MAJOR PAPER

MR Imaging of the Cochlear Modiolus after Intratympanic Administration of Gd-DTPA

Hisashi KAWAI¹, Shinji NAGANAWA^{1*}, Shunichi ISHIHARA¹, Michihiko SONE²,
and Tsutomu NAKASHIMA²

*Departments of ¹Radiology and ²Otorhinolaryngology, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Shouwa-ku, Nagoya 466-8550, Japan*

(Received November 16, 2009; Accepted December 9, 2009)

Purpose: We evaluated whether enhancement of the cochlear modiolus could be visualized 24 hours after intratympanic injection of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA) using a 3-dimensional real inversion recovery sequence combined with a 32-channel head coil at 3 tesla. Intratympanic injection of Gd-DTPA has been reported for visualizing endolymphatic hydrops in Meniere's disease, and its use has shown communication between the cochlear perilymph and cerebrospinal fluid in the internal auditory canal. Although the cochlear modiolus has been considered the route for this communication, this has not been confirmed through direct visualization of its enhancement.

Materials and Methods: We qualitatively and quantitatively evaluated the presence of contrast enhancement in the modiolus in 19 patients with clinically suspected endolymphatic hydrops or hearing loss who underwent imaging as described above.

Results: The contrast ratio (CR) between the cochlear modiolus and cerebellar white matter on the injected side was 1.09 ± 1.23 , and that on the non-injected side was -0.48 ± 0.38 ($P < 0.01$). In all subjects, the CR value was larger on the injected than non-injected side, and enhancement of the cochlear modiolus was also recognized visually.

Conclusions: Intratympanic Gd-DTPA can be administered to visualize enhancement of the cochlear modiolus and may thereby reveal its functional anatomy.

Keywords: *cochlea, labyrinth, magnetic resonance, modiolus*

Introduction

Enhancement of perilymphatic fluid on magnetic resonance (MR) images after intratympanic injection of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA) has been reported¹ and enabled visualization of endolymphatic hydrops in patients with Meniere's disease. In these patients, 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) obtained after intratympanic injection of Gd-DTPA at 3 tesla (T) has demonstrated enlarged endolymphatic space as an area of low signal intensity partly surrounded by perilymphatic fluid of high signal.¹ Further technical developments have enabled the separation of bone, endolymphatic space, and perilymphatic space on a single image using a 3D inversion recovery turbo spin echo with real reconstruction (3D-real IR) sequence instead of

3D-FLAIR.² In this study, we set the inversion time of the 3D-real IR sequence to the average of 2 null points—of endolymph containing no Gd-DTPA and perilymph containing infused Gd-DTPA. By revealing the border between endolymph and surrounding bone, 3D-real IR more convincingly defined endolymphatic hydrops than did 3D-FLAIR.³

After intratympanic injection, Gd-DTPA enters the perilymph in the scala tympani through the round window membrane and diffuses longitudinally toward the upper turn, but enhancement of the scala vestibuli before the Gd-DTPA reaches the helicotrema suggests the possibility of interscalar or radial communication.⁴ This radial communication route is speculated to exist in the lateral wall of the cochlea or spiral ligament.⁴ A recent histological study revealed that the cochlear modiolus is highly porous and allows communication between the perilymph and perivascular and perineural space in the modiolus, serving as the interscalar communication route as well as a communication route

*Corresponding author, Phone: +81-52-744-2327, Fax: +81-52-744-2335, E-mail: naganawa@med.nagoya-u.ac.jp

between the perilymph and cerebrospinal fluid (CSF).⁵

Because CSF in the fundus of the internal auditory canal (IAC) is often enhanced on 3D-FLAIR after intratympanic administration of Gd-DTPA, it has been speculated that communication between the perilymph and CSF occurs mostly through the modiolus and not the cochlear aqueduct or singular canal.⁶ However, confirmation of the existence of micropores in the modiolus of each subject requires direct visualization of enhancement of the cochlear modiolus. To our knowledge, this has not been done using MR imaging. Because the modiolus is a highly porous, small bony structure, optimal evaluation of its enhancement would necessitate a shorter echo train length to avoid blurring. Recently, a 32-channel head coil that provides excellent signal-to-noise ratios has been available clinically at 3T.⁷

We evaluated whether we could visualize enhancement of the cochlear modiolus after intratympanic injection of Gd-DTPA using a 3D-real IR sequence with high spatial resolution combined with a shorter echo train length and a 32-channel head coil at 3T. In addition, we evaluated the correlation of modiolus enhancement with that of CSF in the IAC fundus to confirm further that the modiolus was the actual communication route between the perilymph and CSF in the IAC fundus.

Materials and Methods

Patients

We identified 21 patients who underwent unilateral intratympanic injection of 8-fold diluted Gd-DTPA (gadopentetate dimeglumine; Magnevist, Bayer, Osaka, Japan) from July 1, 2008 to June 30, 2009 and excluded two with head motion during MR scanning. Nineteen patients underwent further evaluation, 15 with clinically diagnosed Meniere's disease, 2 with sudden sensorineural hearing loss, and one each with low-tone sensorineural hearing loss and delayed endolymphatic hydrops. The 10 men and 9 women were aged 16 to 80 years (mean age 50.6 years, standard deviation 18.3).

Patients with severe vertigo were scheduled for therapy with intratympanic injection of gentamicin and those with sensorineural hearing loss, with a steroid. Gd-DTPA was injected intratympanically to evaluate the status of the endolymphatic space and simulate distribution of the therapeutic drug.

The medical ethics committee of our university hospital approved the study, and we obtained written informed consent from all patients.

Intratympanic gadolinium injection

Intratympanic gadolinium injection was detailed in a previous study,¹ in which a delay of 24 hours between injection and MR imaging was found optimal to allow wide distribution of the gadolinium within the perilymphatic space of the labyrinth. With the patient placed supine with his or her head turned approximately 30° away from the sagittal line toward the healthy ear, we injected Gd-DTPA diluted 8-fold with saline (v/v 1:7) through the tympanic membrane using a 23-gauge needle and a one-mL syringe.

MR imaging

All scans were performed on a 3-tesla MR scanner (MAGNETOM Trio, a TIM System, Siemens Medical Solutions; Erlangen, Germany) using a receive-only 32-channel phased-array coil. Images were acquired 24 hours after intratympanic injection of diluted Gd-DTPA.

To obtain reference images of the anatomy of the labyrinthine fluid and space, we performed T₂-weighted, 3-dimensional constructive interference in steady state (3D-CISS) imaging: 0.4-mm isotropic voxels; repetition time (TR), 6.4 ms; echo time (TE), 3.2 ms; and flip angle, 50 degrees. The scan time was 3.5 min.

The 3D-real IR protocol comprised: conventional 3D turbo spin echo (TSE) sequence with constant flip angle of 180 degrees for the TSE train; TR, 6000 ms; TE, 182 ms; inversion time (TI), 1650 ms; slab-selective inversion pulse; echo train length, 27; echo spacing, 12.2 ms; field of view (FOV), 160 mm; matrix 384 × 384 × 30; slice thickness, 0.8 mm with a slice partial-Fourier factor of 6/8; bandwidth, 213 Hz/pixel; and reconstruction mode "real." We employed generalized auto-calibrating partially parallel acquisitions (GRAPPA), a parallel imaging technique, with an acceleration factor of 2, and scan time was 15 min. Voxel size was 0.4 mm × 0.4 mm × 0.8 mm. "Real" reconstruction allows positive and negative signal intensity values.²

Image evaluation

Qualitative evaluation

Two radiologists independently reviewed the 3D-real IR images and resolved discrepancies by consensus. Enhancement in the cochlear modiolus and in the CSF of the IAC fundus was evaluated as negative or positive in reference to the anatomical position of these structures on 3D-CISS.

Contrast enhancement of the modiolus was positive when both (1) signal in the modiolus was apparently higher than that of the non-injected side on 3D-real IR imaging, and (2) it was possible to

evaluate the modiolus on at least one slice of 3D-real IR without the partial-volume effect effectively averaging its signal with that of the perilymph fluid. This was confirmed by review of the neighboring slices of 3D-real IR. To ensure the absence of partial-volume effect from the perilymph, 3D-CISS images were also used for reference.

As previously reported,⁶ contrast enhancement of CSF space in the fundus of the IAC was considered positive if both of the following conditions were satisfied: (1) no mass other than the cranial nerves was observed in the space on 3D-CISS, and (2) the intensity of the space was the same or higher than that of the contralateral side on 3D-real IR images.

Quantitative evaluation

To delineate the cochlear modiolus precisely without including perilymph fluid, we measured the contrast ratio (CR) between the cochlear modiolus and cerebellar white matter by drawing a region of interest (ROI) on 3D-real IR while referring to 3D-CISS images. We carefully excluded the partial-volume averaging effect by referring to the neighboring slices. The ROI for the modiolus was defined as a circle enclosing at least one mm². The ROI for the cerebellar white matter was defined as a circle with a diameter of one cm. The CR value was defined as the signal of the modiolus divided by that of cerebellar white matter on the same side. We used Student's t-test to compare CR values of the injected and non-injected sides in the 19 patients.

We also quantitatively evaluated contrast enhancement of CSF in the IAC fundus using a method similar to that for the modiolus. We measured the contrast ratio (CR) between CSF space of the IAC fundus and cerebellar white matter by drawing an ROI on 3D-real IR while referring to 3D-CISS images to delineate the space precisely. The CR value was defined as the signal of CSF space in the fundus of the ipsilateral IAC divided by that of cerebellar white matter on the same side. We compared CR values of the injected and non-injected sides in the 19 patients using Student's t-test. The ROI for CSF in the IAC fundus was defined as a circle enclosing at least 0.6 mm². The ROI for cerebellar white matter was defined as a circle with a diameter of one cm. We assessed the correlation between the CR of the modiolus and that of CSF in the IAC fundus using Spearman's rank correlation coefficient.

Endolymphatic hydrops

By consensus, 2 radiologists evaluated endolymphatic hydrops using previously proposed grading criteria for the cochlea and vestibule,⁸ assigning a

grade of 0 (none), 1 (mild), or 2 (significant). The correlation between the grade of endolymphatic hydrops and the CR of the ipsilateral modiolus was assessed using Spearman's rank correlation coefficient.

Results

We observed no side effects related to the intratympanic injection. Table details results of enhancement and endolymphatic hydrops. In all subjects, perilymph enhancement was seen on 3D-real IR images, and enhancement of the modiolus and CSF of the IAC fundus was visually recognized in the qualitative analysis (Fig. 1).

In the quantitative analysis, the CR between the cochlear modiolus and cerebellar white matter on the injected side was 1.09 ± 1.23 , and that of the non-injected side was -0.48 ± 0.38 ($P < 0.01$). In all subjects, the CR of the modiolus was larger on the injected side than on the non-injected side. The CR between CSF in the IAC fundus and cerebellar white matter on the injected side was -1.86 ± 0.94 , and that of the non-injected side was -3.87 ± 0.72 ($P < 0.01$).

There was a significant positive correlation between the CR of the modiolus and the CR of CSF in the fundus of the IAC on the injected side ($r_s = 0.64$, $P < 0.01$) (Fig. 2). There was no significant correlation between the CR of the modiolus and the grade of endolymphatic hydrops whether in the cochlea ($r_s = -0.001$) or the vestibule ($r_s = 0.22$).

Discussion

Various reports have investigated the shape and structure of the cochlear modiolus in patients with enlarged endolymphatic duct and sac syndrome,⁹⁻¹¹ agenesis of the cochlear nerve,⁶ and X-linked sensorineural hearing loss¹² and in those who are candidates for a cochlear implant.¹³ The cochlear modiolus is also a target structure for future cell replacement therapy of the inner ear.^{14,15} To our knowledge, ours is the first report evaluating enhancement of the cochlear modiolus by diagnostic imaging.

The distribution routes of an intratympanically administered agent are important in the development of otological medicine, such as intratympanic gentamicin therapy for Meniere's disease, intratympanic steroid therapy for sudden deafness, and future cell replacement therapies for the inner ear. Because human sensory epithelium and spiral ganglion neurons do not regenerate after injury or aging, cell replacement is highly anticipated for

Table. Summary of patients and results of enhancement

	Age (years)	Sex	Disease or symptom	CR of modiolus in inject- ed side	CR of modiolus in non-in- jected side	CR of CSF of IAC fun- dus in in- jected side	CR of CSF of IAC fundus in non-inject- ed side	Grade of endolym- phatic hydrops in cochlea	Grade of endolym- phatic hydrops in vestibule
1	26	M	Meniere's disease	0.88	-0.63	-2.11	-4.88	2	2
2	46	M	Meniere's disease	1.06	-0.58	-1.97	-4.42	2	2
3	65	M	Meniere's disease	1.05	-0.19	-1.55	-4.35	2	2
4	25	F	Meniere's disease	-0.06	-0.65	-2.61	-4.13	1	1
5	16	F	Meniere's disease	-0.55	-0.76	-2.80	-3.30	2	2
6	33	F	Low-tone hearing loss	0.54	-0.08	-0.73	-3.38	1	1
7	54	F	Sudden deafness	1.59	-0.48	-0.97	-3.87	0	0
8	53	M	Meniere's disease	0.21	-0.27	-1.69	-5.00	2	1
9	26	M	Sudden deafness	0.23	-1.17	-2.97	-4.59	2	2
10	57	M	Meniere's disease	2.50	-0.25	-1.69	-3.46	2	2
11	67	F	Meniere's disease	1.54	-0.20	-1.00	-2.90	1	2
12	80	F	Delayed endolym- phatic hydrops	0.14	-0.98	-3.03	-3.43	2	2
13	59	M	Meniere's disease	3.90	-0.59	-0.10	-4.03	2	2
14	53	M	Meniere's disease	4.03	-0.83	-0.45	-3.20	2	2
15	38	F	Meniere's disease	1.32	-0.45	-3.23	-3.45	0	1
16	68	M	Meniere's disease	0.26	-0.20	-3.13	-3.66	2	2
17	67	F	Meniere's disease	0.45	-0.86	-2.09	-5.33	2	2
18	59	M	Meniere's disease	0.63	-0.07	-1.92	-3.20	1	2
19	70	F	Meniere's disease	0.94	0.13	-1.26	-2.97	1	1
Mean	50.6			1.09*	-0.48*	-1.86**	-3.876**		

* $P < 0.01$ ** $P < 0.01$

CR, contrast ratio; CSF, cerebrospinal fluid; IAC, internal auditory canal

treating hearing loss and other disorders of the inner ear.^{14,15} Stem cells and embryonic neurons would be transplanted to the scala tympani through the round window membrane, the most accessible route from outside the inner ear. In an animal model, implanted cells were found near spiral ganglions after migrating through pores in the cochlear modiolus.¹⁴ Knowledge of individual microscopic anatomy of the cochlear modiolus will be important to successful cell replacement therapies.⁵

The cochlear modiolus is also important for homeostasis of the inner ear fluid environment.⁵ Communication between the scala tympani and scala vestibuli depends on the canalicular system in the modiolus. Communication between the perilymph and CSF in the IAC, which also seems to depend on the modiolus, is important for production of perilymph.⁵ Thus, functional evaluation of the cochlear modiolus appears to be vitally important for the development of otological medicine.

A previous study suggested that communication between the perilymph and CSF occurs mostly through the modiolus and not the cochlear aque-

duct or singular canal because no such communication was seen in patients with a potentially immature modiolus.⁶ Those patients with potentially immature modiolus had enlarged endolymphatic duct and sac syndrome or agenesis of the cochlear nerve. The present study showed a positive correlation between the CR of the modiolus and of CSF in the IAC fundus. Combined findings of the previous and current study suggest further support that communication routes exist in the modiolus.

There was no significant correlation between the CR of the modiolus and the grade of endolymphatic hydrops. If there are communication routes between perilymph and CSF in the IAC fundus, the CR of the modiolus would naturally depend on the concentration of Gd-DTPA in the cochlear perilymph space, which, in turn, depends on the permeability of the round window membrane, clearance function of the Eustachian tube, desquamation over the round window, clearance function of the modiolus, and other variables.¹⁶ In addition, the distribution of Gd-DTPA in the perilymph differs greatly among individuals.¹⁶ Even if there is a rela-

Fig. 1. A 59-year-old man with left Meniere's disease. Images were obtained 24 hours after intratympanic injection of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA) into the left ear. (a) The right cochlear modiolus (arrow) is seen as a gray structure on 3-dimensional inversion recovery turbo spin echo with real reconstruction (3D-real IR) imaging, with a signal level similar to that of surrounding bone in the center of the cochlear basal turn. (b) The left cochlear modiolus (arrow) shows a signal intensity between that of surrounding bone and enhanced perilymph (P). (c) Constructive interference in steady state (CISS) image of the right ear for reference. The modiolus is seen as a structure with low signal (arrow). (d) CISS image of the left ear for reference. The modiolus is seen as a structure with low signal (arrow). (e) An example of region of interest (ROI) definition. Referring to neighboring slices of 3D-real IR and CISS imaging, we defined the ROI in the modiolus (ROI #1) to exclude the partial-volume effect from enhanced perilymph. The ROI in the cerebellum (ROI #2) was defined with a diameter of 1 cm.

Fig. 2. This graph shows the correlation between the contrast ratio (CR) of the modiolus on the injected side and the CR of cerebrospinal fluid (CSF) in the fundus of the internal auditory canal (IAC). The number of subjects was 19. There was a significantly positive correlation.

tion between modiolar structure and the grade of endolymphatic hydrops, other factors may mask the correlation.

The present study has several limitations. One is that the study population showed symptoms such as hearing loss or vertigo but included neither healthy subjects nor deaf patients.

In addition, although we struggled to exclude the partial-volume averaging effect of perilymph completely for quantitative analysis of the modiolar signal, the complex shape of the modiolus may have prevented total exclusion, even with the $0.4 \text{ mm} \times 0.4 \text{ mm} \times 0.8 \text{ mm}$ voxel size of the present 3D-real IR protocol.

A previous study using 3D-FLAIR imaging acquired with the SPACE (sampling perfection with application optimized contrasts with different flip angle evolution) technique^{6,17} showed communication between the perilymph and CSF in the IAC fundus and no enhancement of the modiolus with a voxel size of $0.7 \text{ mm} \times 0.7 \text{ mm} \times 0.8 \text{ mm}$. This may have been due to the small size of the modiolus and the small amount of Gd-DTPA it contained as well as to a low signal-to-noise ratio in the vicinity of the modiolus during 3D-FLAIR acquisition with a 12-channel head coil and a relatively long echo train length of 119. We applied higher spatial resolution and shorter echo train length using 3D-real IR and

achieved a higher signal-to-noise ratio using a 32-channel head coil. These factors are thought to have enabled the visualization of cochlear modiolar enhancement synergistically.

In conclusion, space in the cochlear modiolus allows distribution of Gd-DTPA from perilymph in the labyrinth and is suggested to connect perilymph and CSF in the IAC. Use of a 3D-real IR sequence and 32-channel coil at 3T with intratympanic administration of Gd-DTPA can reveal the microscopic anatomy of the cochlear modiolus. This procedure may be useful for evaluating functional abnormalities of the modiolus not detected by conventional imaging tests, although further study is necessary to establish the clinical indication of modiolar evaluation as shown in the present study. Evaluating the functional anatomy of the modiolus in individual patients may be important for developing otological therapies, such as intratympanic drug administration or cell replacement for the inner ear.

References

1. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope* 2007; 117: 415-420.

2. 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; 18:920–924.
3. Nakashima T, Naganawa S, Katayama N, et al. Clinical significance of endolymphatic imaging after intratympanic gadolinium injection. *Acta Otolaryngol Suppl* 2009; 560:9–14.
4. Zou J, Pyykkö I, Bjelke B, Dastidar P, Toppila E. Communication between the perilymphatic scalae and spiral ligament visualized by *in vivo* MRI. *Audiol Neurotol* 2005; 10:145–152.
5. Rask-Andersen H, Schrott-Fischer A, Pfaller K, Glueckert R. Perilymph/modiolar communication routes in the human cochlea. *Ear Hear* 2006; 27: 457–465.
6. Naganawa S, Satake H, Iwano S, Sone M, Nakashima T. Communication between cochlear perilymph and cerebrospinal fluid through the cochlear modiolus visualized after intratympanic administration of Gd-DTPA. *Radiat Med* 2008; 26: 597–602.
7. Naganawa S, Nakashima T. Cutting edge of inner ear MRI. *Acta Otolaryngol Suppl* 2009; 560:15–21.
8. Nakashima T, Naganawa S, Pyykko I, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. *Acta Otolaryngol Suppl* 2009; 560: 5–8.
9. Naganawa S, Ito T, Iwayama E, et al. MR imaging of the cochlear modiolus: area measurement in healthy subjects and in patients with a large endolymphatic duct and sac. *Radiology* 1999; 213: 819–823.
10. Lemmerling MM, Mancuso AA, Antonelli PJ, Kubilis PS. Normal modiolus: CT appearance in patients with a large vestibular aqueduct. *Radiology* 1997; 204:213–219.
11. Naganawa S, Koshikawa T, Iwayama E, et al. MR imaging of the enlarged endolymphatic duct and sac syndrome by use of a 3D fast asymmetric spin-echo sequence: volume and signal-intensity measurement of the endolymphatic duct and sac and area measurement of the cochlear modiolus. *AJNR Am J Neuroradiol* 2000; 21:1664–1669.
12. Talbot JM, Wilson DF. Computed tomographic diagnosis of X-linked congenital mixed deafness, fixation of the stapedial footplate, and perilymphatic gusher. *Am J Otol* 1994; 15:177–182.
13. van Wermeskerken GK, Prokop M, van Olphen AF, Albers FW. Intracochlear assessment of electrode position after cochlear implant surgery by means of multislice computer tomography. *Eur Arch Otorhinolaryngol* 2007; 264:1405–1407.
14. Hu Z, Ulfendahl M. Cell replacement therapy in the inner ear. *Stem Cells Dev* 2006; 15:449–459.
15. Martinez-Monedero R, Edge AS. Stem cells for the replacement of inner ear neurons and hair cells. *Int J Dev Biol* 2007; 51:655–661.
16. Yoshioka M, Naganawa S, Sone M, Nakata S, Teranishi M, Nakashima T. Individual differences in the permeability of the round window: evaluating the movement of intratympanic gadolinium into the inner ear. *Otol Neurotol* 2009; 30:645–648.
17. 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.