TECHNICAL NOTE

Imaging of Endolymphatic and Perilymphatic Fluid after Intravenous Administration of Single-dose Gadodiamide

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To visualize endolymph as bright signal after intravenous injection of single-dose gadodiamide, we shortened the inversion time of heavily T2-weighted 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) to 2050 ms. In 14 patients with suspected Ménière’s disease, we observed high signal of vestibular endolymph in all ears, including 6 ears without vestibular endolymphatic hydrops. We observed high signal of cochlear endolymph in 17 ears with cochlear endolymphatic hydrops but not 11 ears without cochlear endolymphatic hydrops.

Keywords: intravenous, magnetic resonance imaging, Ménière’s disease, 3D imaging

Introduction

Magnetic resonance (MR) imaging using 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) after intratympanic administration of gadolinium-based contrast material (GBCM) enabled visualization of endolymphatic hydrops in patients with Ménière’s disease.1 On 3D-FLAIR images, the signal intensity of perilymph containing GBCM increases, and that of endolymphatic space and surrounding bone both show values near zero. Thus, the boundary between bone and endolymphatic space is unclear (positive perilymph image [PPI]). To clarify the boundaries of endolymphatic space and surrounding bones and rule out partial volume averaging artifact from bones, shortening the inversion time of 3D-FLAIR was proposed.2 Optimal shortening suppresses the signal of perilymph with GBCM, instead giving high signal to endolymph without GBCM (positive endolymph image [PEI]). However, intratympanic administration is off-label use of GBCM and accompanied by a slightly invasive puncture of the tympanic membrane. Development of a method for detecting endolymphatic hydrops by intravenous injection of GBCM is desired. In recent years, heavily T2-weighted 3D-FLAIR (hT2W-3D-FLAIR) and imaging 4 hours after intravenous injection of single-dose GBCM (IV-SD-GBCM) was reported to achieve visualization of endolymphatic hydrops in patients with Ménière’s disease.3 Similar to 3D-FLAIR after intratympanic administration of GBCM, hT2W-3D-FLAIR images obtained after IV-SD-GBCM visualize the bone and endolymph space as nearly zero signals (PPI) so that the boundary between bone and endolymphatic space is unclear. Especially, cochlear endolymphatic space is smaller and closer to bone than vestibular endolymphatic space. Consequently, cochlear endolymphatic space is more susceptible than vestibular endolymph to partial volume averaging effect by surrounding bone.

We aimed to discover the inversion time to suppress perilymph signal and to demonstrate the feasibility of the method for PEI after IV-SD-GBCM in patients with clinically suspected Ménière’s disease.

Materials and Methods

All patients underwent MR scanning 4 hours after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) intravenous administration of gadolinium diethyleneetriaminepentaacetic acid-bis (methylene) (gadodiamide [Gd-DTPA-BMA]; Omniscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. The estimated glomerular filtration rate (eGFR) value of every patient exceeded 60 mL/min/1.73 m². Each
GFR was calculated using an equation reported by the Japanese Society of Nephrology for estimating GFR (eGFR) in Japanese patients based on serum creatinine level (Cr): 
\[ \text{eGFR (mL/min/1.73 m^2)} = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \] (if female, \( \times 0.739 \)).

Typically, inversion time around 2300 ms had been employed for hT2W-3D-FLAIR (PPI) to suppress the signal of endolymph 4 hours after IV-SD-GBCM. Optimal inversion time for 3D-FLAIR to suppress the signal of endolymph varies according to echo train length, echo spacing, and repetition time. As a pilot study, 2 female patients aged 73 and 66 years underwent hT2W-3D-FLAIR scan with decreased number of slices and decreased number of averaging varying the inversion time. Scan time to evaluate one inversion time took 2 min. Inversion time to suppress perilymph in the case of intratympanic GBCM injection was around 1000 ms. Gadolinium concentration in perilymph is expected to be far lower after IV-SD-GBCM than after intratympanic GBCM injection. Optimal inversion time to suppress perilymph signal should be expected to far exceed 1000 ms. We obtained 7 series images with inversion times of 2350, 2250, 2150, 2050, 1950, 1650, and 1350 ms. We measured signal intensity of perilymph and endolymph space for right and left ears in the 2 patients, manually drawing a region on interest (ROI) on a picture archiving and communication system (PACS) viewer (Rapideye, Toshiba Medical Systems, Tokyo, Japan), and selected optimal inversion time for perilymph and endolymph suppression. In both ears of both patients, signal was suppressed most with inversion time of 2050 ms for perilymph and 2250 ms for endolymph (Fig. 1). Therefore, we employed inversion times of 2050 ms for PEI and 2250 ms for PPI for the 14 subsequent patients not including these 2 patients.

We evaluated the 28 ears of the 14 patients (3 men, 11 women, aged 17 to 75 years) with clinically suspected Ménière’s disease based on observation of ear symptoms, vertigo, average hearing level on pure tone audiometry, various ontological tests, and clinical history by experienced otorhinolaryngologists.

All imaging was performed on a 3-tesla MR imaging unit (Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil.

Four hours after IV-SD-GBCM, all 14 patients underwent heavily T2-weighted MR cisternography for anatomical reference of total lymph fluid, with hT2W-3D-FLAIR with 2250-ms inversion time.

![Fig. 1](image_url)  
**Fig. 1.** Signal intensity of the endolymph and perilymph in the vestibule of 4 ears in 2 patients by various inversion time values. In all 4 ears, signal intensity shows lowest values at inversion time of 2250 ms for the endolymph and 2050 ms for the perilymph. E2L, endolymph of Patient #2 in left side; P1L, perilymph of Patient #1 in left side; P1R, perilymph of Patient #1 in right side; S.I., signal intensity. For the plot of endolymph signal, 4 kinds of dashed lines are used. For the plot of perilymph signal, 4 kinds of continuous lines are used.
Positive Endolymph Imaging by IV-GBCM

(hT\textsubscript{2}W-IR-2250, PPI) and hT\textsubscript{2}W-3D-inversion recovery with 2050-ms inversion time (hT\textsubscript{2}W-IR-2050, PEI).

Detailed scan parameters for MR cisternography follow. For heavily T\textsubscript{2}-weighted MR cisternographic images using variable flip angle 3D turbo spin-echo technique (SPACE: sampling perfection-with application-optimized contrasts by using different flip angle evolutions), parameters were: repetition time (TR), 4400 ms; echo time (TE), 544 ms; initial refocusing flip angle, 180°, rapidly decreased to constant flip angle of 120° for the turbo spin-echo refocusing echo train; echo train length, 173 with restore magnetization pulse (fast recovery pulse); matrix size, 322 × 384; 96 1.0-mm-thick axial slices covering the labyrinth; field of view (FOV), 15 × 18 cm; generalized autocalibrating partially parallel acquisition (GRAPPA) parallel imaging technique; acceleration factor, 2; number of excitations (NEX), 1.8; and scan time, 2.9 min.

Detailed scan parameters of hT\textsubscript{2}W-3D-FLAIR for PPI (hT\textsubscript{2}W-IR-2250) were: SPACE sequence; TR, 9000 ms; TE, 544 ms; inversion time, 2250 ms; frequency-selective fat-suppression pre-pulse, initial refocusing flip angle, 180°, rapidly decreased to constant flip angle of 120° for the turbo spin-echo refocusing echo train; echo train length, 173; matrix size, 322 × 384; and 104 axial 1.0-mm-thick slices covering the labyrinth; FOV, 15 × 18 cm; GRAPPA parallel imaging technique; acceleration factor, 2; NEX, 4; and scan time, 14.5 min.

Parameters for PEI (hT\textsubscript{2}W-IR-2050) employed a shorter inversion time of 2050 ms rather than the 2250 ms of PPI based on results of the pilot study. To facilitate the comparison, we employed identical FOV, matrix size, and slice thickness for MR cisternography, PPI, and PEI.

A neuroradiologist with 20 years’ experience in inner ear MR imaging assessed all images on the PACS viewer, referring to MR cisternographic images as maps of total lymphatic fluid anatomy. The vestibule and cochlea were evaluated separately.

First, PPI and MR cisternographic images were reviewed to evaluate the grade of endolymphatic hydrops according to the previously proposed criteria without viewing the PEI images.\textsuperscript{4} In brief, endolymphatic hydrops was scored according to the area ratio of endolymphatic space on PPI against total lymphatic space. Grade of endolymphatic hydrops was scored separately for the cochlea and vestibule as none, mild, or significant.

More than 2 weeks later, the same neuroradiologist reviewed hT\textsubscript{2}W-IR-2050 PEI images and MR cisternographic images. This neuroradiologist evaluated whether the perilymphatic signal is suppressed and apparent high signal at corresponding position of endolymphatic space can be recognized on PEI images or not. The apparent high signal was defined as the high signal similar to cerebrospinal fluid in the cerebellopontine angle cistern on PEI.

Another neuroradiologist, with 5 years’ experience in inner ear MR imaging, also evaluated the hT\textsubscript{2}W-IR-2050 PEI images with reference to MR cisternography to assess whether the perilymphatic signal is suppressed and apparent high signal at corresponding position of endolymphatic space can be recognized or not. The second neuroradiologist did not review the PPI.

We used kappa statistics to evaluate reproducibility between the 2 observers for the presence of apparent high signal of endolymph on PEI. Any discrepancy between the 2 reviewers was resolved by consensus after discussion.

Our institutional medical ethics committee approved the study, and we obtained informed consent from all patients.

Results

The 2 observers disagreed regarding the presence of high signal of cochlear endolymph on PEI in one cochlea with no endolymphatic hydrops on PPI (kappa value: 0.924) but agreed in all ears regarding the presence of high signal of vestibular endolymph on PEI.

Table summarizes patient information, results of endolymphatic hydrops grading on PPI, and visualization of endolymph on PEI. In the vestibule, endolymphatic hydrops was significant in 16 ears, mild in 6 ears, and absent in 6 ears on PPI; endolymph showed apparent high signal on PEI in all 28 ears. In the cochlea, endolymphatic hydrops was significant in 6 ears, mild in 11 ears, and absent in 11 ears on PPI; on PEI, apparent high signal of endolymph was visualized in 17 ears and absent in 11 ears (Fig. 2). In 11 ears without high signal on PEI, no endolymphatic hydrops was observed on PPI.

Discussion

The much larger size of the vestibular endolymph than cochlear endolymph makes grading of vestibular endolymphatic hydrops easier than that of cochlear endolymphatic hydrops on PPI. A previous study reported that cochlear endolymphatic hydrops could not be visualized by IV-SD-GBCM using 3D-FLAIR and 12-channel head coil at 3T.\textsuperscript{5} However, another study using hT\textsubscript{2}W-3D-FLAIR and 32-channel head coil reported visualization of cochlear endolymph, attributable to the increased...
Table. Summary of patient information, results of endolymphatic hydrops grading on PPI, and visualization of endolymphatic fluid on PEI

| Patient No. | Age | Sex | Side | Grading of endolymphatic hydrops on PPI | High signal of endolymph on PEI | Hearing level (dB) | Ear symptom | Vertigo | Clinical diagnosis |
|-------------|-----|-----|------|----------------------------------------|-------------------------------|-------------------|-------------|--------|-------------------|
|             |     |     |      | cochlea | vestibule                          | cochlea | vestibule |             |        |                   |
| 1           | 72  | F   | right| 2       | 0                                  | yes    | no       | 42.5      | tinnitus | no right Ménière's disease |
|             |     |     | left  | 0       | 0                                  | no     | yes      | 11.3      | none    | left Ménière's disease |
| 2           | 68  | F   | right| 2       | 2                                  | yes    | yes      | 63.8      | none    | yes bilateral Ménière's disease |
|             |     |     | left  | 2       | 2                                  | yes    | yes      | 16.3      | tinnitus |                    |
| 3           | 72  | M   | right| 1       | 2                                  | yes    | yes      | 16.3      | none    | yes vestibular Ménière's disease (side unknown) |
|             |     |     | left  | 0       | 1                                  | no     | yes      | 13.8      | none    |                    |
| 4           | 62  | M   | right| 1       | 0                                  | yes    | yes      | 22.5      | none    | no bilateral Ménière's disease |
|             |     |     | left  | 1       | 1                                  | yes    | yes      | 17.5      | tinnitus |                    |
| 5           | 60  | F   | right| 1       | 0                                  | yes    | yes      | 46.3      | tinnitus | no bilateral cochlear Ménière's disease |
|             |     |     | left  | 1       | 2                                  | yes    | yes      | 47.5      | none    |                    |
| 6           | 66  | F   | right| 1       | 1                                  | yes    | yes      | 78.8      | none    | no bilateral cochlear Ménière's disease |
|             |     |     | left  | 0       | 1                                  | yes    | yes      | 72.5      | none    |                    |
| 7           | 45  | F   | right| 1       | 1                                  | yes    | yes      | 21.3      | ear fullness | no right Ménière's disease |
|             |     |     | left  | 1       | 2                                  | yes    | yes      | 10        | none    | left Ménière's disease |
| 8           | 67  | F   | right| 0       | 2                                  | no     | yes      | 17        | none    | no left Ménière's disease |
|             |     |     | left  | 0       | 2                                  | no     | yes      | 20        | ear fullness |                    |
| 9           | 60  | F   | right| 0       | 2                                  | no     | yes      | 22.5      | none    | yes vestibular Ménière's disease (side unknown) |
|             |     |     | left  | 0       | 2                                  | no     | yes      | 20        | none    |                    |
| 10          | 47  | F   | right| 1       | 2                                  | yes    | yes      | 11.3      | ear fullness | no bilateral Ménière's disease |
|             |     |     | left  | 0       | 2                                  | no     | yes      | 11.3      | ear fullness |                    |
| 11          | 17  | F   | right| 1       | 2                                  | yes    | yes      | 5.8       | tinnitus | yes right Ménière's disease |
|             |     |     | left  | 0       | 2                                  | no     | yes      | 50        | none    | left Ménière's disease |
| 12          | 64  | F   | right| 2       | 2                                  | yes    | yes      | 38.8      | ear fullness | yes right Ménière's disease |
|             |     |     | left  | 2       | 2                                  | yes    | yes      | 23.8      | none    |                    |
| 13          | 75  | F   | right| 0       | 1                                  | no     | yes      | 20        | none    | yes left Ménière's disease |
|             |     |     | left  | 2       | 2                                  | yes    | yes      | 52.5      | ear fullness, tinnitus |                    |
| 14          | 53  | M   | right| 1       | 0                                  | yes    | yes      | 33.8      | ear fullness, tinnitus | no right cochlear Ménière's disease |
|             |     |     | left  | 0       | 0                                  | no     | yes      | 22.5      | none    |                    |

Grade of endolymphatic hydrops: 2, significant; 1, mild; 0, none
PPI: positive perilymp image; PEI: positive endolymph image
Hearing level (dB) = (a + 2b + c)/4; a, hearing level at 500 Hz; b, hearing level at 1000 Hz; c, hearing level at 2000 Hz

sensitivity to faint contrast enhancement, but the images suffered more noise than 3D-FLAIR images. In the present study, nondilated cochlear endolymph was not visualized on PEI, perhaps partly due to the small size of the nondilated cochlear endolymph. In one cochlea without endolymphatic hydrops on PPI, 2 observers disagreed regarding the presence of apparent high signal of cochlear endolymph on PEI; one observer recognized a noise-like structure as cochlear endolymph on PEI.

In the present study, we employed inversion times of 2050 ms for PEI and 2250 ms for PPI. The difference between these values, only 200 ms, is much smaller than the difference after intratympanic administration of GBCM. Furthermore, optimal inversion time might differ among patients according to the various degrees of GBCM distribution in perilymph. In previous study, inversion times of 1000 ms for PEI and 2500 ms for PPI were employed using 3D-FLAIR with conventional turbo spin-echo with echo train length of 23. A far smaller gap between 2 null points after IV-SD-GBCM should have made the longitudinal magnetization of perilymph for PPI and of endolymph for PEI much smaller at the timing of excitation. Nevertheless, in the present study, PEI after IV-SD-GBCM was feasible in patients with endolymphatic hydrops at 3T using a 32-channel head coil and heavily T2W-3D inversion recovery sequence. Smaller longitudinal magnetization of endolymph on PEI might be another cause for the nonvisualization of nondilated cochlear endolymph.

The clinical significance of MR imaging evaluation of endolymphatic hydrops has been reported mostly by intratympanic injection of GBCM, and a scale for grading endolymphatic hydrops was proposed using 3D-FLAIR and 3D-inversion recovery with phase-sensitive reconstruction (3D-real IR) images obtained after intratympanic injection of GBCM. Grading has also been applied to images obtained after double- and single-dose IV-GBCM. Especially, acquisition of T2W-3D-FLAIR images after IV-SD-GBCM is expected to spread widely in the clinical field because of the low
Fig. 2. A 75-year-old woman with suspected left-side Ménière’s disease. (a–c) left side, (d–f) right side. (a) Magnetic resonance (MR) cisternography of the left inner ear. (b) Corresponding positive endolymph image (PEI) obtained by heavily T₂-weighted 3-dimensional inversion recovery sequence with inversion time of 2050 ms (hT₂W-3D-IR-2050). Note that the dilated cochlear endolymph (short arrows) and dilated vestibular endolymph (long arrows) show bright signal. (c) Corresponding positive perilymph image (PPI) obtained by hT₂W-3D-fluid-attenuated inversion recovery (FLAIR) sequence with inversion time of 2250 ms (hT₂W-3D-IR-2250). Filling defects are noted at the corresponding locations of high signal on PEI (b). Cochlear endolymph (short arrows) and vestibular endolymph (long arrows) show significant endolymphatic hydrops. (d) MR cisternography of the right inner ear. (e) Corresponding PEI obtained by heavily T₂W-3D-inversion recovery sequence with inversion time of 2050 ms (hT₂W-3D-IR-2050). Note that no apparent high signal of cochlear endolymph (circled area) is seen. Small vestibular endolymph (long arrow) and endolymph in nondilated posterior ampulla (dashed long arrow) shows bright signal. (f) Corresponding PPI obtained by hT₂W-3D-FLAIR sequence with inversion time of 2250 ms (hT₂W-3D-IR-2250). No cochlear endolymphatic hydrops is seen. There is very small filling defect at the location of the cochlear endolymph (short arrows). These are difficult to differentiate from partial volume averaging of surrounding bone, intercalar septum, and osseous spiral lamina. Filling defects are noted in the vestibule (long arrow) and posterior ampulla (dashed long arrow) at the corresponding locations of high signal on PEI (e). In the upper location slice (not shown), there is mild endolymphatic hydrops in the vestibule.
invasiveness of this procedure.

Cochlear endolymph is spatially smaller than vestibular endolymph. PPI by $hT_2W$-3D-FLAIR is susceptible to partial volume averaging artifact, especially in the cochlea. Surrounding bone and interscalar septum might mimic filling defect by cochlear endolymph on PPI. PEI might help increase confidence for diagnosis of cochlear endolymphatic hydrops. Further study is necessary to confirm the clinical supplemental value of PEI in reducing uncertain interpretation.

Conclusions

Reducing the inversion time of $hT_2W$-3D-FLAIR for PPI makes PEI feasible in ears with endolymphatic hydrops even after IV-SD-GBCM.

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