals. Black areas indicated by arrow (a) represent endolymphatic hydrops (ELH) in the basal and upper turns of cochlea. Large black areas indicated by arrows (b) represent noticeable vestibular ELH. (B1) Three-dimensional inversion recovery utilizing real reconstruction (3D real IR) MRI obtained 1 day after intratympanic injection of gadolinium (left ear of patient no. 5 in Table I). (B2) Line diagram of (B1). Arrows: (a) endolymphatic space in the cochlea; (b) endolymphatic space in the vestibule. Gadolinium is visible in basal and upper turns of cochlea and vestibule. Black areas indicated by arrows (a, b) are surrounded by gadolinium-filled perilymph. Noticeable ELH in basal and second turns of cochlea and vestibule, respectively, are visible.

The aetiology of DELH is not adequately proven. Bachor et al. proved pathologically that ELH could derive from juvenile-onset unilateral profound deafness and from congenital deafness [9,10]. However, most labyrinthitis caused by virus infection, for example by measles, rubella or mumps, causes collapse of the inner ear [11,12]. There is not sufficient histological evidence for the vertigo induced by unilateral profound deafness resulting from mumps.

Schuknecht et al. demonstrated that ELH exists in contralateral DELH because asymptomatic virus infection exists in the opposite inner ear. The damage to the opposite inner ear is negligible, so it takes a long time for ELH to be clinically apparent [13]. Alternatively, Harris and Aframian suggested that it results from an autoimmune response in the inner ear [14].

Intratympanically administered gadolinium moves first into the perilymphatic space of the inner ear. Precise MR images obtained 1 day after intratympanic administration can reveal the border between the endolymphatic and perilymphatic spaces. Injection of gadolinium into the tympanic cavity with the use of 3 T 3D-FLAIR is effective in the evaluation of the ear affected. If the endolymphatic space cannot be detected, this may be because the endolymph has collapsed, or because an extremely large ELH may prevent the intratympanically administered contrast enhancement material from moving into either or both of the cochlea and labyrinth. When recurrent episodic vertigo is intractable and cannot be cured through conservative treatment, intratympanic gentamicin administration [15], labyrinthectomy and vestibular neurectomy of the responsible ear are clinically indicated. Injection of gadolinium into the tympanic cavity with the use of 3 T 3D-FLAIR is effective in the evaluation of the ear affected. This should be taken into consideration for administration of intratympanic gentamicin therapy in patients with DELH, especially in cases with poor contrast of the vestibule and semicircular canal [16].

Patient no. 5 was diagnosed clinically with contralateral DELH, but we demonstrated ELH in both ears and a different degree of ELH in the cochlea and vestibule. Although electrocochleography and the glycerol test, which suggest the presence of ELH, cannot be performed in profound sensorineural hearing loss, we could detect ELH in profound sensorineural hearing loss with the combined use of 3 T 3D-FLAIR MRI and 3D real IR MRI at 1 day after intratympanic administration of gadolinium.

We did not perform intratympanic injection of gadolinium in the asymptomatic ears with normal hearing for ethical reasons. We will be able to detect whether or not subclinical ELH is present in the ears if we are permitted to inject gadolinium in the unaffected side.

In conclusion, we observed ELH in all seven cases of clinically diagnosed DELH using 3 T MR at 1 day after intratympanic injection of gadolinium. The identification of the ear affected may be useful in cases of resistance to conservative therapy and in understanding the aetiology of DELH.

Acknowledgements

This study was supported by research grants from the Ministry of Health, Labor, and Welfare and from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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

References

[1] Kamei T. Delayed endolymphatic hydrops as a clinical entity. Int Tinnitus J 2004;10:137–43.
[2] Albernaz PL. Unusual cases of delayed endolymphatic hydrops. Acta Otolaryngol 2007;127:355–9.
[3] Nakashima T, Naganawa S, Sugiura M, Teranishi M, Sone M, Hayashi H, et al. Visualization of endolymphatic hydrops in patients with Ménière's Disease. Laryngoscope 2007;117: 415–20.
[4] Naganawa S, Komada T, Fukatsu H, Ishigaki T, Takizawa O. Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol 2006;16:733–7.
[5] Sugiura M, Naganawa S, Teranishi M, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in patients with sudden sensorineural hearing loss. Laryngoscope 2006;116:1451–4.
[6] Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid at 3T after intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. Am J Neuroradiol 2008;29:724–6.
[7] Naganawa S, Satake H, Kawamura M, Fukatsu H, Sone M, Nakashima T. Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. Eur Radiol 2008;18:920–4.
[8] Naganawa S, Satake H, Iwano S, Fukatsu H, Sone M, Nakashima T. Imaging endolymphatic hydrops at 3 tesla using 3D-FLAIR with intratympanic Gd-DTPA administration. Magn Reson Med Sci 2008;7:85–91.
[9] Schuknecht HF, Wright JL. Pathology in a case of profound congenital deafness. J Laryngol Otol 1973;87:947–55.
[10] Bachor E, Karmody CS. Endolymphatic hydrops in children. J Otorhinolaryngol 1995;57:129–34.
[11] Lindsay JR, Davey PR, Ward PH. Inner ear pathology in deafness due to mumps. Ann Otol Rhinol Laryngol 1960;69: 718–35.
[12] Lindsay JR, Hemenway WG. Inner ear pathology due to measles. Ann Otol Rhinol Laryngol 1954;63:751–71.

[13] Shuknecht HF, Suzuka Y, Zimmermann C. Delayed endolymphatic hydrops and its relationship to Ménière's disease. Ann Otol Rhinol Laryngol 1990;99:843–53.
[14] Harris JP, Aframian D. Role of autoimmunity in contralateral delayed endolymphatic hydrops. Am J Otol 1994;15: 710–6.
[15] Atlas JT, Parnes LS. Intratympanic gentamicin therapy for intractable Ménière's disease. Am J Otol 1999;20:357–63.
[16] Nomura Y. Otological significance of the round window. Adv Otorhinolaryngol 1984;33:1–162.

Audiology Japan 52, 179～187, 2009

総　説

突発性難聴の画像所見と病態

中島　務
名古屋大学医学部耳鼻咽喉科

要旨：3テスラ　3D-FLAIR MRIにより突発性難聴の約3分の2の症例で患側内耳に異常陰影を認めた。異常陰影を認めた内耳の約半数は，ガドリニウム造影陽性であった。血管内に入れたガドリニウムが内耳に漏れるということは，内耳の血管透過性が亢進しており，血液迷路関門の破綻を意味する。炎症では血管透過性が亢進するが，突発性難聴において抗炎症作用を持つステロイドが有効な症例は，ガドリニウム造影陽性症例の中にあるという仮説を述べ，血液迷路関門破綻の病態につき，実験的，臨床的データをもとに概説した。

ーキーワードー
突発性難聴，血液迷路関門，MRI

はじめに

内耳出血ではMRIT1にて内耳に陰影を認め，ガドリニウム造影効果がない[1,2]。蝸牛内聴神経腫瘍や前庭内聴神経腫瘍では，聴神経腫瘍全般に共通するが，辺縁が明瞭に造影される。内耳炎では，辺縁が不鮮明に造影される。突発性難聴と思われた症例の画像診断において，聴神経腫瘍がみつかれば診断は突発性難聴から除外されるが，内耳出血所見がみつかっても，現状では突発性難聴から除外されることは少ない。それは「内耳出血の疑い」と画像診断される例が多いからである。

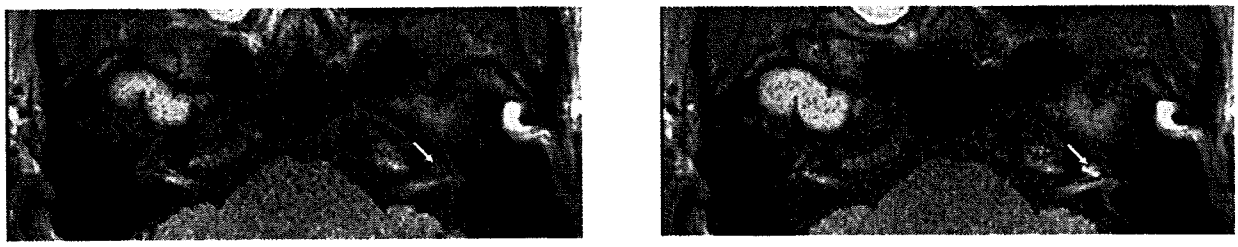
突発性難聴におけるMRI画像において，最近内耳液内の微量の出血，あるいは微量のタンパク質が3D-FLAIRという方法により描出されるようになり[3-5]，内耳異常の検出率が飛躍的に高まってきた。本稿では，突発性難聴やその周辺疾患における画像所見と病態との関係を実験的データも紹介しつつ述べる。

突発性難聴の画像所見

1）MRIにおける単純および造影所見

MRIのFluid attenuated inversion recovery（FLAIR）画像は，最近，脳の血管性病変の描出に広く用いられるようになってきているが，3テスラMRIの3D-FLAIRで突発性難聴内耳の約3分の2の症例において内耳液のタンパク質濃度の上昇，もしくは微量の内耳出血が認められた[5]。3D-FLAIRでは，内耳液の微量のタンパク質を描出でき，微量の内耳出血によるタンパク質濃度の上昇も検出できる。さらに，ガドリニウム造影剤を静脈内に投与すると，この3分の2の症例のうち約半数でガドリニウムが内耳に漏れてくることがわかった[5]。図1は，ガドリニウム造影前に患側内耳に陰影を認め，ガドリニウム造影で陰影がさらに増強した例を示す。

我々の48例の突発性難聴のMRI結果を示すと図2のようであった。ガドリニウム造影剤を静脈に投与する前から，患側内耳が健側内耳に比し高信号であったのが48症例中31例あり，造影後，さらに内耳



a b

図1 43歳男性の左突発性難聴。
3D-FLAIR MRIにて造影所見が明らかな1例。
a：ガドリニウム造影前に患側内耳に陰影（矢印）
b：ガドリニウム造影にて，陰影増強（矢印）

の高信号が増強したのは16例あった。造影前に高信号を呈し造影しても信号強度が変化しなかった15例の高信号の原因は，破壊された内耳組織が内耳液に浮かんでいるか，血液迷路関門の破綻とまでいかなくても，血液のタンパク質，あるいは微量の出血が内耳液に出現したと推察している。いずれにしても少なくとも突発性難聴の3分の1の症例では，内耳血管系に異常があると考えられた。

2）突発性難聴耳と正常耳の形態的差異

突発性難聴耳のCT所見やMRIT2所見を対側耳と比較しても一見とくに変わりはない。しかしながら，実際に内耳のサイズをいろいろな観点から測定し，その平均と標準偏差を突発性難聴耳と正常耳で比較すると統計学的に差があることが報告されている[6,7]。前庭水管の大きさは，突発性難聴では大きい傾向がある[8]。この点，メニエール病では前庭水管の発育が悪い症例が多く対照的である[9,10]。蝸牛軸の大きさは，突発性難聴では小さい傾向がある[7]。蝸牛の外形には差がないので，蝸牛における内耳液の体積は，突発性難聴耳で大きい傾向がある。半規管でも突発性難聴ではその体積が大きいと推察され[7]，前庭水管も含めて内耳液の体積が突発性難聴では大きい傾向を認める。

内耳液の体積が大きいことと突発性難聴罹患との関係は不明であるが，網膜剥離が大きい眼球（硝子体の体積が大きい眼球）に起こりやすいということと原因論的に類似のものがあるかもしれない[11]。網膜剥離は，突然の視力障害をおこす疾患の中で最も頻度的に多いものである。

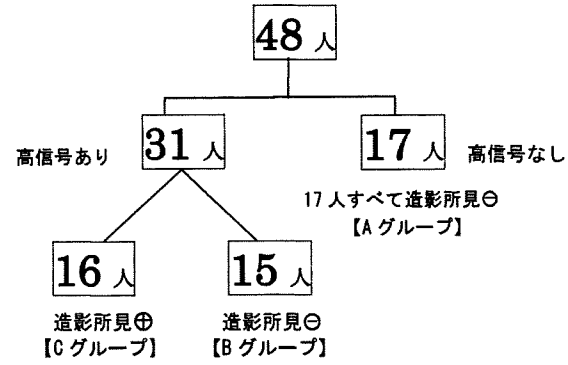


図2 突発性難聴症例における3D-FLAIR MRI所見
48例の突発性難聴のうち，ガドリニウム造影効果がなかったAグループ，造影前に患側内耳に高信号を認めるも造影効果がなかったBグループ，造影前に患側内耳に高信号を認め，造影後にさらに信号の増強を認めたCグループは，数的にほぼ同じであった。造影効果がなかったAグループは，造影前にも内耳信号を認めなかった。（文献5より作成）

血液迷路関門と血液脳関門

血液迷路関門（blood-labyrinthine barrier）は，脳でいえば血液脳関門にあたる。血液脳関門において重要な役割を担うP糖タンパクは，血液迷路関門においても同様な役割を担っている[12]。血液脳脊髄液関門（blood-CSF barrier）という言葉があり，これは内耳でいえば血液内耳液関門にあたる。血液内耳液関門には，血液外リンパ関門（blood-perilymph barrier）と血液内リンパ関門（blood-endolymph barrier）という区別があるが，血液内リンパ関門は血液外リンパ関門に比してはるかに強い。しかし，Jahnke[13]は，トレーサーを用いモルモットの内耳血管を電子顕微鏡的に観察し，血液外

リンパ関門は構造的に血液脳関門と同様であると述べている。また，外リンパ内リンパ関門（perilymph-endolymph barrier）という言葉があるが，実際，外リンパに入った薬剤はなかなか内リンパには到達しない。MRIのガドリニウム造影剤は，外リンパに入っても，ほとんど内リンパには入らない[14]。

血液内耳関門（blood-inner ear barrier）とも表現される血液迷路関門は血液内耳液関門と区別されるべきものである。血液内の成分が血管条に漏れても内リンパには漏れない状態では，血液迷路関門に破綻があっても血液内リンパ関門には破綻がないことになる[15]。しかし，内耳実質組織の内耳液に対する体積比は，脳の脳脊髄液に対する体積比にくらべて圧倒的に小さく，また内耳の大きさ自体も脳にくらべて圧倒的に小さい。現段階のMRIでは，血液内耳液関門と血液迷路関門を区別することがむずかしく，広義の血液迷路関門は，血液内耳液関門を含むとしている。

実験的内耳障害と血液迷路関門

血液迷路関門の破綻がどのようなときにおこるのか基礎的研究がなされている。血液迷路関門の破綻もしくは異常は，自己免疫モデルマウス[16]，内耳への光刺激を用いて作成した微小循環障害[17]で認められたが，ラットにおけるシスプラチンやゲンタマイシンによる内耳障害では認められなかった[18]。音響外傷では血液迷路関門の異常がおこったとする報告[15,19]とおこらなかったとする報告[20]の両者がある。内耳音響外傷に内耳血流障害が関与しているとする報告があるが[21]，血液迷路関門にまで影響があるかどうかは実験条件の違いにより異なるものと考えられる。

突発性難聴以外の内耳障害における MRI所見（臨床例）

急性髄膜炎，急性中耳炎などの炎症がひきがねとなった急性感音難聴やWegener肉芽腫[22]，血管拡張サインであるシュワルツェ徴候を伴う蝸牛耳硬化症[23]では，血液迷路関門の破綻が認められた。また，中耳真珠腫による内耳瘻孔から感音難聴やめまいがおきた症例にも血液迷路関門の破綻がある[24]。

Ramsay Hunt症候群では，造影効果は顔面神経に認められることが多いが，内耳にも認められることがある[25,26]。ムンプス難聴では，造影前に内耳に陰影が認められた[27]。ウイルス性内耳炎であるので血液迷路関門の破綻がおきていると思われるが，ムンプス難聴の多くが子供であり，まだ造影効果については検討されていない。

内耳出血では，内耳に陰影が認められても造影効果はみられないのが原則である[1,2]。SLEによる内耳出血と思われる症例でも，血液迷路関門の破綻は認められかった[28]。

聴神経腫瘍では，内耳液にコロイド様物質が貯留しやすいことが側頭骨病理所見から報告されている。聴神経腫瘍の3テスラMRIでは，造影前，内耳液の高タンパクを示す内耳陰影所見があり，造影効果を認めることが多い。この内耳造影効果は，腫瘍が内耳道底を充満するように存在する症例では著明であることが多く聴神経腫瘍における内耳循環障害を示唆する所見である。なお，急性低音障害型感音難聴の初発時に画像的に内リンパ水腫がどの程度存在するかは，まだ報告されていないが，その後，聴力の変動をきたした例では，めまいがなくても8例すべてに内リンパ水腫が認められた[29]。

血液迷路関門の破綻と病態

動物実験および突発性難聴以外の臨床例の検討から，血液迷路関門の破綻は内耳血管障害または内耳炎に伴うものと理解できる。内耳血管の梗塞でも血液迷路関門の破綻[17]がおきるが，内耳出血だけでは，血液迷路関門の破綻は認められない[28]。しかし，内耳出血でも，内耳血管系に影響が大きければ，血液迷路関門に影響がでると思われる。炎症の本態は血管透過性の亢進であり，内耳炎でも血液迷路関門の破綻がおきるが，耳毒性薬物による内耳障害では血液迷路関門への直接的影響は認められない[18]。側頭骨外傷による急性感音難聴例でも我々の経験では内耳造影効果は認められなかった。

突発性難聴の3分の1の症例では，血液内のガドリニウム造影剤が内耳に漏れるので，突発性難聴の少なくとも3分の1の症例で内耳血管系の異常があると考えられる[5]。この内耳血管系の異常には，血管系以外の原因から二次的に血管系に異常がおこっているものも含まれていると思われる。

同じ感覚器障害として網膜疾患における血管透過性に関する状況も参考になる。直接眼底が観察できる網膜疾患での血管透過性の異常は，フルオレスチンやインドシアニングリーンを静注し，それが網膜の血管外に漏れてくるかどうかで調べられる。網膜でも血管系の異常や炎症で血管透過性の異常亢進（血液網膜関門の破綻）がおきると理解され，血管系に異常がなければ，血管透過性には異常がおこらないと考えられている。

血管障害関連遺伝子と突発性難聴

欧米では突発性難聴患者において遺伝子多型検索により突発性難聴発症リスクとなる候補遺伝子が発表されている。欧米で突発性難聴発症リスクを高めると報告された遺伝子には下記のようなものがある。

- platelet glycoprotein Ia（GPIa）の C807T[30]
- Methylenetetrahydrofolate reductase（MTHFR）の C677T, A1298C[31,32,33]
- methionine synthase（MTR）の A2756G[31]
- factor V Leiden の G1691A, R506Q[32,34]

これら遺伝子は，血管障害もしくは血流障害の関連遺伝子である。Factor V Leiden については，追試では必ずしも有意ではないとする報告[35]もあるが，遺伝子検査からは突発性難聴発症に血管系の異常が関与しているとする論文が多い。遺伝子多型による発症リスクの検討は，民族，国ごとに検討される必要があり，遺伝子多型の面から日本でも突発性難聴発症リスクを検討する必要がある。

突発性難聴の成因・病態の解明へのアプローチ

突発性難聴の成因・病態の解明へのアプローチを図３に示した。画像検査，遺伝子検査は比較的最近になって行われるようになってきたが，この両者は突発性難聴における血管，血流障害の関与を示唆している。

以前から行われている疫学調査でも，最近の発症数の増加，生活習慣病との関連から血管障害との関連が推察できる。突発性難聴発症の年齢的ピークは，50歳代から60歳代に多くなってきており，ここ30年間でみると年齢別の人口比でみても高い年齢層にだんだん発症率が増えてきている[36]。糖尿病や高

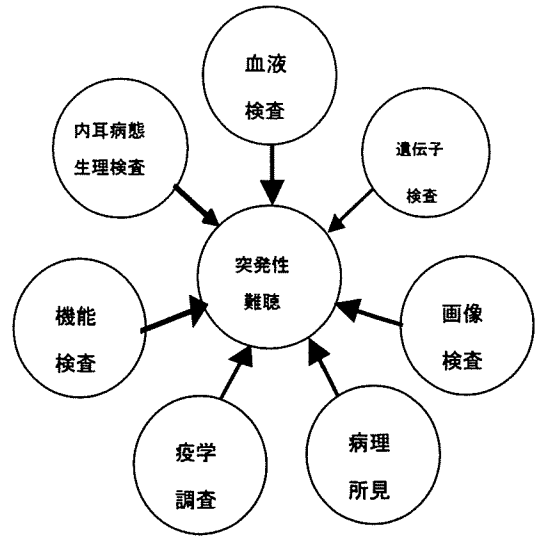


図３ 突発性難聴の原因，病態解明へのアプローチ
病態解明の画像検査と遺伝子検査は，最近になって研究が行われるようになった。

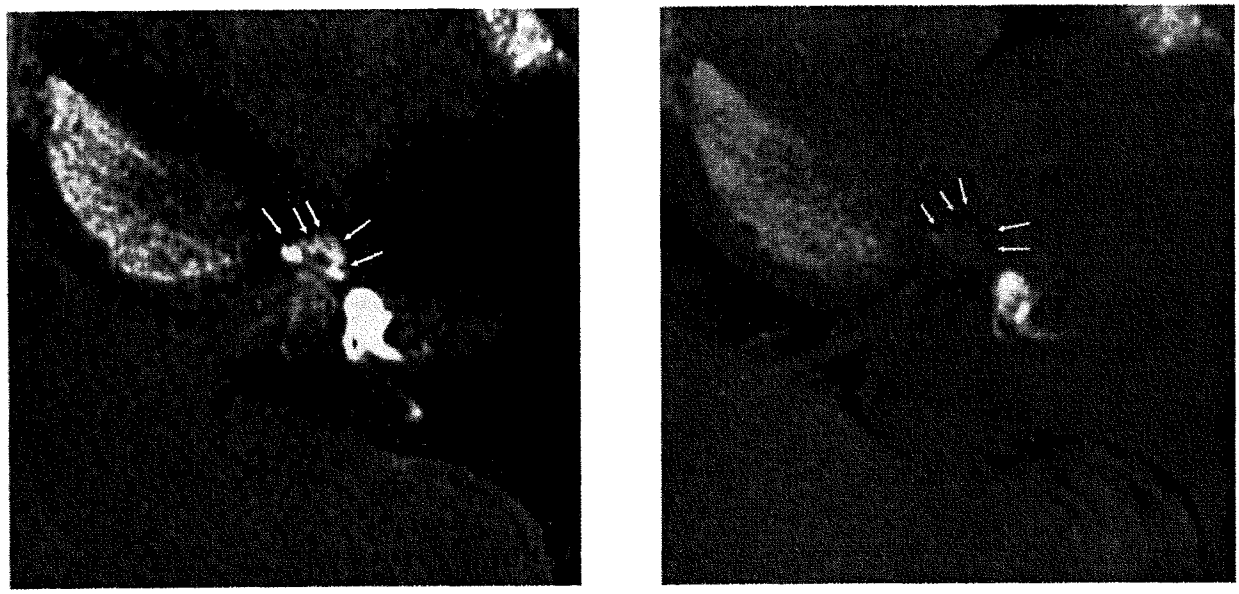
血圧を持っている人に多く発症する傾向があり[36]，食事では日本食より西洋型の食事を好む人に発症リスクが高くなる傾向を認める[37]。

一方，側頭骨病理からの報告では，循環障害よりウイルス性内耳炎が多いと報告されている[38]。しかし，最近，循環障害でもウイルス性でもないとする１例報告がなされた[39]。この報告をした Merchant らは，突発性難聴の多くは血管性でもウイルス性でもないと推察している[39]。

突発性難聴患者の外リンパ酸素分圧測定では，その値が低い例が報告されており[40]，両側突発性難聴にて人工内耳手術が行われたときのレーザードップラー法による血流測定でも蝸牛血流が低い例がある[41]。

画像所見と聴力の予後

図２の３つのグループのうち造影前に FLAIR で内耳に陰影が認められなかったグループは認められたグループより聴力の回復が良かった。年齢，初診時聴力，めまいの有無，発症から受診までの日数などの因子を含めて多変量的に解析しても造影前に内耳に陰影を認めないことは，独立して予後を良くする因子であった。逆にいうと造影前に内耳に陰影を認めることは独立して予後を悪くする因子であっ



a　　b

図4　54歳男性の左変動性感音難聴。
回転性めまいの経験は1度もないが，左蝸牛に内リンパ水腫を認める（矢印）。はじめ急性低音障害型感音難聴の診断で，聴力は正常にもどったが，その後，再発し，低音部を中心に聴力の変動を繰り返している。
a：3D-FLAIR MRI。FLAIR画像では，蝸牛内リンパと外側壁がともに黒くみえるので，水腫所見は，矢印のようにくさび型のくぼみにみえる。正常では，このようなくぼみは認められない。
b：3D real inversion recovery（3D real IR）MRI。
real IR MRIでは，水腫と外側壁が区別され，水腫の形をとらえやすい。ただし，ガドリニウムの陰影が，FLAIRより薄く描出されるので，ガドリニウムの内耳への移行が少ない例ではコントラストが悪く不鮮明になりやすい。矢印は，蝸牛の拡大した内リンパ腔。内リンパ腔にはガドリニウムが入らないので黒くみえる。

た[5]。ただし，造影前に陰影を認めた中で，造影所見陽性か陰性かは予後とは直接の関係を認めなかった[5]。

図2のほとんどすべての症例にステロイドが用いられており，ステロイド効果を比較することはできないが，内耳造影効果があってもなくても予後が変わらなかったのは，ステロイド効果による可能性がある。仮説として，造影効果のある内耳は血管透過性の亢進にステロイドの抗炎症作用が効いたが，血管透過性に異常がない例にはステロイドの効果はなかったと考えることができる。ただし，血管透過性に異常があってもムンプス難聴のようにコルチ器まで高度に障害がおこっていればステロイドの効果は期待できない。

内耳MRI画像検査の今後

突発性難聴の3テスラMRIによる3D-FLAIR画像の評価は東大からも報告された。8例中1例では造影前に内耳陰影像がみとめられ，8例中7例にガドリニウム造影剤による内耳造影効果が認められた[42]。用いる機種，撮影条件などによる違いがあると思われるが，3D-FLAIR画像が，内耳病態の検索や治療法の選択に有用であることが明らかになれば，今後，多くの施設から報告されることになる。

最近，内耳陰影の程度を半定量的に評価することが可能になり，造影効果についても，ある程度客観的に評価可能になってきている。突発性難聴の内耳造影効果にはかなりの幅があり，その程度評価も必要と考えている。

内リンパ水腫の評価には，ガドリニウム造影剤を鼓室内に入れる必要があったが（図4），ガドリニウム造影剤を静脈内に投与し，内耳ガドリニウム濃度上昇のため4時間待ってMRIを撮り内リンパ水腫を評価する試みが行われている[43,44]。現在のところ，静脈内への造影剤投与によって内リンパ水腫の程度を評価するには，ガドリニウム造影剤の通常量

では不足で，造影剤を倍量用いる必要がある。この倍量投与は，転移性脳腫瘍の評価では保険で認められているが，通常量の投与で内リンパ水腫の程度が評価できるようになると，血液迷路関門の状態も，より高いレベルで評価できるようになると考えている。内リンパ水腫の有無，程度，血液迷路関門の評価がガドリニウム造影剤の静脈内投与後のMRIで評価できるようになれば，内耳疾患における画像診断の意義は飛躍的に高まると思われる。

病態にあった治療法の開発

突発性難聴の成因，病態には種々のものが含まれており，それぞれの病態にあった治療法を選択する必要がある。MRIによる血液迷路関門の破綻は少なくとも3分の1の症例にあり，血液迷路関門の破綻の有無で，ステロイドの効果がどのようになるか検討すべき課題である。今まで，突発性難聴の3D-FLAIR MRIはステロイドの治療後に撮影されていたが，今後，ステロイド治療前後のMRIも検討していくつもりである。ステロイドは，血液迷路関門に影響を与えないシスプラチンによる内耳障害には効果がない[45]。抗炎症作用を持つステロイドの効果があるとすれば，血液迷路関門に異常がある症例であろうと考えている。また，我々の経験したステロイド依存性感音難聴（聴力変動例）でも，血液迷路関門の破綻が認められた。

原因不明の突発性難聴の病態を血液迷路関門の面からある程度分類できるMRIは，治療法，とくにステロイドの効果につき予測できる可能性を持っている。

突発性難聴におけるステロイド治療

ステロイドの作用で重要なものは抗炎症作用と免疫抑制作用であり，免疫抑制作用は抗炎症作用よりも多量のステロイドを必要とする。ステロイドの投与量について，突発性難聴において二重盲検にてステロイドの有効性を報告したWilsonらは，初期量としてデキサメタゾン（デカドロン）4.5mg内服を用いている[46]。一方，ドイツ耳鼻咽喉科学会は，突発性難聴の治療に初期量としてプレドニン250mg内服をすすめている[47]。プレドニン250mg（プレドニン5mg錠で50錠）は，全身への影響を考慮すべき量であり，全身への影響を抑え，内耳のステロイド濃度を高くするために，ステロイドを鼓室内に投与する報告が多くなされている[48,49]。鼓室内投与では，薬剤が正円窓を通って内耳に入っていくが，13%の症例では正円窓の透過性が無いか透過性が悪い[50]。突発性難聴でのステロイド鼓室内投与の効果については，有効とする報告が多い[48,49]が，その効果については今後さらに検討すべきである[47,51]。鼓室内投与で事前に正円窓の透過性が悪い症例を除けば，鼓室内投与の有効率は，もう少し上がる可能性がある。

ステロイド静脈内投与，鼓室内投与でどの程度内耳にステロイドが到達するか検討する必要がある。一般的に，プレドニン250mg内服より鼓室内投与で，内耳ステロイド濃度をより高くすることができる。

結　語

突発性難聴の臨床において，病態にあった治療法を選択できる指標が求められている。MRIは，ガドリニウム造影効果をみることにより血液迷路関門の破綻（血管透過性の亢進）を描出できる。抗炎症作用を持つステロイドが突発性難聴に有効かどうか血液迷路関門異常の有無別に検討する必要がある。現在，MRIによる内リンパ水腫の描出が可能であり，MRIは，内耳病態の解明に今後さらに貢献すると思われる。

謝　辞

名古屋大学での内耳画像の読影は，共同研究者の名古屋大学放射線科　長縄慎二教授による。本論文は，文部科学省　基盤研究（B）突発性難聴における血液迷路関門の破綻と血管障害関連遺伝子（21390460）の補助を受けた。

Disrupted blood-labyrinthine barrier revealed by MRI in patients with sudden sensorineural hearing loss

Tsutomu Nakashima

Department of Otorhinolaryngology, Nagoya

University

Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) has recently been developed to detect high concentrations of protein or hemorrhage. Two-thirds of patients with sudden sensorineural hearing loss showed high-intensity signals in the affected inner ear on precontrast 3D-FLAIR at 3 Tesla. Postcontrast enhancement was recognized after intravenous gadolinium administration in a half of the inner ears showing precontrast high-intensity signals. Abnormal passage of the gadolinium reflects increased permeability of blood vessels or disruption of the blood-labyrinthine barrier in the inner ears. We hypothesized that glucocorticoids, which have anti-inflammatory actions and suppress the increased permeability of blood vessels, are effective in some cases showing postcontrast enhancement. Experimental and clinical reports on disrupted blood-labyrinthine barrier were reviewed.

参考文献

1) Weissman JL, Curtin HD, Hirsch BE, et al: High signal from the otic labyrinth on unenhanced magnetic resonance imaging. AJNR Am J Neuroradiol **13**: 1183-1187, 1992

2) Shinohara S, Yamamoto E, Saiwai S, et al: Clinical features of sudden hearing loss associated with a high signal in the labyrinth on unenhanced T1-weighted magnetic resonance imaging. Eur Arch Otorhinolaryngol **257**: 480-484, 2000

3) Sugiura M, Naganawa S, Teranishi M, et al: Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in patients with sudden sensorineural hearing loss. Laryngoscope **116**: 1451-1454, 2006

4) 吉田忠雄, 杉浦 真, 寺西正明, 他: 内耳性難聴における血液迷路関門の破綻症例について。Audiology Japan **50**: 157-162, 2007

5) Yoshida T, Sugiura M, Naganawa S, et al: Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings and prognosis in sudden sensorineural hearing loss. Laryngoscope **118**: 1433-1437, 2008

6) Sugiura M, Nakashima T, Naganawa S, et al: Sudden sensorineural hearing loss associated with inner ear anomaly. Otol Neurotol **26**: 241-246, 2005

7) Ishida IM, Sugiura M, Naganawa S, et al: Cochlear modiolus and lateral semicircular canal in sudden deafness. Acta Otolaryngol **127**: 1157-1161, 2007

8) Sugiura M, Naganawa S, Ishida IM, et al: Vestibular aqueduct in sudden sensorineural hearing loss. J Laryngol Otol **122**: 887-892, 2008

9) Lorenzi MC, Bento RF, Daniel MM, et al: Magnetic resonance imaging of the temporal bone in patients with Meniere's disease. Acta Otolaryngol **120**: 615-619, 2000

10) Krombach GA, van den Boom M, Di Martino E, et al: Computed tomography of the inner ear: size of anatomical structures in the normal temporal bone and in the temporal bone of patients with Meniere's disease. Eur Radiol **15**: 1505-1513, 2005

11) 中島 務: 突発性難聴の原因。学士会会報 No.**870**: 104-109, 2008

12) Saito T, Zhang ZJ, Tsuzuki H, et al: Expression of P-glycoprotein in inner ear capillary endothelial cells of the guinea pig with special reference to blood-inner ear barrier. Brain Res **767**: 388-392, 1997

13) Jahnke K. The blood-perilymph barrier: Arch Otorhinolaryngol **228**: 29-34, 1980

14) Nakashima T, Naganawa S, Katayama N, et al: Clinical significance of endolymphatic imaging after intratympanic gadolinium injection. Acta Otolaryngol Suppl **560**: 9-14, 2009

15) Suzuki M, Yamasoba T, Ishibashi T, et al: Effect of noise exposure on blood-labyrinth barrier in guinea pigs. Hear Res **164**: 12-18, 2002

16) Lin DW, Trune DR: Breakdown of stria vascu-

laris blood-labyrinth barrier in C3H/lpr autoimmune disease mice. Otolaryngol Head Neck Surg **117**: 530-534, 1997

17) Zhang X, Wang J: Effects of microcirculatory disorders of inner ear on blood-labyrinth barrier permeability in guinea pigs. Zhonghua Er Bi Yan Hou Ke Za Zhi **35**: 339-341, 2000

18) Laurell G, Viberg A, Teixeira M, et al: Blood-perilymph barrier and ototoxicity: an in vivo study in the rat. Acta Otolaryngol **120**: 796-803, 2000

19) Hukee MJ, Duvall AJ, 3rd: Cochlear vessel permeability to horseradish peroxidase in the normal and acoustically traumatized chinchilla: a re-evaluation. Ann Otol Rhinol Laryngol **94**: 297-303, 1985

20) Laurell GF, Teixeira M, Duan M, et al: Intact blood-perilymph barrier in the rat after impulse noise trauma. Acta Otolaryngol **128**: 608-612, 2008

21) Nakashima T, Naganawa S, Sone M, et al: Disorders of cochlear blood flow. Brain Res Brain Res Rev **43**: 17-28, 2003

22) Sone M, Mizuno T, Naganawa S, et al: Imaging analysis in cases with inflammation-induced sensorineural hearing loss. Acta Otolaryngol **129**: 239-243, 2009

23) Sugiura M, Naganawa S, Sone M, et al: Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in a patient with cochlear otosclerosis. Auris Nasus Larynx **35**: 269-272, 2008

24) Sone M, Mizuno T, Sugiura M, et al: Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging investigation of inner ear disturbances in cases of middle ear cholesteatoma with labyrinthine fistula. Otol Neurotol **28**: 1029-1033, 2007

25) Jonsson L, Tien R, Engstrom M, et al: Gd-DPTA enhanced MRI in Bell's palsy and herpes zoster oticus: an overview and implications for future studies. Acta Otolaryngol **115**: 577-584, 1995

26) Sugiura M, Naganawa S, Nakata S, et al: 3D-FLAIR MRI findings in a patient with Ramsay Hunt syndrome. Acta Otolaryngol **127**: 547-549, 2007

27) Otake H, Sugiura M, Naganawa S, et al: 3D-FLAIR magnetic resonance imaging in the evaluation of mumps deafness. Int J Pediatr Otorhinolaryngol **70**: 2115-2117, 2006

28) Sugiura M, Naganawa S, Teranishi M, et al: Inner ear hemorrhage in systemic lupus erythematosus. Laryngoscope **116**: 826-828, 2006

29) Teranishi M, Naganawa S, Katayama N, et al: Image evaluation of endolymphatic space in fluctuating hearing loss without vertigo. Eur Arch Otorhinolaryngol (in press)

30) Rudack C, Langer C, Stoll W, et al: Vascular risk factors in sudden hearing loss. Thromb Haemost **95**: 454-461, 2006

31) Gross M, Friedman G, Eliashar R, et al: Impact of methionine synthase gene and methylenetetrahydrofolate reductase gene polymorphisms on the risk of sudden sensorineural hearing loss. Audiol Neurootol **11**: 287-293, 2006

32) Capaccio P, Ottaviani F, Cuccarini V, et al: Genetic and acquired prothrombotic risk factors and sudden hearing loss. Laryngoscope **117**: 547-551, 2007

33) Capaccio P, Cuccarini V, Ottaviani F, et al: Prothrombotic gene mutations in patients with sudden sensorineural hearing loss and cardiovascular thrombotic disease. Ann Otol Rhinol Laryngol **118**: 205-210, 2009

34) Gorur K, Tuncer U, Eskandari G, et al: The role of factor V Leiden and prothrombin G20210A mutations in sudden sensorineural hearing loss. Otol Neurotol **26**: 599-601, 2005

35) Ballesteros F, Alobid I, Tassies D, et al: Is there an overlap between sudden neurosensorial hearing loss and cardiovascular risk factors? Audiol Neurootol **14**: 139-145, 2009

36) Teranishi M, Katayama N, Uchida Y, et al:

Thirty-year trends in sudden deafness from four nationwide epidemiological surveys in Japan. Acta Otolaryngol **127**: 1259-1265, 2007

37) Nakamura M, Whitlock G, Aoki N, et al: Japanese and Western diet and risk of idiopathic sudden deafness: a case-control study using pooled controls. Int J Epidemiol **30**: 608-615, 2001

38) 野村恭也: 突発性難聴の病理。Audiology Japan **49**: 777-781, 2006

39) Merchant SN, Adams JC, Nadol JB, Jr: Pathology and pathophysiology of idiopathic sudden sensorineural hearing loss. Otol Neurotol **26**: 151-160, 2005

40) Nagahara K, Fisch U, Yagi N: Perilymph oxygenation in sudden and progressive sensorineural hearing loss. Acta Otolaryngol **96**: 57-68, 1983

41) Nakashima T, Hattori T, Sone M, et al: Blood flow in the ears of patients receiving cochlear implants. Ann Otol Rhinol Laryngol **113**: 426-430, 2004

42) 山岨達也, 安井拓也, 青木茂樹: 急性感音難聴におけるMRI所見の検討。厚生労働科学研究費補助金 難治性疾患克服研究事業 急性高度難聴に関する調査研究 平成20年度総括・分担研究報告書 48-52, 2009

43) Naganawa S, Komada T, Fukatsu H, et al: Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol **16**: 733-737, 2006

44) Carfrae MJ, Holtzman A, Eames F, et al: 3 Tesla delayed contrast magnetic resonance imaging evaluation of Meniere's disease. Laryngoscope **118**: 501-505, 2008

45) 川出和彦, 横井 久, 柳田則之: 抗腫瘍剤（ナイトロミン, シスプラチン）による蝸牛障害とステロイドの影響。日本耳鼻咽喉科学会会報 **81**: 177-191, 1986

46) Wilson WR, Byl FM, Laird N: The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. Arch Otolaryngol **106**: 772-776, 1980

47) Plontke SK, Lowenheim H, Mertens J, et al: Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. Laryngoscope **119**: 359-369, 2009

48) Ho HG, Lin HC, Shu MT, et al: Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. Laryngoscope **114**: 1184-1189, 2004

49) Xenellis J, Papadimitriou N, Nikolopoulos T, et al: Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. Otolaryngol Head Neck Surg **134**: 940-945, 2006

50) Yoshioka M, Naganawa S, Sone M, et al: Individual difference of permeability of the round window: evaluation of movement of intratympanic gadolinium into the inner ear. Otol Neurotol (in press)

51) Nakashima T, Teranishi M, Yoshida T: In Reference to Randomized, double blind, placebo controlled trial on the safety and efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. Laryngoscope (in press)

（原稿受付 平成21. 7. 7）

別冊請求先: 〒466-8550
名古屋市昭和区鶴舞町65
名古屋大学医学部耳鼻咽喉科
中島 務

Reprint request:
Tsutomu Nakashima
Department of Otorhinolaryngology, Nagoya University School of Medicine
65, Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

ELSEVIER

Auris Nasus Larynx xxx (2009) xxx–xxx

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

The Ala54Thr polymorphism in the fatty acid-binding protein 2 (FABP2) gene is associated with hearing impairment: A preliminary report

Yasue Uchida [a,*], Saiko Sugiura [a], Tsutomu Nakashima [b], Fujiko Ando [c,d], Hiroshi Shimokata [d]

[a] *Department of Otorhinolaryngology, National Center for Geriatrics and Gerontology, 36-3 Gengo, Morioka, Obu City, Aichi Prefecture 474-8511, Japan*
[b] *Department of Otorhinolaryngology Cognitive and Speech Medicine, Nagoya University School of Medicine, 65 Tsuruma-Cho, Showa Ward, Nagoya City, Aichi Prefecture 466-8550, Japan*
[c] *Faculty of Medical Welfare, Aichi Shukutoku University, 23 Sakuragaoka, Chikusa Ward, Nagoya City, Aichi Prefecture 464-8671, Japan*
[d] *Department of Epidemiology, National Center for Geriatrics and Gerontology, 36-3 Gengo, Morioka, Obu City, Aichi Prefecture 474-8511, Japan*

Received 27 July 2009; accepted 5 January 2010

Abstract

Objective: The fatty acid-binding protein 2 (FABP2) is involved in the transport and metabolism of fatty acids. The FABP2 gene has been proposed as a candidate gene for diabetes and obesity. This study evaluates the hearing impairment risk in the Ala54Thr polymorphism of FABP2 in middle-aged and elderly Japanese.
Methods: Our sample population comprised 1428 community-dwelling Japanese aged 40–86 years (mean ± standard deviation [SD]: 63.1 ± 9.8) who participated in the Study of Aging between 2004 and 2006. An average hearing threshold level greater than 25 dB in the better ear for frequencies 500, 1000, 2000 and 4000 Hz was defined as hearing impairment. Data were analyzed by means of a multiple logistic regression with adjustment for potential confounders.
Results: The per-allele odds ratio for hearing impairment risk was 1.262 (95% confidence interval [CI]: 1.012–1.574) in model 1, adjusting for age, sex, history of ear disease, and history of occupational noise exposure; and 1.259 (CI: 1.009–1.571) in model 2, which adjusted for diabetes, body mass index and the histories of heart disease and hypertension, as well as the moderators in model 1. A significant adverse effect of the Thr54 variant on hearing was observed and the effect was independent of both diabetes and obesity in the present analyses.
Conclusions: This study demonstrated that the Ala54Thr polymorphism of FABP2 was associated with a risk of hearing impairment in middle-aged and elderly people. The results might support caloric restriction theory indirectly, but additional researches are desired.

Keywords: FABP2 gene; Polymorphism; Age-related hearing loss; Population-based study

1. Introduction

With the expected rapid increase in the number of elderly in Japan, hearing difficulty has become a common social and health problem. Numerous studies indicate that age-related hearing loss, known as presbycusis, is likely polygenic and multifactorial; however, little is known about common sequence variants that may have some phenotypic effect on age-related hearing loss.

Fatty acid-binding protein 2 (FABP2) belongs to the family of cytoplasmic proteins involved in the intracellular transport and metabolism of long-chain fatty acids. The expression of FABP2 gene is limited to the small intestine [1]. A G-to-A nucleotide polymorphism in codon 54 results in the substitution of threonine (Thr) for alanine (Ala). In vitro experiments have shown that this substitution increases the affinity of FABP2 for long-chain fatty acids, and is associated with increased triglyceride transport in human intestinal cells [2].

Because its product is involved in fatty acid absorption and may affect insulin sensitivity and glucose metabolism, the FABP2 gene has been proposed as a candidate gene for diabetes and obesity. In the meantime, researches have obtained preceding evidence that diabetic subjects [3] and adults with high body mass index (BMI) are at increased risk for hearing loss [4]. In this study, we examined the association between the Ala54Thr polymorphism of FABP2

* Corresponding author. Tel.: +81 562 46 2311; fax: +81 562 44 8518.
E-mail address: yasueu@ncgg.go.jp (Y. Uchida).

0385-8146/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.anl.2010.01.006

Please cite this article in press as: Uchida Y, et al. The Ala54Thr polymorphism in the fatty acid-binding protein 2 (FABP2) gene is associated with hearing impairment: A preliminary report. Auris Nasus Larynx (2010), doi:10.1016/j.anl.2010.01.006

and hearing impairment in a population of middle-aged and elderly Japanese. No previous trials have studied the effect of the FABP2 gene polymorphism on hearing.

2. Materials and methods

Data were collected from Japanese men and women who participated in the fourth-wave examination of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), an ongoing population-based study conducted in the National Center for Geriatrics and Gerontology, with a 2-year follow-up. The details of the NILS-LSA have been described elsewhere [5,6].

Briefly, the participants of NILS-LSA were residents, who were randomly selected from a register stratified by both age and gender, in cooperation with the local government. The study consisted of various gerontological and geriatric measurements such as medical examinations, blood chemical analysis, physical function, nutritional analysis, psychological tests, and assays of visual and auditory function. The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology. Written informed consents were obtained from all subjects. A blood sample was drawn from each subject after an overnight fast. With respect to DNA analysis, a number of candidate genes for geriatric diseases such as Alzheimer's disease, arteriosclerosis, osteoporosis, benign prostate hypertrophy, diabetes mellitus and other lifestyle-related diseases were examined with the agreement of the participants. Venous blood samples for genetic analysis were collected only in the first wave of examinations implemented between 1997 and 2000; sera and DNA samples were stored in deep freezers for later examination. In the present study, data obtained in the fourth-wave examination (2004–2006) from participants who took part in both the first and fourth waves were analyzed cross-sectionally. Participants without any missing values were 1428 adults, aged 40–86 years (mean ± SD: 63.1 ± 9.8) at the fourth-wave examination visit.

Histories of ear disease, occupational noise exposure, heart disease and hypertension were obtained in the self-reported account. Each of these was treated as a binary variable (presence = 1, absence = 0). Definition of diabetes was based on medical history obtained by questionnaires. We also classified as "diabetic" any subject with a fasting plasma glucose concentration greater than 126 mg/dl and an HbA1c of more than 6.5%, as well as any subject taking medication to lower blood glucose levels. BMI was calculated as weight (in kg) divided by height (in m) squared.

DNA samples were isolated from peripheral blood cells. Genotypes were determined using an allele-specific primer/polymerase chain reaction (PCR) assay system (Toyobo Gene Analysis, Tsuruga, Japan). Genotypes were also determined in control blood known to be from subjects homozygous for the wild-type genotype and heterozygous and homozygous for each variant genotype.

Air-conduction pure-tone thresholds at octave intervals from 125 to 8000 Hz were obtained using a diagnostic audiometer (AA-73A and AA-78; Rion, Tokyo, Japan). The presence of hearing impairment was defined as a pure-tone average of hearing thresholds (AHT) at 500, 1000, 2000, and 4000 Hz greater than 25 dB HL (hearing level) in the better ear, according to the World Health Organization grades. This definition means bilateral hearing impairment.

Statistical analyses were conducted using Statistical Analysis System (SAS) version 9.13 (SAS Institute, Cary, NC, USA). Genotypes were coded as follows: wild-type homozygotes, GG; heterozygotes, GA; and mutant homozygotes, AA. Because no preceding information regarding the mode of inheritance of the Ala54Thr FABP2 polymorphism on hearing impairment can be found, we considered different modes of inheritance as follows: the additive per-allele model, the A allele was compared between cases and controls by assigning scores of 0, 1, and 2 to homozygotes for the G allele, heterozygotes, and homozygotes for the A allele, respectively; the dominant model compared genotypes GG versus GA and AA; and the recessive model compared genotype GG and GA versus AA. A multiple logistic regression was carried out to obtain odds ratios (ORs) for hearing impairment in subjects with the Ala54Thr FABP2 polymorphism; in this analysis, we used two adjusted models, adjusting for different combinations of confounding variables. In model 1, age, sex, history of ear disease, and history of occupational noise exposure were taken as moderator variables. History of heart disease, history of hypertension, diabetes, and BMI were added as moderators in model 2 to those in model 1.

The results were presented as means ± standard errors (SEs) and p values of less than 0.05 were considered statistically significant unless otherwise stated.

3. Results

According to univariate analysis, the characteristics of the participants (other than hearing impairment) were not significantly different among FABP2 Ala54Thr (G/A) genotypes (Table 1). Prevalence rate of heart disease, hypertension and diabetes were not significantly different among FABP2 genotypes (data not shown). The genotype frequencies were not significantly different from those expected based on the Hardy–Weinberg equilibrium (χ^2 test, $p > 0.05$).

The results from the analyses of multiple logistic regression are presented in Table 2. The per-allele odds ratio for hearing impairment risk was 1.262 (95% confidence interval [CI]: 1.012–1.574) in model 1, with fewer moderators; and 1.259 (CI: 1.009–1.571) in model 2, which adjusted for diabetes, BMI and the histories of heart disease and hypertension, as well as the moderators in model 1.

Please cite this article in press as: Uchida Y, et al. The Ala54Thr polymorphism in the fatty acid-binding protein 2 (FABP2) gene is associated with hearing impairment: A preliminary report. Auris Nasus Larynx (2010), doi:10.1016/j.anl.2010.01.006