Neuroradiology (2012) 54:1161–1169
DOI 10.1007/s00234-012-1078-9

HEAD AND NECK RADIOLOGY

Gadolinium distribution in cochlear perilymph: differences between intratympanic and intravenous gadolinium injection

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Received: 23 April 2012 / Accepted: 23 July 2012 / Published online: 3 August 2012

Abstract
Introduction Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging 24 h after intratympanic gadolinium injection (IT method) or 4 h after intravenous injection (IV method) has been used to visualize endolymphatic hydrops in Ménière's disease. The aims of this study were to evaluate the difference in gadolinium distribution in cochlear perilymph between the two methods by comparing the enhancement of the basal and apical turns and clarify the pharmacokinetics in cochlear perilymph.
Methods A total of 24 ears of 22 patients who underwent the IT method (gadolinium-diethylene-triamine pentaacetic acid was diluted eightfold with saline) and 28 ears of 17 patients who underwent the IV method (double dose of gadoteridol (0.5 mmol/ml); 0.2 mmol/kg body weight in total amount) at 3 T was analyzed retrospectively. Regions of interest of the perilymph of the cochlear basal turn (B), of the apical turn (A), and the medulla oblongata (M) were determined on each patient. The signal intensity ratios between B and M (BMR), A and M (AMR), and A and B (ABR) were subsequently evaluated.
Results The IT-BMR (2.63±1.22) was higher than the IV-BMR (1.46±0.45) ($p<0.001$). There was no significant difference between the IT- (1.46±0.76) and IV-AMRs (1.21±0.48) ($p=0.15$). The IT-ABR (0.58±0.17) was lower than the IV-ABR (0.84±0.22) ($p<0.001$).
Conclusion Gadolinium was predominantly distributed in the basal turn compared with the apical turn in the IT method, whereas it was more uniformly distributed in the IV method. These characteristics might reflect the distribution of therapeutic medications administered either intratympanically or systemically.

Keywords Magnetic resonance imaging · Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) · Intratympanic gadolinium injection · Intravenous gadolinium injection · Cochlear pharmacokinetics

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Introduction

Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging can minimize the undesired ghosts of fluid flow [1] and enable recognition of the subtle compositional changes and the contrast effect in the lymph fluid in the inner ear [2–4]. 3D-FLAIR imaging 24 h after intratympanic gadolinium injection (IT method) has been reported to visualize perilymph and endolymph fluid separately and to identify the presence of endolymphatic hydrops [5–7]. 3D-FLAIR has been reported to be suited for contrast enhancement assessment 24 h after intratympanic gadolinium injection [8]. On the other hand, 3D-FLAIR imaging 4 h after intravenous gadolinium injection (IV method) has also been recently reported to visualize endolymphatic hydrops [9, 10]. The characteristics of the distribution of gadolinium in the cochlear perilymph after intratympanic or intravenous injection might reflect the distribution of therapeutic medications administered either intratympanically or systemically, such as gentamicin or steroids [11–16]. However, to the best of our knowledge, a detailed

investigation of the characteristics of gadolinium distribution in the cochlear perilymph for the two methods in human patients has not been previously reported. Consequently, the principal purpose of the present study was to clarify these characteristics through evaluation of the signal intensity of the cochlear perilymph in both the basal and apical turns of the cochlea.

Materials and methods

Study population

The records of 52 ears of 39 patients who underwent the IT method (24 ears of 22 patients) or IV method (28 ears of 17 patients) magnetic resonance imaging (MRI) of the inner ear at our hospital were retrospectively examined. All patients were clinically suspected of having Ménière's disease, and they underwent the IT method or the IV method for detailed examination to determine whether endolymphatic hydrops was present. The IT method group included 22 consecutive patients (10 men, 12 women; aged 16–70 years; mean age, 49.5 years) who underwent intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid (Gd-DTPA: Magnevist, Bayer, Osaka, Japan) from October 2008 to August 2009. Twenty patients underwent unilateral intratympanic gadolinium injection, and two patients underwent bilateral injection. Therefore, the IT method group of the present study consisted of 24 ears. On the other hand, the IV method group included 17 consecutive patients (7 men, 10 women; aged 21–81 years; mean age, 47.5 years) who underwent double dose intravenous administration of gadoteridol (Gd-HP-DO3A: ProHance, Eisai, Tokyo, Japan) from September 2009 to June 2010. Eleven patients were suspected to have bilateral Ménière's disease, and six patients were suspected to have unilateral disease. Affected and unaffected sides were determined by the otologist in charge based on clinical assessments of hearing loss, tinnitus, and aural fullness. Previous reports suggested that there is a difference in the contrast effect of the perilymph of the cochlear basal turns between the affected and unaffected sides in patients with unilateral Ménière's disease [17, 18]. Therefore, the IV method group of the present study consisted of only 28 affected ears (22 ears of 11 bilateral patients and 6 ears of 6 unilateral patients) to avoid the influence of the existence or nonexistence of Ménière's disease. In the present study, the IT and IV method groups were divided between August and September 2009, and the observation periods and the number of ears observed in the two groups were almost the same. Written, informed consent was obtained from all patients, and the study was approved by the Ethics Review Committee of our institution (approval numbers 369, 369–2, 369–3, and 369–4).

Intratympanic gadolinium injection

Intratympanic injection of gadolinium was performed as reported previously [5]. The results of the previous study indicated a delay of 24 h between intratympanic gadolinium injection and MRI to be optimal to allow wide gadolinium distribution in the perilymphatic space of the labyrinth.

Briefly, Gd-DTPA (500 mmol/L) was diluted eightfold with saline (*v*/*v* 1:7) and injected intratympanically using a 23-gauge needle and a 1-mL syringe after the patient was placed in the supine position with the head turned approximately 30° away from the sagittal line toward the opposite ear. The diluted Gd-DTPA was injected until a backflow of fluid into the external ear was observed through a microscope, resulting in an injected volume of 0.4 to 0.5 mL per patient. After the injection, the patient remained in the supine position for 60 min with the head turned approximately 60° away from the sagittal line toward the opposite ear. In the two patients who underwent bilateral injection, the injection of one ear was performed after the injection of the opposite ear was finished. Gentamicin was not injected at the same time as Gd-DTPA. All patients underwent MRI 24 h after intratympanic gadolinium injection.

Intravenous gadolinium injection

All patients underwent intravenous administration of a double dose (0.4 mL/kg body weight, i.e., 0.2 mmol/kg body weight) of Gd-HP-DO3A. Although the standard dose of gadolinium contrast agent is 0.2 mL/kg body weight, a dose of 0.4 mL/kg body weight for Gd-HP-DO3A is permitted only in our country by the Japanese governmental health insurance system if the aim is to visualize metastatic brain tumors. Therefore, Gd-HP-DO3A was used for double dose intravenous administration with written, informed consent from all patients as a research tool, along with study approval from the Ethics Review Committee of our institution. The gadolinium contrast agents used in the IT and IV methods were different because the evaluation of endolymphatic hydrops by the IT method using Gd-DTPA was performed in a separate clinical study prior to the administration of the IV method using a double dose of Gd-HP-DO3A. All patients underwent MRI 4 h after intravenous gadolinium injection, because a delay of 4 h between intravenous gadolinium injection and MRI is reported to be optimal to allow wide gadolinium distribution in the lymphatic space of the labyrinth in healthy subjects [19].

MRI protocol

All scans were performed on a 3 T MRI scanner (Magnetom Trio; Siemens AG, Erlangen, Germany) using a receive-only, 32-channel, phased-array coil. Surface coils were not used to avoid extreme nonuniformity in field of view.

Furthermore, it was impossible to add coils to a 32-channel head coil because of the limitation of connector. Patients underwent 3D-FLAIR imaging 24 h after intratympanic injection of diluted Gd-DTPA or 4 h after intravenous injection of a double dose of Gd-HP-DO3A. The images of MR cisternography (3D-constructive interference in the steady state: 3D-CISS or 3D-turbo spin echo T2-weighted imaging: TSE T2WI) for anatomical reference were also obtained at the same time.

The parameters for 3D-FLAIR were as follows: repetition time (TR), 9,000 ms; effective echo time (TE), 458 ms; inversion time (TI), 2,500 ms; variable flip-angle echo train with average flip angle, 120°; echo train length, 119; matrix size, 256×256; 48 axial, 0.8-mm-thick slices covering the labyrinth with a 180-mm×150-mm field of view (FOV); generalized autocalibrating partially parallel acquisition (GRAPPA) acceleration factor, 2; voxel size, 0.7 mm× 0.7 mm×0.8 mm; number of excitations (NEX), 2; scan time, 5 min 26 s; readout bandwidth, 592 Hz/pixel; and echo spacing, 3.7 ms.

The parameters for 3D-CISS were as follows: TR, 6.4 ms; TE, 3.2 ms; flip angle, 50°; matrix size, 256×256; 128 axial, 0.4-mm-thick slices; FOV, 140 mm×140 mm; voxel size, 0.5 mm×0.5 mm×0.4 mm; NEX, 1; scan time, 5 min 8 s; and readout bandwidth, 543 Hz/pixel.

The parameters for 3D-TSE T2WI were as follows: TR, 1,500 ms with driven equilibrium pulse (RESTORE); effective TE, 134 ms; flip angle, 90°; echo train length, 23; matrix size, 384×384; 12 axial, 2-mm-thick slices; FOV, 160 mm×160 mm; GRAPPA acceleration factor, 2; voxel size, 0.4 mm×0.4 mm×2 mm; NEX, 1; scan time, 2 min 32 s; readout bandwidth, 213 Hz/pixel; and echo spacing, 12.2 ms.

MRI and patient group evaluation

The images were analyzed on a picture archiving and communication system (PACS) workstation (Rapideye Station; Toshiba Medical Systems Corporation, Otawara, Japan). For each patient who underwent intratympanic gadolinium injection, a circular 0.6-mm^2 regions of interest (ROI) of the injected side cochlea and a circular 50-mm^2 ROI of the medulla oblongata were determined on 3D-FLAIR images at a workstation (Fig. 1). In the same way, for each patient who underwent intravenous gadolinium injection, a circular 0.6-mm^2 ROI of the affected side cochlea and a circular 50-mm^2 ROI of the medulla oblongata were determined on 3D-FLAIR images (Fig. 2). On each cochlea, the ROIs were set on the perilymphatic space of the scala tympani of the basal and apical turns referring to the cisternography. The ROI of the medulla oblongata was set on the center of the medulla oblongata at the identical slice of the basal turn of the cochlea. The ratio of the signal intensity of basal turn perilymph of each cochlea to that of the medulla oblongata (BMR), the ratio of the signal intensity of apical turn perilymph of each cochlea to that of the medulla oblongata (AMR), and the ratio of the signal intensity of apical to basal turn perilymph of each identical cochlea (ABR) were evaluated. The results by simple measurement of the signal intensity ratio on MRI have been reported to correlate well with those by a more quantitative method [20]. One radiologist (M.Y.) with knowledge of prior intratympanic or intravenous gadolinium injection and clinical diagnoses performed these measurements. Blinded measurement of the signal without knowing which method was performed was not feasible in the present study because the unilaterally injected IT method patients show a high signal of the unilateral inner ear (Fig. 1), while the IV method patients show a contrast effect on both inner ears (Fig. 2). To assure the reliability of the signal intensities measured in the small ROIs of the cochlea and to diminish the measurement error, every ROI was determined twice for each patient on different days, and the signal intensities of the two measurements were averaged for analysis.

The degree of cochlear endolymphatic hydrops on MRI, the average hearing level, and the percentage of patients with rotatory vertigo were also compared with the IT and IV methods. On a PACS workstation, one experienced radiologist (S.N.) graded the degree of cochlear endolymphatic hydrops on the IT and IV methods from 0 to 2 according to the previously reported grading criteria [21], with 2 indicating significant; 1, mild; and 0, no endolymphatic hydrops (Fig. 3). Enhancement of the perilymph that was too faint to evaluate endolymphatic hydrops was graded as "faint." To evaluate the reproducibility of grading, another radiologist (M.Y.) who had experience of grading and no knowledge of the results of grading by prior observer also graded the degree of cochlear endolymphatic hydrops on the IT and IV methods and the interobserver variability was calculated. For each patient, the average hearing level calculated as the mean of the hearing levels measured at 500, 1,000, and 2,000 Hz was searched on the electronic medical record within 5 months of MRI. The presence of rotatory vertigo prior to MRI was also searched on the electronic medical record for each patient.

The existence or nonexistence of gross body motion (i.e., induced motion artifact that precluded the detection of the cochlear margin), visible signal intensity abnormalities of the medulla oblongata (e.g., infarction, degenerative disorder), or mastoid air cells (e.g., otitis media, cholesterol granuloma) was assessed visually at the same time as cochlear MRI analysis. The presence or absence of side effects (e.g., nausea, vomiting, rash, subjective exacerbation of vertigo or hearing loss) attributed to the IT method or IV method was also reviewed using the patients' electronic medical records.

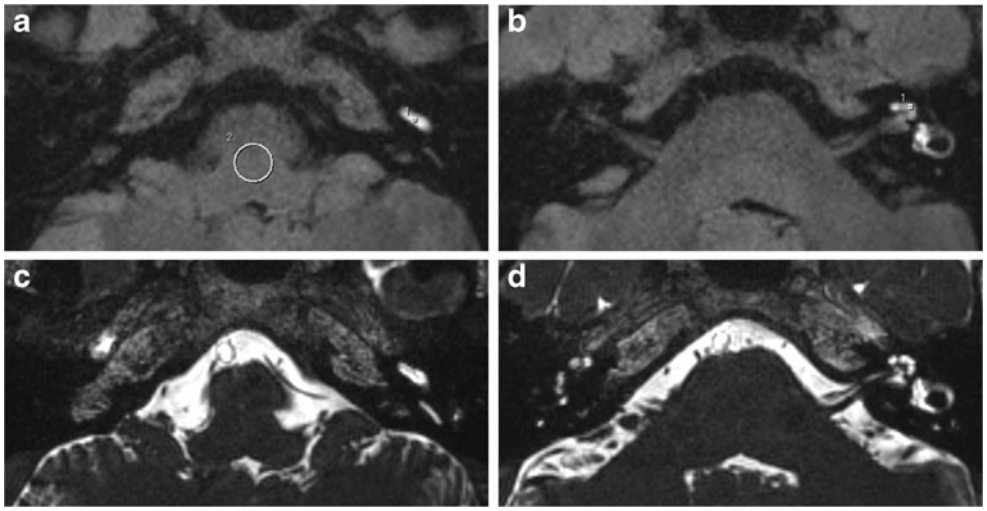

Fig. 1 3D-FLAIR images at the levels of the cochlear basal turns (**a**) and apical turns (**b**) after intratympanic gadolinium injection of the left side (IT method) of a 45-year-old woman who was suspected to have Ménière's disease are presented. The identical slices of 3D-CISS images are also presented (**c**, **d**). The intratympanic gadolinium injection was administered 24 h prior to MRI, and the left inner ear perilymph shows extremely high signal intensity on 3D-FLAIR. On these 3D-FLAIR images, 0.6 mm^2 circular ROIs on the scala tympani of the cochlear basal turn and apical turn of the gadolinium-injected side are set referring to the 3D-CISS. The 50-mm^2 circular ROI on the center of the medulla oblongata is also set at the identical slice of the basal turns of the cochleae

Statistical analysis

Student's t test was used to compare differences in BMR, AMR, and ABR between the IT and IV methods and in the mean age and average hearing level between the IT and IV method patients. Fisher's exact test was used to compare the difference in the sex ratio, the degree of cochlear endolymphatic hydrops, and the percentage of patients with rotatory vertigo between the IT and IV methods. The κ coefficient was used to evaluate the interobserver variability on the grading of the degree of cochlear endolymphatic hydrops. In this study, $p<0.05$ was taken as significant.

Results

No image of any patient showed gross body motion during examination or visible abnormalities of the medulla oblongata

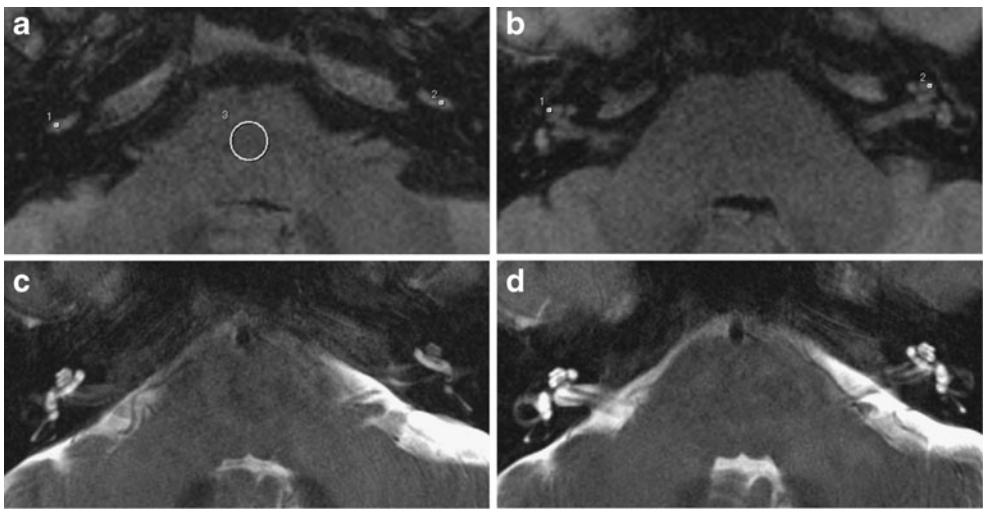

Fig. 2 3D-FLAIR images at the levels of the cochlear basal turns (**a**) and apical turns (**b**) after intravenous gadolinium injection (IV method) of a 38-year-old man who was suspected to have bilateral Ménière's disease are presented. The identical slices of 3D-TSE T2WI are also presented (**c**, **d**). The intravenous gadolinium injection was administered 4 h prior to MRI, and the perilymph of both inner ears shows a high signal intensity on 3D-FLAIR. On these 3D-FLAIR images, 0.6 mm^2 circular ROIs on the scala tympani of the cochlear basal turns and apical turns of both sides are set referring to the 3D-TSE T2WI. The 50-mm^2 circular ROI on the center of the medulla oblongata is also set at the identical slice of the basal turns of the cochleae

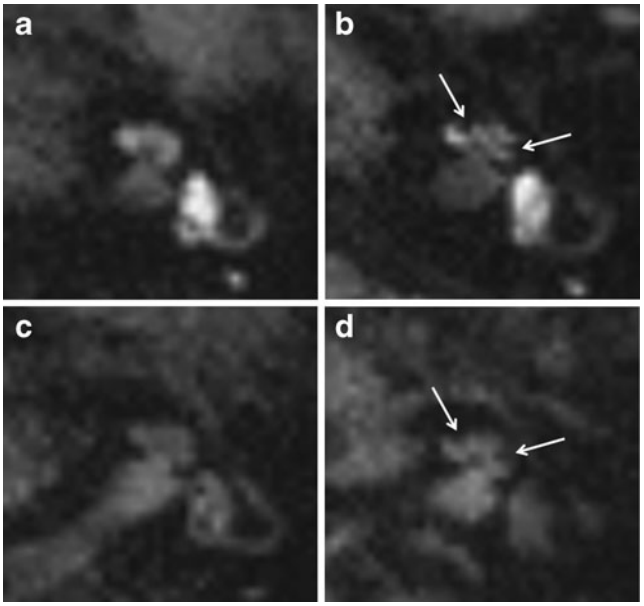

Fig. 3 3D-FLAIR images of the left cochlea at the level of the modiolus of a 67-year-old woman (**a**), a 68-year-old man (**b**), a 63-year-old woman (**c**), and a 28-year-old man (**d**) with suspected Ménière's disease are presented. Images **a** and **b** were obtained 24 h after intratympanic gadolinium injection and images **c** and **d** were obtained 4 h after intravenous gadolinium injection. On all images, the perilymph of the cochlea shows a high signal intensity. On images **b** and **d**, significant endolymphatic hydrops in the cochlea can be recognized as areas of low intensity (*arrows* on **b** and **d**) and the area of the endolymphatic space exceeds the area of the scala vestibule (endolymphatic hydrops grade 2). In contrast, on images **a** and **c**, there are no endolymphatic hydrops in the cochlea and the recognition of the endolymphatic space is difficult (endolymphatic hydrops grade 0)

or mastoid air cells. The IT method BMR (2.63±1.22; range, 0.43 to 4.37; n=24) was significantly higher than the IV method BMR (1.46±0.45; range, 0.64 to 2.67; n=28) (p< 0.001, Fig. 4). There was no significant difference between the IT method AMR (1.46±0.76; range, 0.26 to 3.21; n=24) and the IV method AMR (1.21±0.48; range, 0.59 to 2.72; n=28) (p=0.15, Fig. 5). The IT method ABR (0.58±0.17; range, 0.29 to 0.81; n=24) was significantly lower than the IV method ABR (0.84±0.22; range, 0.59 to 1.65; n=28) (p< 0.001, Fig. 6).

Tables 1 and 2 represent the patients' characteristics using the IT and IV methods. The mean age (IT method—49.5±16.1, n=22; IV method—47.5±15.8, n=17), sex ratio, average hearing level (IT method—39.1±22.9 dB, n= 24; IV method—45.2±31.2 dB, n=28), and percentage of patients with rotatory vertigo did not differ significantly between the IT method and IV method patients (p=0.70 for mean age, p=0.52 for sex ratio, p=0.43 for average hearing level, p=0.22 for rotatory vertigo). The degree of endolymphatic hydrops could be evaluated on 22 of 24 ears of the IT method and all 28 ears of the IV method patients. Two ears of IT method patients could not be evaluated because of faint enhancement. The degree of endolymphatic hydrops was significantly higher on the IT method than on the IV method (p<0.01). This grading of the degree of cochlear endolymphatic hydrops had substantial coincidence with the grading by another observer (IT method: κ coefficient, 0.702; 95 % confidence interval (CI), 0.470, 0.934; IV method: κ coefficient, 0.671; 95 % CI, 0.412, 0.929).

The results of the comparison of BMR, AMR, and ABR between IT and IV methods only in ears with endolymphatic hydrops (i.e., ears graded as significant or mild endolymphatic hydrops) were the same as the results in all ears which were described above (The IT method BMR (2.86±1.22; range, 1.21 to 4.37; n=15) was significantly higher than the IV method BMR (1.37±0.23; range, 1.06 to 2.00; n=13; p< 0.001); there was no significant difference between the IT method AMR (1.42±0.75; range, 0.55 to 3.21; n=15) and

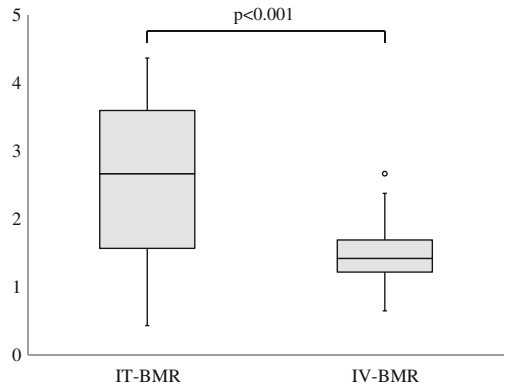

Fig. 4 Signal intensity ratios between basal turn perilymph of each cochlea and medulla oblongata (BMR) on 3D-FLAIR imaging 24 h after intratympanic gadolinium injection (IT method) and 3D-FLAIR imaging 4 h after intravenous gadolinium injection (IV method). The IT method BMR (2.63±1.22; range, 0.43 to 4.37; n=24) is significantly higher than the IV method BMR (1.46±0.45; range, 0.64 to 2.67; n=28) (p<0.001)

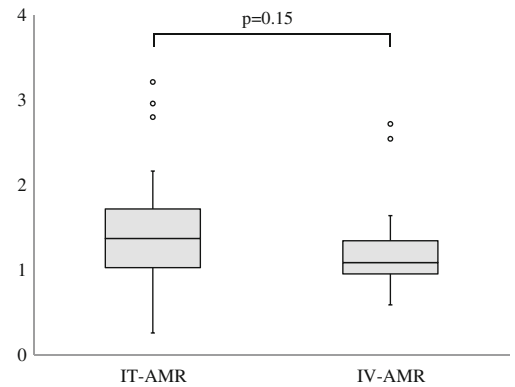

Fig. 5 Signal intensity ratios between apical turn perilymph of each cochlea and medulla oblongata (AMR) on 3D-FLAIR imaging 24 h after intratympanic gadolinium injection (IT method) and 3D-FLAIR imaging 4 h after intravenous gadolinium injection (IV method). There is no significant difference between the IT method AMR (1.46±0.76; range, 0.26 to 3.21; n=24) and the IV method AMR (1.21±0.48; range, 0.59 to 2.72; n=28) (p=0.15)

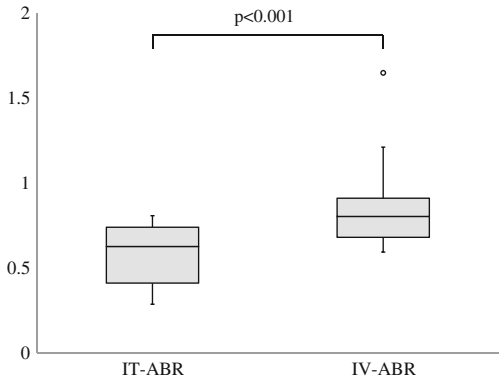

Fig. 6 Signal intensity ratios between apical turn perilymph and basal turn perilymph of each identical cochlea (ABR) on 3D-FLAIR imaging 24 h after intratympanic gadolinium injection (IT method) and 3D-FLAIR imaging 4 h after intravenous gadolinium injection (IV method). The IT method ABR (0.58±0.17; range, 0.29 to 0.81; n=24) is significantly lower than the IV method ABR (0.84±0.22; range, 0.59 to 1.65; n=28) (p<0.001)

the IV method AMR (1.06±0.22; range, 0.73 to 1.49; n=13; p=0.11); the IT method ABR (0.52±0.19; range, 0.29 to 0.80; n=15) was significantly lower than the IV method ABR (0.78±0.11; range, 0.59 to 0.93; n=13; p<0.001)). No side effects were observed in either IT or IV method patients.

Discussion

The results of the present study suggest that the IT method provides higher perilymph enhancement of the basal turn than the IV method, and the gadolinium contrast agents distribute predominantly in the basal turn perilymph compared with the apical turn on the IT method. This distribution would arise as a result of the transition of gadolinium agents from the tympanic cavity to the perilymph space of the scala tympani of the basal turn through the round window and diffusion in the perilymph of the scala tympani. The result that the agents injected intratympanically distribute predominantly in the cochlear basal turn compared with the apical turn is in agreement with the results of the previous animal studies using markers such as horseradish peroxidase or trimethylphenylammonium [22, 23]. In those previous studies, nonuniform distribution was noted, with marker concentration higher in the basal turn near the round window than in the apical turn. The present study is the first to report comparable results to those previous animal studies using MRI with intratympanic gadolinium injection technique in human patients.

It is important to understand the characteristic pharmacokinetics in the inner ear after intratympanic drug

Table 1 Patients' characteristics using the IT method

Patient no.	Age	Sex	Side	Average hearing level (dB)[a]	Rotatory vertigo	Degree of endolymphatic hydrops[b]
1	16	F	L	13.3	−	1
2	57	M	L	16.7	−	2
3	40	F	L	11.7	+	faint
4	27	F	R	63.3	+	2
5	38	F	L	30	−	1
6	45	M	L	50	+	2
7	70	F	L	73.3	+	2
8	41	M	R	16.7	+	1
9	39	M	R	51.7	+	1
10	53	M	R	63.3	+	2
11	38	F	R	51.7	−	0
12	68	M	L	43.3	+	2
13	67	F	L	81.7	+	2
14	59	F	L	58.3	−	2
15	70	F	L	45	−	1
16	45	F	L	30	+	0
17	26	M	L	10	−	0
18	65	F	L	51.7	−	2
19	65	M	R	65	+	2
20	36	M	L	55	+	faint
21	67	F	R	15	+	0
			L	15		0
22	58	M	R	13.3	−	0
			L	13.3		0

[a]The mean of the hearing levels measured at 500, 1,000, and 2,000 Hz

[b]Two indicating significant; 1, mild; and 0, no endolymphatic hydrops. The degree of endolymphatic hydrops could be evaluated on 22 of 24 ears. Two ears could not be evaluated because of faint enhancement

Table 2 Patients' characteristics using the IV method

Patient no.	Age	Sex	Side	Average hearing level (dB)[a]	Rotatory vertigo	Degree of endolymphatic hydrops[b]
1	63	F	R	45	−	0
			L	50		0
2	38	M	R	20	−	0
			L	23.3		1
3	55	M	R	26.7	−	0
4	29	F	R	23.3	−	0
			L	106.7		0
5	36	F	R	31.7	−	0
6	46	F	R	80	+	1
			L	50		1
7	42	F	L	86.7	−	0
8	28	M	R	20	+	1
			L	115		2
9	44	F	R	10	−	0
			L	8.3		0
10	62	M	R	45	−	1
11	21	F	R	38.3	+	0
			L	38.3		0
12	81	M	R	70	+	1
			L	95		1
13	52	M	R	40	−	2
14	59	F	L	16.7	+	1
15	55	M	R	83.3	+	0
			L	11.7		1
16	33	F	R	56.7	−	0
			L	55		0
17	64	F	R	10	+	1
			L	10		1

[a]The mean of the hearing levels measured at 500, 1,000, and 2,000 Hz

[b]Two indicating significant; 1, mild; and 0, no endolymphatic hydrops

injection because intratympanic injection therapies have been used clinically [11–14]. The previous studies suggest that steroids delivered intratympanically can achieve higher concentrations in perilymph than when administered by either intravenous or oral routes [24–26]. However, the permeability of the round window was reported to be poor in 13 % of ears in patients with inner ear disorders who underwent intratympanic gadolinium injection [27]. On the other hand, the recently published, randomized study showed that intratympanic treatment was not inferior to oral prednisone treatment among patients with idiopathic sudden sensorineural hearing loss (SNHL) [28]. From the results of the present study and the previous reports [22, 23], the intratympanically injected drugs should distribute predominantly in the basal turn rather than in the apical turn perilymph. However, gentamicin and steroids do not necessarily behave in the same way as gadolinium. In fact, there is a recent report that showed that the use of intratympanic gadolinium had no added value in predicting the clinical outcome of intratympanic gentamicin application [29].

On the other hand, the results of the present study suggest that the gadolinium contrast agents distribute more uniformly in cochlear perilymph in the IV method than in the IT method. This distribution would arise as a result of the transition of gadolinium agents from the cochlear blood vessels to the cochlear perilymph [30], whereas gadolinium agents would diffuse gradually in the perilymph of the scala tympani from the basal turn near the round window to the apical turn in the IT method. It is also important to understand the characteristic pharmacokinetics in the inner ear after systemic drug administration as in the case of intratympanic injection, because the systemic administration of steroids for the treatment of sudden SNHL has been reported previously [15, 16]. In patients treated by such systemic therapies, the drugs would distribute more uniformly in the cochlear perilymph compared with the patients administered

drugs intratympanically, based on the results of the present study. However, systemically administered drugs do not necessarily behave in the same way as gadolinium, as was described for intratympanic injection above.

The grading of the degree of cochlear endolymphatic hydrops could be made on the IV method as reliable as the IT method with substantial interobserver coincidence. In addition, the degree of endolymphatic hydrops could be evaluated on all ears of the IV method patients, although 2 of the 24 ears of IT method patients could not be evaluated because of faint enhancement. Furthermore, the IV method is able to investigate both ears with a single injection, less invasive, and able to avoid off-label use of gadolinium.

In the present patient groups, the degree of cochlear endolymphatic hydrops was higher with the IT method than with the IV method. Therefore, we cannot exclude the possibility of the effect of the difference in the degree of endolymphatic hydrops on the results of the present study. The relationship between the degree of endolymphatic hydrops and the gadolinium distribution in cochlear perilymph should be clarified in the future research project. It was also a limitation of the present study that the gadolinium contrast agents used in the IT and IV methods were different, and a control study of the contrast effect of these agents was not done (Gd-DTPA for the IT method—molecular weight, 742.79; osmotic pressure ratio to saline, approximately 7; viscosity, 3.03 mPa s, 37 °C; and T1 relaxivity (r1), 4.9 $(mmol/L)^{-1}s^{-1}$; Gd-HP-DO3A for the IV method—molecular weight, 558.69; osmotic pressure ratio to saline, approximately 2; viscosity, 1.3 mPa s, 37 °C; and r1, 4.6 $(mmol/L)^{-1}s^{-1}$). However, these differences in the gadolinium contrast agents would not have seriously affected the results of the present study because the r1s of Gd-DTPA and Gd-DO3A are approximately equal.

Overall, gadolinium contrast agents distributed predominantly in the basal turn perilymph, rather than in the apical turn, in the IT method group, whereas gadolinium contrast agents distributed more uniformly in the cochlear perilymph in the IV method group. These characteristics of the distribution of gadolinium contrast agents in the cochlear perilymph after intratympanic or intravenous injection in human patients might reflect the distribution of therapeutic medications administered either intratympanically or systemically. In addition, the grading of the degree of cochlear endolymphatic hydrops could be made on the IV method as reliable as the IT method.

Acknowledgments The authors would like to thank the radiological technologists of the MRI unit at Nagoya University Graduate School of Medicine for their contribution to the MRI examinations and Dr. Mitsuru Ikeda for his advice on the statistical analysis.

Conflict of interest We declare that we have no conflict of interest.

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