MAJOR PAPER

Visualization of Endolymphatic Hydrops in Ménière's Disease after Single-dose Intravenous Gadolinium-based Contrast Medium: Timing of Optimal Enhancement

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Purpose: Visualization of endolymphatic hydrops (EH) in patients with Ménière's disease (MD) is now possible by heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) obtained 4 hours after intravenous (IV) administration of single dose gadolinium-based contrast medium (GBCM). Although maximum enhancement has been reported 4 hours after contrast administration in healthy volunteers, the timing of optimal enhancement in patients with MD is not reported. We investigated if that optimal timing is earlier or later than 4 hours.

Materials and Methods: We evaluated 10 consecutive patients with suspected MD whom we randomly divided into 2 groups. We obtained hT₂W-3D-FLAIR before GBCM administration and 10 min, 3.5 hours, and 4 hours after GBCM administration in Group A and before and 10 min, 4 hours, and 4.5 hours after GBCM administration in Group B. We compared signal intensity ratio (SIR) values of the perilymph and pons between 3.5 and 4 hours in Group A and between 4 and 4.5 hours in Group B and evaluated grades of EH at 3.5 and 4 hours in Group A and at 4 and 4.5 hours in Group B.

Results: SIR values did not differ significantly between 3.5 and 4 hours in Group A and between 4 and 4.5 hours in Group B. However, SIR values at 4 hours were significantly higher in Group A than Group B. Grades of EH agreed between 3.5 and 4 hours in Group A and between 4 and 4.5 hours in Group B.

Conclusion: The optimal timing of contrast enhancement in patients with suspected MD remains unclear, but evaluation of EH may be possible from 3.5 to 4.5 hours after contrast administration.

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

Introduction

Visualization of endolymphatic hydrops (EH) in patients with Ménière's disease was made possible first by 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging obtained 24 hours after intratympanic (IT) administration of gadolinium-based contrast medium (GBCM)¹; then by 3D-FLAIR imaging 4 hours after intravenous (IV) injection of double-dose GBCM²; and recently, following the development of heavily T₂-weighted 3D-FLAIR (hT₂W-3D-FLAIR) imaging, after IV injection of single-dose GBCM.³ These 3 methods utilize

the preferential enhancement of the perilymph for separate visualization of the endo- and perilymph. A scale for grading EH on MR images has been proposed using 3D-FLAIR and 3D-real inversion recovery sequences obtained after IT administration of GBCM.⁴ Grading on MR images has been correlated with results of various clinical tests, such as evaluations of vestibular-evoked myogenic potential⁵ and low frequency hearing,⁶ and the degree of EH has been associated with progressive loss of auditory and sacculus function in patients with Ménière's disease.⁶ During follow-up of treatment response in these patients, the degree of endolymphatic hydrops correlated with hearing level.⁷ No study has directly compared EH grades on images obtained following IT and IV administration of

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gadolinium, but one report correlated EH grade using the IV method with low frequency hearing level.⁸ Grades of endolymphatic hydrops are significantly higher in ears with Ménière's disease than the contralateral healthy ears.⁸ Thus, EH grading using IV-administered GBCM is also expected to have widespread application across clinical fields.

We employed a 4-hour waiting period after IV administration of GBCM based on a previously reported study in which scans of normal subjects at 0, 2, 4, and 6 hours after IV administration of single-dose GBCM demonstrated peak enhancement of the perilymph at 4 hours after contrast administration.⁹ Recently, stronger enhancement of the perilymph has been reported in the diseased ears of patients with unilateral Ménière's disease than in the contralateral ears.⁸ The optimal timing to evaluate EH degree in patients with Ménière's disease has not been investigated. Clarification might require a study in which images are obtained 3, 4, and 5 hours after IV administration of GBCM, with patients entering the magnet 3 times to avoid a single uncomfortable stay in the scanner magnet exceeding 60 min. It is not clinically practical to perform a study in which images are obtained at many time points after IV administration of GBCM.

The purpose of this study was to know if the optimal timing to evaluate the degree of endolymphatic hydrops in patients with suspected Ménière's disease is earlier or later than 4 hours after GBCM administration. In this study, we conducted measurements at 2 time points around 4 hours, separating the patients into 2 groups. We compared enhancement at 3.5 and 4 hours after contrast administration in one group and at 4 and 4.5 hours in the second group. Patients can undergo 2 scans 30 min apart during a single stay in the MR scanner magnet.

Materials and Methods

The medical ethics committee of our institution approved this study, and we obtained informed consent from all patients. We evaluated 10 consecutive patients with suspected Ménière's disease (6 men, 4 women, aged 27 to 67 years). Bilateral disease was suspected in one patient; "cochlear-type" Ménière's disease, in which there is low-tone or fluctuating hearing loss, was suspected in 2 patients (but they did not demonstrate rotating vertigo) and unilateral disease was suspected in the other 7 patients. Experienced otolaryngologists made the clinical diagnosis based on the 2008 Japanese guideline for diagnosing Ménière's disease.

The patients underwent scanning before and after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) intravenous administration of gadolinium-diethylenetriamine pentaacetic acid-bis (methylamide) (Gd-DTPA-BMA; Omniscan, Daiichi-Sankyo Co., Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. The estimated glomerular filtration rate (eGFR) in all patients exceeded 60 mL/min/1.73 m². We calculated each GFR using an equation reported by the Japanese Society of Nephrology for estimating GFR (eGFR) in Japanese patients based on serum creatinine level (Cr): $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}$ (if female, $\times 0.739$). We divided the 10 patients randomly into 2 groups of 5 patients each.

We performed all MR imaging using a 3-tesla unit (Verio, Siemens, Erlangen, Germany) with a 32-channel array head coil. For anatomical reference of the total fluid space of the labyrinth and cistern, we obtained heavily T₂-weighted fast recovery 3D turbo-spin-echo images: repetition time (TR), 1500 ms; echo time (TE), 130 ms; 180° flip angle (constant throughout echo train) for the conventional turbo-spin-echo refocusing echo train; echo train length, 23 with restore magnetization pulse (fast recovery pulse); matrix size, 384 × 384; 12 axial slices of 2.0-mm thickness covering the labyrinth; field of view (FOV), 16 × 16 cm; generalized autocalibrating partially parallel acquisition (GRAPPA) parallel imaging technique; acceleration factor, 2; number of excitations (NEX), one; and scan time, 2.7 min.

Scan parameters of hT₂W-3D-FLAIR were: TR, 9000 ms; TE, 546 ms; TI, 2350 ms; frequency-selective fat-suppression pre-pulse initial refocusing flip angle, 180°, rapidly decreased to constant 120° flip angle for the turbo-spin-echo refocusing echo train; echo train length, 107; matrix size, 214 × 256; 112 axial slices of 0.8-mm thickness covering the labyrinth; FOV, 15 × 18 cm; GRAPPA technique; acceleration factor, 2; NEX, 2; and scan time, 5.7 min.

All patients underwent MR cisternography and hT₂W-3D-FLAIR prior to single-dose IV administration of GBCM (first scan) and a second hT₂W-3D-FLAIR scan 10 min after contrast administration, then came out of the magnet to rest. The 5 members of Group A then underwent hT₂W-3D-FLAIR scanning at 3.5 (third scan) and 4 hours (fourth scan) after contrast administration, and members of Group B, at 4 (third scan) and 4.5 hours (fourth scan) after GBCM administration.

On the PACS viewer (RapidEye, Toshiba, Tokyo, Japan), a radiologist with 22 years' experience drew regions of interest (ROI) in the cochlear

and vestibular perilymph, vestibular endolymph, and cerebrospinal fluid (CSF) space in the fundus of the internal auditory canal (IAC) on the hT₂W-3D-FLAIR images obtained 3.5, 4, and 4.5 hours after IV administration of GBCM. The ROIs were drawn as circles of: 0.7-mm diameter in the scala tympani of the cochlear basal turn based on reference to MR cisternography for the cochlear perilymph; one-mm diameter in the anterior superior part of the vestibular perilymph area for the vestibular perilymph; one-mm diameter in the utricle,

that is, the area of low signal in the upper part of the vestibule, for the vestibular endolymph; and one-mm in the CSF space in the area between the cochlear nerve and inferior vestibular nerve based on reference to MR cisternography for the CSF space in the fundus of the IAC. Figure 1 shows an example of the ROI placement. We normalized signal intensity values of the ROIs by dividing them by the signal intensity value of the pons and defined this normalized value as the signal intensity ratio (SIR). We measured the signal intensity of the pons

Fig. 1. Example of region of interest (ROI) placement. A 48-year-old man with right Ménière's disease in Group A. (a) Magnetic resonance (MR) cisternographic image at cochlear level. (b) Corresponding heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) image at the cochlear level obtained 3.5 hours after intravenous (IV) injection of gadolinium-based contrast medium (GBCM). Circular ROI in the scala tympani of the cochlear basal turn. (c) and (d), hT₂W-3D-FLAIR images obtained 3.5 hours after IV administration of GBCM. Circular ROI in the vestibular endolymph (c) and vestibular perilymph (d). (e) MR cisternographic image at the level of the cochlear nerve. (f) Circular ROI for the cerebrospinal fluid in the internal auditory canal on hT₂W-3D-FLAIR image obtained 3.5 hours after IV administration of GBCM.

in a circular ROI of 5-mm diameter drawn in the center of the pons.

We compared the average SIR values for each ROI of all 10 ears (right and left side in 5 patients) between 3.5 and 4 hours for Group A and between 4 and 4.5 hours for Group B and performed the same comparison for only those ears with endolymphatic hydrops in either the cochlea or vestibule, excluding nondiseased ears. We analyzed statistics using Student's *t*-test.

Two neuroradiologists with 22 and 12 years' experience independently reviewed the images for qualitative analysis. They evaluated all precontrast hT_2W -3D-FLAIR images and those obtained at 10 min, 3.5 and 4 hours, or 4 and 4.5 hours after IV administration of GBCM for presence or absence of high signal equivalent to that of vestibulocochlear nerve bundle in labyrinthine fluid and CSF in the internal auditory canal. The 2 reviewers resolved any discrepancy by consensus after discussion. They also graded the degree of EH separately for the cochlea and vestibule as none, mild, or significant according to previously reported criteria⁴ on the images obtained 3.5 and 4 hours after IV administration of GBCM in Group A and 4 and 4.5 hours after in Group B. Table 1 shows the grading criteria. We evaluated endolymphatic grading in 2 sessions 2 weeks apart; in the first, we evaluated either the third or fourth scan and in the second session, the other scan. We used weighted kappa statistics to assess the reproducibility of endolymphatic grading for the 2 observers. The 2 reviewers resolved any discrepancy in grading by consensus after discussion.

For the images obtained 4 hours after IV ad-

ministration of GBCM in both groups, we compared SIR values for each ROI between groups. We also performed this comparison excluding ears with no EH in the cochlea and vestibule, and we compared EH grades between groups and used Mann-Whitney U test for intergroup statistical analysis.

Results

No patient demonstrated high signal equivalent to that of vestibulocochlear nerve bundle in labyrinthine fluid and CSF in the internal auditory canal on images obtained prior to IV administration of GBCM and those obtained 10 min after contrast administration. In labyrinthine fluid and CSF in the internal auditory canal, there are similar or higher signal compared to that of vestibulocochlear nerve bundle on the images obtained at 3.5 and 4 hours or 4 and 4.5 hours after IV administration of GBCM in both ears of all patients (Figs. 2, 3). Areas of increased signal in the labyrinth corresponded to the locations of perilymph. The 2 radiologists agreed regarding the presence and absence of high signal in the labyrinth and CSF in the internal auditory canal.

Table 2 lists average SIR values of the ROIs. Quantitative analysis revealed no significant difference between SIR values in the cochlear and vestibular perilymph, vestibular endolymph, and CSF in the IAC fundus at 3.5 and 4 hours in Group A ($P > 0.05$) or at 4 and 4.5 hours for Group B ($P > 0.05$).

When assessment was limited to ears with EH in either the cochlea and/or vestibule and excluded ears without EH, SIR values did not differ significantly in the cochlear and vestibular perilymph, vestibular endolymph, and CSF in the internal auditory canal fundus between 3.5 and 4 hours in Group A ($n = 9$ ears) and between 4 and 4.5 hours in Group B ($n = 7$ ears) ($P > 0.05$) (Table 3).

The SIR values of the cochlear and vestibular perilymph were significantly higher in Group A than B at 4 hours ($P < 0.05$). No significant difference was found for the vestibular endolymph and CSF in the internal auditory canal fundus ($P > 0.05$). When limited to ears with endolymphatic hydrops in either the cochlea and/or vestibule and excluding ears without EH, the SIR values of the cochlear and vestibular perilymph were significantly higher in Group A than B at 4 hours ($P < 0.05$). No significant difference was found for the vestibular endolymph and CSF in the IAC fundus ($P > 0.05$).

Although the difference was not significant, the SIR values of the cochlear and vestibular perilymph

Table 1. Grading of endolymphatic hydrops using magnetic resonance imaging

Grade of hydrops	Vestibule (area ratio*)	Cochlea
None	no more than 1/3	no displacement of Reissner's membrane
Mild	more than 1/3, no more than 50%	displacement of Reissner's membrane area of cochlear duct not larger than area of scala vestibuli
Significant	more than 50%	area of cochlear duct exceeds area of scala vestibuli

* Ratio of the area of the endolymphatic space to that of the fluid space (sum of the endolymphatic and perilymphatic spaces) in the vestibule measured on tracings of images

Fig. 2. A 48-year-old man with right Ménière's disease in Group A, same patient as Fig. 1. (a) Pre-contrast-enhanced heavily T_2 -weighted 3-dimensional fluid-attenuated inversion recovery (hT_2W -3D-FLAIR) image at the cochlear nerve level. (b) Image obtained 10 min after intravenous (IV) injection of gadolinium-based contrast medium (GBCM). (c) Image obtained 3.5 hours after IV administration of GBCM. (d) Image obtained 4 hours after IV administration of GBCM. (e) Corresponding MR cisternographic image. Note that there is no high signal lymph fluid in the labyrinth and cerebrospinal fluid (CSF) in the internal auditory canal (IAC) equivalent to that of vestibulocochlear nerve (VIII) on (a) and (b). On the other hand, high signal is seen in the labyrinth and IAC on (c) and (d). On these slices, mild vestibular endolymphatic hydrops (EH) can be appreciated as low signal (arrow on [c] and [d]) surrounded by enhanced perilymph.

were larger for the fourth scan than the third in Groups A and B ($P > 0.05$).

Table 4 shows the results of endolymphatic hydrops grading. One patient demonstrated no EH in either the cochlea or vestibule on either side. The other 9 patients had either cochlear or vestibular EH in at least one ear. Grading of endolymphatic hydrops on images obtained at 3.5 and 4 hours and at 4 and 4.5 hours after contrast administration agreed completely in both 2 observers. However, the observer with shorter experience underestimated significant EH as mild in one cochlea in images obtained at 3.5 and 4 hours after IV administration of GBCM in Group A (weighted kappa value, 0.941) and in 2 cochleas in images obtained at 4 and 4.5 hours after GBCM administration in Group B (weighted kappa value, 0.889). The 2 observers agreed regarding EH grading of the vestibule.

EH grading of the cochlea did not differ sig-

nificantly between Groups A and B, but vestibular grades were significantly higher in Group A than B ($P < 0.05$).

Discussion

The hT_2W -3D-FLAIR technique has been reported to be more sensitive than conventional 3D-FLAIR in detecting low concentrations of GBCM in fluid.¹⁰ Evaluation of endolymphatic hydrops in the clinical setting is now feasible using hT_2W -3D-FLAIR and single-dose GBCM administered intravenously.³

EH grades on images obtained after IV administration of GBCM correlated with low frequency hearing level.⁸ However, the degree of perilymph enhancement after IV administration of GBCM does not correlate with hearing level in patients with Ménière's disease.¹¹ More widespread use of this method in the clinic requires knowledge of the

Fig. 3. A 74-year-old woman with right Ménière’s disease in Group B. (a) Pre-contrast-enhanced heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) image at the cochlear nerve level. (b) Image obtained 10 min after intravenous (IV) injection of gadolinium-based contrast medium (GBCM). (c) Image obtained 4 hours after IV administration of GBCM. (d) Image obtained 4.5 hours after IV administration of GBCM. (e) Corresponding magnetic resonance (MR) cisternographic image. Note that there is no high signal lymph fluid in the labyrinth and cerebrospinal fluid (CSF) in the internal auditory canal (IAC) equivalent to that of vestibulocochlear nerve (VIII) on (a) and (b). On the other hand, high signal is seen in the labyrinth and IAC on (c) and (d). On these slices, significant cochlear endolymphatic hydrops (EH) can be appreciated as low signal (arrow on [c] and [d]).

Table 2. Comparison of signal intensity ratio in all ears
Group A (10 ears)

	3.5 hours		4 hours		
	average	SD	average	SD	
cochlear perilymph	11.5	3.3	12.2	4.3	n.s.
vestibular perilymph	12.1	3.0	12.7	3.1	n.s.
CSF in IAC	12.4	5.0	13.1	5.9	n.s.
vestibular endolymph	0.6	0.5	0.4	0.5	n.s.

Group B (10 ears)

	4 hours		4.5 hours		
	average	SD	average	SD	
cochlear perilymph	7.9	1.8	8.3	0.8	n.s.
vestibular perilymph	9.0	2.9	9.1	2.4	n.s.
CSF in IAC	8.9	3.7	9.3	4.4	n.s.
vestibular endolymph	0.7	0.7	0.5	0.6	n.s.

CSF in IAC, cerebrospinal fluid in internal auditory canal; n.s., not significant; SD, standard deviation

Table 3. Comparison of signal intensity ratio in ears with endolymphatic hydrops
Group A (9 ears)

	3.5 hours		4 hours		
	average	SD	average	SD	
cochlear perilymph	11.8	3.4	12.5	4.4	n.s.
vestibular perilymph	12.3	3.1	12.8	3.3	n.s.
CSF in IAC	12.6	5.2	13.5	6.1	n.s.
vestibular endolymph	0.7	0.5	0.5	0.5	n.s.

Group B (7 ears)

	4 hours		4.5 hours		
	average	SD	average	SD	
cochlear perilymph	7.9	2.1	8.2	1.0	n.s.
vestibular perilymph	9.3	3.2	9.5	2.5	n.s.
CSF in IAC	10.1	2.8	11.0	3.8	n.s.
vestibular endolymph	0.7	0.6	0.5	0.6	n.s.

CSF in IAC, cerebrospinal fluid in internal auditory canal; n.s., not significant; SD, standard deviation

Table 4. Summary of patients and grading of endolymphatic hydrops
Group A (3.5 versus 4 hours)

age/disease	gender	side	cochlea	vestibule
34	male	right	2	2
right Ménière's disease		left	0	2
67	male	right	2	2
right cochlear type Ménière's disease		left	0	0
60	male	right	2	2
right Ménière's disease		left	2	2
48	male	right	2	1
right Ménière's disease		left	0	2
50	male	right	1	1
right Ménière's disease		left	0	1

Group B (4 versus 4.5 hours)

age/disease	gender	side	cochlea	vestibule
27	female	right	0	1
left Ménière's disease		left	2	0
74	female	right	2	2
right Ménière's disease		left	0	0
66	female	right	2	0
bilateral Ménière's disease		left	2	0
31	female	right	2	1
bilateral cochlear type Ménière's disease		left	2	0
33	male	right	0	0
right Ménière's disease		left	0	0

Grade of endolymphatic hydrops: 0, none; 1, mild; 2, significant

optimal timing after IV administration of GBCM for evaluating endolymphatic grade in patients with Ménière's disease.

Our study results showed no high signal in the labyrinthine fluid and CSF in the internal auditory canal equivalent to that of vestibulocochlear nerve bundle on hT₂W-3D-FLAIR images obtained before and 10 min after IV administration of GBCM. However, high signal was observed in the labyrinth and IAC in all ears on hT₂W-3D-FLAIR images obtained 3.5 and 4 hours or 4 and 4.5 hours after IV administration of GBCM and can be concluded to represent contrast enhancement resulting from the slow permeation of GBCM.

In the present study, SIR values did not differ significantly between hT₂W-3D-FLAIR images obtained 3.5 hours and 4 hours after IV administration of GBCM in Group A and 4 and 4.5 hours after GBCM administration in Group B. However, SIR values of the cochlear vestibular perilymph differed significantly at 4 hours between Groups A and B. Therefore, we cannot conclude that there is no significant difference between SIR values at 3.5 hours in Group A and 4.5 hours in Group B.

Though the differences were not significant, the average SIR values of the cochlear and vestibular perilymph were larger on the fourth scan than the third in both groups. This tendency in a small number of patients suggests that optimal timing might be later than 4 hours.

Grading of endolymphatic hydrops agreed between 3.5 and 4 hours in Group A and between 4 and 4.5 hours in Group B. Furthermore, weighted kappa values for cochlear grading between the 2 observers were as high as 0.941 for Group A and 0.889 for Group B. Vestibular grading by the 2 observers agreed completely. Therefore, EH grading may be feasible between 3.5 and 4.5 hours after contrast administration, though we could not conclude the optimal timing of enhancement within this wide range in patients with Ménière's disease. Further study comparing SIR values at 3 time points, such as at 3, 4, and 5 hours, in the same subjects might clarify the optimal timing of enhancement.

Our study is limited by the small number of patients and our inclusion of ears with both mild and significant endolymphatic hydrops as ears with

EH. However, because we cannot know if a patient has endolymphatic hydrops in the clinical setting before MR examination, it is practical to target scan timing for ears without EH as well as ears with mild and significant EH. In the present study, we used the results of endolymphatic hydrops grading to separate ears with and without EH. Even excluding ears without EH, our comparison showed no significant difference between SIR values on the third (3.5 hours in Group A; 4 hours in Group B) and fourth scan (4 hours in Group A; 4.5 hours in Group B). These findings resemble those of comparison between the third and fourth scans for all ears.

Another limitation is the dissimilarity of Groups A and B. The degree of vestibular endolymphatic hydrops differed between the 2 groups, and SIR values differed significantly at 4 hours between them. As a result, we could not determine whether the optimal timing of enhancement is earlier or later than 4 hours. However, at least our results indicate that a clinically convenient timing for grading endolymphatic hydrops might be feasible between 3.5 and 4.5 hours after IV administration of GBCM.

In previous study, 14 ears with Ménière's disease showed 36% more intense enhancement than 10 asymptomatic contralateral ears of patients with unilateral Ménière's disease, and hydrops grade correlated significantly with contrast effect.⁸ In the present study, significantly higher grades of vestibular endolymphatic hydrops in Group A than B may be responsible for the significantly higher SIR values of the perilymph at 4 hours in Group A than B. In some pathological states, such as sudden deafness,¹² labyrinthine fistula caused by cholesteatoma,¹³ and Ramsay-Hunt syndrome,¹⁴ prompt contrast enhancement has been observed in the labyrinth on images obtained 10 min after IV administration of GBCM. Maximum perilymph enhancement might be observed much earlier than 4 hours in these pathological states. In the present study, no ear showed contrast enhancement in the labyrinth on images obtained 10 min after IV administration of GBCM, which suggests that ears with Ménière's disease do not have the severely increased permeability of the blood-perilymph barrier as do the pathological states described above.

In conclusion, we could not determine the optimal timing of enhancement to visualize endolymphatic hydrops in patients with Ménière's disease but believe that its grading may be feasible 3.5 to 4.5 hours after IV administration of GBCM. Although there was no significant difference, the SIR values of the fourth scan were larger than those

of the third in both Group A and B. Further study comparing the SIR values on images obtained at 3 time points, such as 3, 4, and 5 hours, after IV administration of GBCM in patients with Ménière's disease may be necessary to determine whether the optimal timing is earlier or later than 4 hours.

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