TECHNICAL NOTE

Visualization of Endolymphatic Hydrops in Ménière's Disease with Single-dose Intravenous Gadolinium-based Contrast Media using Heavily T₂-weighted 3D-FLAIR

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Heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) technique has been reported to be more sensitive than conventional 3D-FLAIR in detecting low concentrations of gadolinium-based contrast media (GBCM) in fluid. We applied hT₂W-3D-FLAIR to visualize endolymphatic hydrops of Ménière's disease in 3 patients 4 hours after single-dose intravenous injection of GBCM and successfully visualized endolymphatic hydrops in either the cochlea or vestibule in all patients. This technique can be implemented in a clinical setting.

Keywords: *advanced imaging techniques, magnetic resonance imaging, Ménière's disease, 3D imaging*

Introduction

Intratympanic administration of gadolinium-based contrast media (GBCM),¹ such as Gd-DTPA-BMA and Gd-DTPA, has permitted visualization of endolymphatic hydrops in patients with Ménière's disease using 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) at 3 tesla, opening the door to the objective diagnosis of the condition in these patients for the first time in history. However, intratympanic administration of GBCM is off-label use, risks puncture of the patient's tympanic membrane, and requires 24 hours before imaging, limitations that have hindered the method's widespread use. Although some advanced institutions have begun to try this method,^{2,3} a less invasive technique, such as intravenous administration of GBCM, has been desired, and successful use of 3D-FLAIR after double-dose intravenous administration of GBCM has been reported in patients with Ménière's disease.⁴ Three-dimensional FLAIR is far more sensitive than T₁-weighted images to faint enhancement by low concentrations of gadolinium,⁵ but the concentration of GBCM in the perilymph after single-dose intravenous injection is too low to be detected

even by 3D-FLAIR in patients without impaired permeability of the blood labyrinthine barrier.⁶

Three-dimensional FLAIR using conventional turbo spin-echo sequence (3D-FLAIR-CONV) and 3D-FLAIR using variable flip angle turbo spin-echo sequence (3D-FLAIR-VFL), a kind of SPACE (sampling perfection with application of optimized contrasts using different flip angle evaluation) sequence optimized for brain tissue, have been utilized for inner ear study.^{5,7} As well, in another study, a longer effective echo time turbo spin-echo sequence with different refocusing flip angle transit schedule in the turbo spin-echo echo train⁸ was optimized for fluid with longer T₂-value,⁹ and the optimized protocol (heavily T₂-weighted 3D-FLAIR-VFL; hT₂W-3D-FLAIR) was compared with 3D-FLAIR-CONV in a phantom and patients.

In both phantom and patients, better detection of low concentrations of GBCM was demonstrated by hT₂W-3D-FLAIR than 3D-FLAIR-CONV after double-dose intravenous injection of GBCM.⁹ However, reports correlating use of GBCM with nephrogenic systemic fibrosis (NSF) have limited its choice for high dose intravenous administration. A method to visualize endolymphatic hydrops using single-dose intravenous administration of GBCM is desired for the further spread of endolymphatic hydrops imaging.

We challenged the separate visualization of

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endo- and perilymph fluid after single-dose administration of GBCM using hT₂W-3D-FLAIR in patients with suspected Ménière's disease.

Materials and Methods

We evaluated 3 patients suspected with bilateral endolymphatic hydrops, an 82-year-old woman, 42-year-old man, and 38-year-old man, all having an estimated glomerular filtration rate (eGFR) exceeding 60 mL/min/1.73 m². The patients underwent scanning 4 hours after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) intravenous administration of Gadoteridol (Gd-HP-DO3A; Prohance, Eisai, Tokyo, Japan) in the woman and gadolinium-diethylene-triamine pentaacetic acid-bis (methanamide) (Gd-DTPA-BMA; Omniscan, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan) in the men. All scans were performed on a 3-tesla magnetic resonance (MR) unit (MAGNETOM Trio, a TIM system, Siemens, Erlangen, Germany) using a 32-channel array head coil.¹⁰

We obtained MR cisternography, 3D-FLAIR-CONV, 3D-FLAIR-VFL, and hT₂W-3D-FLAIR in the female patient, but contrast enhancement of the perilymph on 3D-FLAIR-CONV was quite poor. Previously reported results of phantom study showed the normalized contrast-to-noise ratio (CNR_{norm}) of hT₂W-3D-FLAIR to be 2.5 to 2.9 times higher than that by 3D-FLAIR-CONV.⁹ Results of patient study in the same report showed that nonvisualized cases of endolymphatic space by 3D-FLAIR-CONV occurred 8 times more frequently than by hT₂W-3D-FLAIR, even after double-dose contrast administration. The mean CNR_{norm} between endolymph and perilymph was also 3.02 times higher on hT₂W-3D-FLAIR than 3D-FLAIR-CONV. Consequently, the possibility of visualizing endolymphatic space on 3D-FLAIR-CONV after single-dose contrast administration was thought to be quite small, and 3D-FLAIR-CONV was skipped in the 2 male patients in the present single-dose study. For 3D-FLAIR-VFL, the phantom experiments were also performed to compare the CNR_{norm} between 3D-FLAIR-VFL and hT₂W-3D-FLAIR using the same method as that of the previous study.⁹ The phantom was designed using disposable plastic 20-mL syringes (Terumo, Tokyo, Japan) filled with diluted Gd-DTPA-BMA and saline; the original Gd-DTPA-BMA (0.5 mmol/L solution) was diluted 4000-, 8000-, 16000-, 24000-, and 32000-fold with saline. Three-dimensional FLAIR-VFL and hT₂W-3D-FLAIR were then obtained using the same voxel size and scan time, and CNR_{norm} was compared between the 2 sequences.

The CNR_{norm} value of hT₂W-3D-FLAIR was 2.2 times higher than that of 3D-FLAIR-VFL at the concentration of 1/4000, 2.2 times at 1/8000, 2.3 times at 1/16000, 2.8 times at 1/24000, and 3.0 times at 1/32000. These values are almost comparable to those comparing hT₂W-3D-FLAIR and 3D-FLAIR-CONV in the previous study. Although the possibility of visualizing endolymph space by 3D-FLAIR-VFL is also considered quite small, this sequence was included for all 3 patients because the scan time is only 5.3 min.

For anatomical reference of total fluid space of the labyrinth and cistern, we obtained heavily T₂-weighted fast recovery 3D-turbo spin-echo images using SPACE technique⁸ with MR cisternography and parameters: repetition time (TR), 2750 ms; echo time (TE), 540 ms; 120° flip angle (constant in the later echo train) for the turbo spin-echo refocusing echo train; echo train length, 147 with restore magnetization pulse (fast recovery pulse); matrix size, 270 × 320; 72 axial 0.8-mm-thick 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), 4; and scan time, 2.7 min.

The parameters for 3D-FLAIR-CONV were: TR, 9000 ms; TE, 128 ms; inversion time (TI), 2500 ms; 180° flip angle (constant) for the turbo spin-echo refocusing echo train; echo train length, 23; matrix size, 384 × 384; 12 axial 2-mm-thick slices covering the labyrinth; FOV, 16 cm square; GRAPPA parallel imaging technique; acceleration factor, 2; NEX, 1; and scan time, 15 min.

The parameters for 3D-FLAIR-VFL were: TR, 9000 ms; effective TE, 458 ms, TI, 2500 ms; variable flip-angle echo train with average flip angle, 120°; echo train length, 119; echo spacing, 3.72 ms; matrix size; 214 × 256; 48 axial 0.8-mm-thick slices covering the labyrinth; FOV, 15 × 18 cm; bandwidth, 592 Hz per pixel; GRAPPA acceleration factor, 2; voxel size, 0.7 × 0.7 × 0.8 mm; 2 excitations' and total scan time, 5.3 min. We used non-selective inversion pulses and slab-selective excitation pulses.

Scan parameters of hT₂W-3D-FLAIR were: TR, 9000 ms; TE, 540 ms; TI, 2350 ms; initial refocusing flip angle, 180°, rapidly decreased to constant flip angle, 120° for the turbo spin-echo refocusing echo train in SPACE sequence; echo train length, 144; matrix size, 270 × 320; 72 axial 0.8-mm-thick slices covering the labyrinth; FOV, 15 × 18 cm; GRAPPA acceleration factor, 2; voxel size, 0.56 mm × 0.56 mm × 0.8 mm, which is smaller than 3D-FLAIR-VFL and 3D-FLAIR-CONV; NEX, 4; and

scan time, 10.7 min.

Three neuroradiologists with 21, 12 and 4 years' experience evaluated the images independently. The one with the longest experience was not blinded to the detailed symptoms and history of the patients, but the other two were. They graded the degree of endolymphatic hydrops in the cochlea and vestibule for each 3D-FLAIR-CONV, 3D-FLAIR-VFL and hT₂W-3D-FLAIR image as either none, mild, or significant, according to criteria proposed previously.¹¹ If the signal difference between endo- and perilymph was too small to evaluate the endolymphatic hydrops, it was graded as unclear.

This study was approved by medical ethics committee of our institution, and we obtained informed consent from all patients.

Results

Enhancement of the perilymph on hT₂W-3D-FLAIR was sufficient to grade the degree of endolymphatic hydrops in all 6 ears of 3 patients, but confident recognition of endolymphatic space was impossible on either 3D-FLAIR-CONV or 3D-FLAIR-VFL in all ears (Figs. 1, 2). Grading by all 3 observers agreed completely (Table 1). Significant hydrops seen in both the cochlea and vestibule of one ear suggested diagnosis of definite-type Ménière's disease, and observation of significant hydrops in either the cochlea or vestibule only in the other 5 ears suggested diagnosis of cochlear- or vestibular-type Ménière's disease.

Fig. 1. An 82-year-old female patient with suspected bilateral Ménière's disease. Images were obtained 4 hours after the intravenous administration of single-dose Gd-HP-DO3A. **A:** Magnetic resonance (MR) cisternography shows both peri- and endolymph fluid with the same high signal intensity. **B:** On heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR), significant endolymphatic hydrops in the cochlea (long arrows) and non-dilating endolymphatic space in the vestibule (short arrows) can be recognized as areas of low intensity. **C:** On 3D-FLAIR using conventional turbo spin-echo sequence (3D-FLAIR-CONV), enhancement of the perilymph fluid is so faint that it is impossible to recognize the endolymphatic space. **D:** On 3D-FLAIR using variable flip angle turbo spin-echo sequence (3D-FLAIR-VFL), enhancement of the perilymph fluid is stronger than on 3D-FLAIR-CONV, but recognition of the endolymphatic space is still impossible.

Fig. 2. A 42-year-old man suspected with bilateral Ménière's disease. Images were obtained 4 hours after the intravenous administration of single-dose gadolinium-diethylene-triamine pentaacetic acid-bis (methylamide) (Gd-DTPA-BMA). **A:** Magnetic resonance (MR) cisternography shows both peri- and endolymph fluid with the same high signal intensity. **B:** On 3D-FLAIR using variable flip angle turbo spin-echo sequence (3D-FLAIR-VFL), enhancement of the perilymph fluid is still too faint to recognize the endolymphatic space confidently. **C:** On heavily T_2 -weighted 3-dimensional fluid-attenuated inversion recovery (hT_2W -3D-FLAIR), significant endolymphatic hydrops in the cochlea (long arrows) and vestibule (short arrows) can be recognized as an area of low intensity.

Discussion

Three-dimensional FLAIR-CONV has been reported more useful than 3D-FLAIR-VFL for visualizing cochlear endolymphatic hydrops after intratympanic injection of GBCM because of image blur of 3D-FLAIR-VFL based on SPACE sequence.⁷ Therefore, even with its shorter scan time, 3D-FLAIR-VFL could not replace 3D-FLAIR-CONV for evaluating the cochlea, although these sequences were comparable for evaluation of the vestibule. In the present study, we set smaller voxel volume for hT_2W -3D-FLAIR than that for 3D-FLAIR-CONV and 3D-FLAIR-VFL to evaluate cochlear endolymphatic hydrops, compensating for the blur by the nature of the SPACE sequence. Fur-

thermore, the number of averaging in hT_2W -3D-FLAIR was four and in 3D-FLAIR-VFL, two, so comparison between the 2 methods was not completely balanced. In the phantom study, CNR_{norm} values between saline and diluted GBCM were 2 to 3 times higher on hT_2W -3D-FLAIR than 3D-FLAIR-CONV or 3D-FLAIR-VFL. In the present study, on 3D-FLAIR-VFL, we were unable to visualize the endolymph, even in the vestibule, in all 3 patients. Because vestibular endolymphatic space is larger than cochlear endolymphatic space, 3D-FLAIR-VFL might not perform as well as hT_2W -3D-FLAIR in visualizing endolymphatic space, if the same voxel size and number of averaging was used for both methods.

Although we investigated only 3 cases in this

Table. Results of endolymphatic hydrops grading in 6 ears in 3 patients

	82-year-old woman			
	right		left	
	cochlea	vestibule	cochlea	vestibule
3D-FLAIR-CONV	unclear	unclear	unclear	unclear
3D-FLAIR-VFL	unclear	unclear	unclear	unclear
hT ₂ W-3D-FLAIR	significant	none	none	significant
	42-year-old man			
	right		left	
	cochlea	vestibule	cochlea	vestibule
3D-FLAIR-CONV	not obtained			
3D-FLAIR-VFL	unclear	unclear	unclear	unclear
hT ₂ W-3D-FLAIR	significant	significant	none	significant
	38-year-old man			
	right		left	
	cochlea	vestibule	cochlea	vestibule
3D-FLAIR-CONV	not obtained			
3D-FLAIR-VFL	unclear	unclear	unclear	unclear
hT ₂ W-3D-FLAIR	none	significant	none	significant

3D-FLAIR-CONV = three-dimensional FLAIR using conventional turbo spin-echo sequence

3D-FLAIR-VFL = 3D-FLAIR using variable flip angle turbo spin-echo sequence

hT₂W-3D-FLAIR = heavily T₂-weighted 3D-FLAIR-VFL

study, our results are promising and open the possibility of endolymphatic hydrops imaging using single-dose intravenous administration of GBCM. This procedure is easily included in routine clinical practice at 3 tesla. Accumulation of knowledge regarding endolymphatic hydrops and various inner ear symptoms will facilitate the further progress of evidence-based medicine in the management of Ménière's disease.

Some issues remain to be solved. Optimal timing after the intravenous administration of GBCM in Ménière's disease is unclear. Optimal timing of 4 hours after intravenous injection has been reported in healthy subjects,¹² but we do not know whether the permeability of the blood-labyrinthine barrier in Ménière's disease is healthy. Neither do we know which GBCM is most suitable for intravenous administration in imaging of endolymphatic hydrops. We used 2 kinds of non-ionic GBCM but cannot definitively discuss the difference in perilymph enhancement between the two because of our small number of patients, although there seemed to be no distinct difference. In addition, contamination of

the perilymph and endolymph occurs in cases with rupture of Reissner's membrane, and endolymphatic hydrops may not be visualized using either intratympanic or intravenous GBCM administration.

In conclusion, hT₂W-3D-FLAIR may enable visualization of endolymphatic hydrops in patients with Ménière's disease after single-dose intravenous administration of GBCM, and this technique can be easily implemented in a clinical setting at 3 tesla. Further study using this technique is warranted to establish a clinically feasible method for objective diagnosis of Ménière's disease.

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