TECHNICAL NOTE

Imaging of Ménière's Disease after Intravenous Administration of Single-dose Gadodiamide: Utility of Subtraction Images with Different Inversion Time

Shinji NAGANAWA^{1*}, Masahiro YAMAZAKI¹, Hisashi KAWAI¹, Kiminori BOKURA¹,
Michihiko SONE², and Tsutomu NAKASHIMA²

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

(Received January 5, 2012; Accepted April 4, 2012)

For the separate visualization of endolymph, perilymph, and bone on a single image after intravenous injection of single-dose gadodiamide, we fused gray-scale inverted positive endolymph (PEI) with native positive perilymph (PPI) images, that is, we subtracted PEI from PPI. Subtraction significantly improved the contrast noise ratio between endolymph and perilymph and the subjective visibility score for endolymphatic space. The 24 patients with the suspect of Ménière's disease were included.

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

Introduction

Ménière's syndrome is an inner ear disorder characterized by spontaneous attacks of rotating vertigo, fluctuating low frequency sensorineural hearing loss, aural fullness, and tinnitus. When the syndrome is idiopathic and cannot be attributed to any other cause, such as syphilis, inflammatory inner ear disease, or trauma, it is termed Ménière's disease.¹ Endolymphatic hydrops has long been considered the pathologic basis for Ménière's disease.¹

Visualization of endolymphatic hydrops in patients with Ménière's disease was first achieved by MR imaging using 3-dimensional (3D) fluid attenuated inversion recovery (FLAIR) after intratympanic (IT) administration of gadolinium-based contrast material (GBCM).² On 3D-FLAIR images, the signal of perilymph containing GBCM increases and the intensity of signals of the endolymphatic space and surrounding bone are both near zero (positive perilymph image; PPI). On 3D-FLAIR, the boundary between bones and endolymphatic space is unclear. Shortening of the inversion time of 3D-FLAIR has been proposed to clarify those boundaries and rule out partial volume averaging artifact from bones.³ Optimal shortening of the inversion time in 3D-FLAIR suppresses the signal of perilymph containing GBCM, instead giving

high signal to endolymph without GBCM (positive endolymph image; PEI).

Although the clinical significance of MR imaging evaluation of endolymphatic hydrops is reported,^{4–6} the IT administration of GBCM requires a slightly invasive puncture of the tympanic membrane, is off-label use, and requires 24 hours of waiting time. Thus, the development of a method for detecting endolymphatic hydrops by intravenous (IV) injection of GBCM was explored for wider application in the clinical field. Heavily T₂-weighted 3D-FLAIR (hT₂W-3D-FLAIR) and imaging 4 hours after IV injection of single-dose GBCM (IV-SD-GBCM) have been reported to visualize endolymphatic hydrops in patients with Ménière's disease.⁷ Similar to acquisition of PPI and PEI after IT administration of GBCM, their acquisition after IV-SD-GBCM was possible based on the hT₂W-3D-FLAIR technique.⁸

Separate visualization of the endolymph, perilymph, and bone on a single image has been reported using 3D-inversion recovery sequence with "real" reconstruction (3D-real IR) in cases after IT administration of GBCM.⁹ Use of 3D-real IR images facilitated recognition of endolymph space,¹⁰ but the method has not succeeded in cases of IV-SD-GBCM, probably because of the lower GBCM concentration in the perilymph.

While we were fusing PPI and PEI images obtained after IV-SD-GBCM to evaluate misregistration between the 2 images, we noticed that the fusion of gray-scale inverted PEI with native gray-

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

scale PPI, that is, subtraction of PEI from PPI, might enable the 3D-real IR-like image presentation. We named this processed image HYDROPS (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph signal).

We evaluated the utility of the HYDROPS image obtained 4 hours after IV administration of SD-GBCM for recognizing endolymphatic space.

Materials and Methods

Patients

We evaluated images of 24 patients with clinically suspected Ménière's disease (12 men, 12 women, aged 27 to 74 years) who underwent magnetic resonance (MR) scanning 4 hours after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) IV administration of gadolinium-diethylene-triamine pentaacetic acid-bis (methanamide) (gadodiamide: Gd-DTPA-BMA; Omniscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. The estimated glomerular filtration rate (eGFR) of all patients exceeded 60 mL/min/1.73 m², as calculated using an equation reported by the Japanese Society of Nephrology for estimating GFR in Japanese patients and based on serum creatinine level (Cr): $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times Cr^{-1.094} \times \text{Age}^{-0.287}$ (if female, $\times 0.739$). Clinical suspicion of Ménière's disease was determined by experienced otorhinolaryngologists based on the presence of ear symptoms, vertigo, average hearing level on pure tone audiometry, various otological tests, and clinical history.

MR imaging

All MR imaging was performed on a 3-tesla unit (Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil. According to our hospital's clinical protocol for the evaluation of endolymphatic hydrops, each of the 24 patients underwent heavily T₂-weighted MR cisternography (MRC) for the anatomical reference of total lymph fluid, hT₂W-3D-FLAIR with inversion time of 2250 ms (PPI), and hT₂W-3D-inversion recovery with inversion time of 2050 ms (PEI). Parameters were set as previously reported.⁸

Detailed scan parameters for MRC were: heavily T₂-weighted MRC images using variable flip angles, 3D turbo spin echo technique (SPACE: sampling perfection with application-optimized contrasts by using different flip angle evolutions): repetition time (TR), 4400 ms; echo time (TE), 544 ms; initial refocusing flip angle (FA) of 180° rapidly decreased to constant FA of 120° for the turbo-spin-echo

refocusing echo train, for the SPACE turbo spin-echo refocusing echo train; echo train length, 173 with restore magnetization pulse (fast recovery pulse); matrix size, 322 × 384; 96 axial slices of 1.0-mm thickness; 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 hT₂W-3D-FLAIR for PPI were: SPACE sequence; TR, 9000 ms; TE, 544 ms; inversion time, 2250 ms; frequency-selective fat-suppression pre-pulse, initial refocusing FA of 180° rapidly decreased to constant FA 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 with a 15 × 18-cm FOV; acquired using the GRAPPA parallel imaging technique with acceleration factor of 2; NEX, 4; and scan time, 14.5 min.

Parameters for PEI employed shorter inversion time—2050 instead of the 2250 ms of PPI. MR cisternography, PPI, and PEI employed identical FOV, matrix size, and slice thickness to facilitate comparison.

We generated HYDROPS images on the scanner console by subtracting PEI from PPI, saved them, and transferred them to a PACS server as a separate series. For subtraction results, we allowed negative signal value.

Image analysis

For quantitative evaluation, we measured the contrast-to-noise ratio (CNR) between perilymph and endolymph for PPI, PEI, and HYDROPS images. CNR was measured in the vestibule, where the endolymph space is usually larger than the cochlea, yielding a reduction in the partial volume averaging effect. We manually placed a circular region of interest (ROI) of 1.2-mm diameter on the PACS viewer (Rapideye, Toshiba Medical Systems, Tokyo, Japan). ROIs were set on PPI images with reference to MRC. For the vestibular endolymph, we placed the ROI in the center of the area with low signal in the utricle of the vestibule on the PPI image at the slice level of the superior vestibular nerve. For the vestibular perilymph, we placed the ROI in the area of high signal surrounding the utricle on the PPI image. If the vestibule was entirely occupied by endolymph, we set the ROI in the area of high signal in the lateral semicircular canal. Noise level was defined as the standard deviation (SD) of air signal in the lower corner of the image. A circular ROI of 10-mm diameter was drawn for noise. ROIs were copied from PPI onto PEI and

onto HYDROPS images. CNR was defined as the difference of signal intensity value between the perilymph and endolymph divided by the SD of the air signal. We compared the average CNR of PPI, PEI, and HYDROPS images using one-factor ANOVA and Bonferroni/Dunn procedure for multiple comparison. $P < 0.05$ was considered statistically significant difference.

For qualitative analysis, 2 neuroradiologists with 5 and 22 years' experience in inner ear MR imaging independently evaluated images on the PACS viewer. Reviewers knew all patients had clinically suspected Ménière's disease. They evaluated the vestibule and cochlea separately. They first reviewed the MRC + PPI + PEI image set and subjectively scored the recognition of endolymphatic space as poor, fair, good, or excellent. Then, more than 2 weeks later, they similarly reviewed the MRC + PPI + PEI + HYDROPS image set and scored recognition of the endolymphatic space. Review order of the patients was randomized. For HYDROPS images, they scored the presence of misregistration artifact as positive or negative. Apparent double contour of the labyrinth was considered positive for misregistration. In both review sessions, MRC images served as reference maps of the total lymph fluid anatomy. Any discrepancies between the 2 reviewers were resolved by consensus after discussion. Recognition scores for endolymphatic space were compared using Wilcoxon signed-ranks test between the MRC + PPI + PEI and MRC + PPI + PEI + HYDROPS image sets; recognition scores for endolymphatic space between the vestibule and cochlea were also compared for both image sets. $P < 0.05$ was considered statistically significant difference.

Our institutional medical ethics committee approved this retrospective study, and informed consent was waived.

Results

In the quantitative analysis, the average CNR $\pm$ SD of PPI was 63.8 ± 28.3 ; of PEI, 62.5 ± 28.8 ; and of HYDROPS, 89.6 ± 26.5 . One-factor ANOVA indicated significant difference among groups. Using Bonferroni/Dunn procedure for multiple comparison, we observed significant difference between PPI and HYDROPS images and between PEI and HYDROPS images. There was no significant difference between PPI and PEI.

In the qualitative analysis, the subjective score for recognition of endolymphatic space was significantly better for the MRC + PPI + PEI + HYDROPS set than the MRC + PPI + PEI set for

both the cochlea and vestibule (Figs. 1, 2). Recognition of the vestibular endolymph was good or excellent in all ears for the image set with HYDROPS and for all ears except one for the image set without HYDROPS. Recognition of the cochlear endolymph was good or excellent in 34 ears for the image set with HYDROPS and in 18 ears for the image set without HYDROPS. Recognition scores were significantly better for the vestibule than cochlea for both image sets. No misregistration artifact was noticed in any ear.

Table 1 summarizes the patients and average CNRs, and Table 2 lists the results of endolymphatic space recognition scores for each image set.

Discussion

The HYDROPS image has facilitated recognition of the endolymphatic space on a single type of image even after clinically feasible IV-SD-GBCM. On the HYDROPS image, perilymph shows positive signal, endolymph shows negative signal, and surrounding bone shows no signal. The image contrast is like that of 3D-real IR images obtained after IT-GBCM. The image processing technique used in the present study was simple subtraction of PEI from PPI. Although subtraction itself does not generate new information, combining the information of 2 kinds of image onto a single image type might have facilitated recognition of the anatomical relationship between the endolymphatic space and surrounding structures. The increased CNR between endo- and perilymphatic space by subtraction might have synergistically facilitated recognition.

The average score was lower for recognition of the cochlear endolymph than for the vestibular endolymph on both image sets with and without HYDROPS images. This is probably attributable to 2 reasons—that the cochlear endolymph is usually smaller in size than the vestibular endolymph and that the cochlear endolymph is partly surrounded by bone. Without the HYDROPS image, the boundary between small cochlear endolymph and surrounding bone is difficult to recognize.

A potential risk of subtraction is misregistration between the 2 kinds of images from patient motion, but we observed no misregistration or motion between PPI and PEI scans in any patient. Scan time of PPI and PEI is relatively long; each takes 14.5 min. In a larger number of patients, some should likely show misregistration between the 2 scans. The labyrinth is in the rigid skull, so in cases with significant motion between the 2 scans, an image registration program for rigid body, which is

Fig. 1. A 27-year-old man with bilateral Ménière's disease. **(a)** Heavily T_2 -weighted magnetic resonance (MR) cisternography of the right inner ear. **(b)** Corresponding positive endolymph image (PEI) obtained by heavily T_2 -weighed 3-dimensional (3D)-inversion recovery sequence with inversion time of 2050 ms. Note that the significantly dilated cochlear endolymph (short arrows) and significantly dilated vestibular endolymph (long arrows) show bright signal. **(c)** Corresponding positive perilymph image (PPI) obtained by hT_2W -3D-FLAIR sequence with inversion time of 2250 ms. Filling defects are noted at the corresponding locations of high signal on PEI. The boundary between the cochlear endolymph (short arrows) and bone are unclear. The boundary between the vestibular endolymph (long arrows) and bone are also unclear. **(d)** The corresponding HYDROPS (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image obtained by subtracting the PEI image from the PPI image. Note that the perilymph, endolymph, and bone show different signal; the perilymph shows positive signal (white on the image), and the endolymph shows negative signal (black on the image). Bone shows no signal (gray on the image). Short arrows indicate significantly dilated cochlear endolymph, and long arrows indicate significantly dilated vestibular endolymph. In this particular patient, the subjective grade for recognition of the endolymph is "excellent" for the cochlea and vestibule by both image sets with and without HYDROPS image.

equipped on most scanners and 3D workstations might be helpful.

We successfully suppressed the perilymph signal on PEI in all ears. However, in cases with impaired blood-labyrinthine-barrier, use of the present PEI scan parameters might not effectively suppress the perilymph signal. Therefore, to prevent misdiagnosis in the clinical setting, image interpretation should include PPI and PEI as well as HYDROPS images.

Our study has some limitations. One was that we might not be able to visualize endolymphatic hydrops in cases with ruptured Reissner's mem-

brane, in which the endo- and perilymph might be contaminated. In the present study, we believe that there was no case with rupture. This situation is seen in minority of cases in histological specimen.^{11,12}

In this study, although we applied a parallel imaging technique, we estimated noise in the background air area. Use of parallel imaging and multi-channel phased array coil yields uneven noise distribution across the image.¹³ However, in the present study, we measured CNR for comparison between PEI, PPI, and HYDROPS images in each subject. We estimated signals of the inner ear and of noise

Fig. 2. A 70-year-old woman with bilateral Ménière's disease. **(a)** Heavily T₂-weighted MR cisternography of the left inner ear. **(b)** Corresponding positive endolymph image (PEI). Note that the mildly dilated cochlear endolymph (short arrows) shows slight bright signal. **(c)** Corresponding positive perilymph image (PPI). Filling defects are barely noted at the corresponding locations of high signal on PEI. **(d)** Corresponding HYDROPS (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image obtained by subtraction of PEI image from PPI image. Note that the perilymph, endolymph, and bone show different signal. Short arrows indicate slightly dilated cochlear endolymph. In this particular patient, the subjective grade for recognition of the cochlear endolymph is "fair" by the image set without HYDROPS image and "good" by the image set with HYDROPS image. Vestibular endolymph is not visualized on this particular slice.

in the background air area in the lower corner of the image in the identical place in a given subject, and those places differed little among subjects. Therefore, our method for measuring CNR was not ideal, but we believe it was reasonably appropriate for our study purpose.

Another limitation of this preliminary study is that we did not include normal subjects, so we cannot conclude that use of a HYDROPS image would improve recognition of the endolymphatic space in patients without endolymphatic hydrops. A previous report indicated that nondilated endolymph of the cochlea did not produce noticeably high signal on PEI,⁸ and without such signal, we cannot expect improvement on a HYDROPS image.

Use of HYDROPS images facilitates recognition of the endolymphatic space. However, easier recog-

nition and increased CNR might lead to overdiagnosis of endolymphatic hydrops; we cannot obtain histological confirmation of endolymphatic hydrops in living subjects. To establish the clinical significance of HYDROPS images for the diagnosis of endolymphatic hydrops, we should evaluate inter- and intraobserver diagnostic variability in more cases among more observers. Evaluation of the appropriateness of diagnosis using HYDROPS images should correlate clinical symptoms and otological tests in more patients.

Conclusions

A simple subtraction of PEI from PPI facilitated recognition of the endolymphatic space on images obtained after IV-SD-GBCM. Further clinical

Table 1. Contrast-to-noise ratio between perilymph and endolymph of vestibule

Patient No.	Age (years)	Sex	Side	PPI (positive perilymphatic image)	PEI (positive endolymphatic image)	HYDROPS image
1	71	M	R	31.0	52.0	59.3
			L	41.0	49.0	64.3
2	74	F	R	22.5	31.7	37.8
			L	30.0	25.3	37.0
3	67	F	R	51.3	133.8	134.5
			L	62.5	50.0	81.8
4	32	M	R	52.9	68.0	88.8
			L	71.4	94.0	121.3
5	63	M	R	121.4	107.1	160.0
			L	152.9	22.9	123.0
6	59	F	R	47.1	71.4	83.0
			L	71.4	22.9	66.0
7	62	F	R	25.7	114.3	98.0
			L	34.3	60.0	66.0
8	76	M	R	77.1	50.0	89.0
			L	67.1	27.1	66.0
9	40	M	R	61.7	73.3	101.3
			L	48.3	55.0	77.5
10	61	F	R	56.3	28.6	65.0
			L	96.3	44.3	108.0
11	59	M	R	85.7	60.0	108.0
			L	78.6	58.8	102.0
12	37	M	R	14.3	30.0	31.0
			L	71.4	74.3	102.0
13	67	M	R	50.0	80.0	91.0
			L	115.7	51.4	117.0
14	51	M	R	82.9	77.1	112.0
			L	50.0	78.6	90.0
15	27	M	R	27.1	158.6	130.0
			L	35.7	92.9	90.0
16	46	F	R	55.7	74.3	91.0
			L	31.4	51.4	58.0
17	46	M	R	40.0	71.4	78.0
			L	64.3	64.3	90.0
18	60	F	R	80.0	71.4	106.0
			L	97.1	42.9	98.0
19	70	F	R	75.7	74.3	105.0
			L	88.6	28.6	82.0
20	52	F	R	55.7	62.9	83.0
			L	54.3	54.3	76.0
21	44	M	R	108.6	34.3	100.0
			L	90.0	81.4	120.0
22	50	F	R	44.3	85.7	91.0
			L	77.1	48.6	88.0
23	63	F	R	38.6	31.4	49.0
			L	71.4	38.6	77.0
24	58	F	R	64.3	47.1	78.0
			L	92.9	95.7	132.0
mean				63.8*	62.5#	89.6*,#
SD				28.3	28.8	26.5

SD, standard deviation

*, #; statistically significant difference ($P < 0.05$)

HYDROPS, HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal

Table 2. Scores for the recognition of endolymphatic space of 48 ears

		excellent	good	fair	poor	
Recognition score for cochlear endolymph	Image set without HYDROPS image	5	13	22	8	*,#
	Image set with HYDROPS image	15	19	11	3	*,§
Recognition score for vestibular endolymph	Image set without HYDROPS image	8	39	1	0	**,#
	Image set with HYDROPS image	13	35	0	0	**,§

HYDROPS, HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal
*, **, #, §; statistically significant difference ($P < 0.05$)

study is warranted for the routine use of this subtracted (HYDROPS) image.

References

1. Agrawal Y, Minor LB. Physiologic effects on the vestibular system in Ménière's disease. *Otolaryngol Clin North Am* 2010; 43:985–993.
2. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Ménière's disease. *Laryngoscope* 2007; 117: 415–420.
3. Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid at 3T after intratympanic administration of gadolinium-diethylenetriamine pentaacetic acid. *AJNR Am J Neuroradiol* 2008; 29:724–726.
4. Gürkov R, Flatz W, Louza J, Strupp M, Krause E. *In vivo* visualization of endolymphatic hydrops in patients with Ménière's disease: correlation with audiovestibular function. *Eur Arch Otorhinolaryngol* 2011; 268:1743–1748.
5. Yamamoto M, Teranishi M, Naganawa S, et al. Relationship between the degree of endolymphatic hydrops and electrocochleography. *Audiol Neurotol* 2010; 15:254–260.
6. Katayama N, Yamamoto M, Teranishi M, et al. Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. *Acta Otolaryngol* 2010; 130:917–923.
7. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière's disease with single-dose intravenous gadolinium-based contrast media using heavily T₂-weighted 3D-FLAIR. *Magn Reson Med Sci* 2010; 9:237–242.
8. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid after intravenous administration of single-dose gadodiamide. *Magn Reson Med Sci* 2011; 11:145–150.
9. Naganawa S, Satake H, Kawamura M, Fukatsu H, Sone M, Nakashima T. Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. *Eur Radiol* 2008; 18:920–924.
10. Nakashima T, Naganawa S, Katayama N, et al. Clinical significance of endolymphatic imaging after intratympanic gadolinium injection. *Acta Otolaryngol* 2009; 129:9–14.
11. Nakashima T, Naganawa S, Pykko I, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. *Acta Otolaryngol* 2009; 129:5–8.
12. Sperling NM, Paparella MM, Yoon TH, Zelterman D. Symptomatic versus asymptomatic endolymphatic hydrops: a histopathologic comparison. *Laryngoscope* 1993; 103:277–285.
13. Dietrich O, Raya JG, Reeder SB, Reiser MF, Schoenberg SO. Measurement of signal-to-noise ratios in MR images: influence of multichannel coils, parallel imaging, and reconstruction filters. *J Magn Reson Imaging* 2007; 26:375–385.