Imaging of Ménière’s Disease after Intravenous Administration of Single-dose Gadodiamide: Utility of Multiplication of MR Cisternography and HYDROPS Image

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A HYDROPS (HYbriD Of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image, created by subtracting a positive endolymph image from a positive perilymph image after intravenous injection of single-dose gadodiamide, has been reported to facilitate recognition of endolymphatic hydrops. To further increase the contrast-to-noise ratio (CNR) of HYDROPS images, we multiplied a T2-weighted MR cisternographic image onto the HYDROPS image. Ten patients with suspected Ménière’s disease were included. The average CNR of generated images increased to more than 200 times that of HYDROP images.

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

Introduction

Endolymphatic hydrops in patients with Ménière’s disease was first visualized by magnetic resonance (MR) imaging using 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) after intratympanic (IT) administration of gadolinium-based contrast material (GBCM). On 3D-FLAIR images, the signal of perilymph containing GBCM increases, and signals of both the endolymphatic space and surrounding bone show values near zero (positive perilymph image; PPI). However, PPI images are limited by their unclear boundaries between bones and endolymph. Shortening the inversion time of 3D-FLAIR was proposed to clarify those boundaries and rule out partial volume averaging artifact from bones. Optimal shortening of that time suppresses the signal of perilymph with GBCM distribution and enhances the signal of endolymph without GBCM distribution (positive endolymph image; PEI).

Though the clinical significance of endolymphatic hydrops evaluation by MR imaging is reported, the IT administration of GBCM is off-label use, involves a slightly invasive puncture of the tympanic membrane, and requires 24 hours of waiting time before imaging. Thus, the development of a method for detecting endolymphatic hydrops by intravenous injection (IV) of GBCM was explored for wider use in the clinical field. Heavily T2-weighted 3D-FLAIR (hT2W-3D-FLAIR) and imaging 4 hours after IV administration of single-dose GBCM (IV-SD-GBCM) were reported to achieve visualization of endolymphatic hydrops in patients with Ménière’s disease. Similarly to PPI and PEI after IT administration of GBCM, PPI type image and PEI type image could be obtained after IV administration of SD-GBCM based on the hT2W-3D-FLAIR technique.

Separate visualization of endolymph, perilymph, and bone on a single image has been reported using 3D inversion recovery sequence with “real” reconstruction (3D-real IR) after IT administration of GBCM, and 3D-real IR images have facilitated recognition of endolymphatic space. However, this method has not succeeded in cases using IV administration of SD-GBCM, probably because of lower GBCM concentration in the perilymph. Subtraction of the PEI from the PPI has yielded
images resembling those by 3D-real IR even after IV-SD-GBCM. This processed image has been named HYDROPS (HYbrid D of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal). Although the contrast-to-noise ratio (CNR) between the endo- and perilymph is approximately 40% higher on HYDROPS than PEI or PPI images, HYDROPS images remain noisy. Automatic segmentation of the endolymph is still difficult, and results are susceptible to slight change in the threshold value.

On the HYDROPS image, signal intensity values of background pixels are near zero with some noise, and those of the perilymph are positive and of the endolymph, negative. Usually on heavily T2-weighted MR cisternographic images, the signal intensity values of bone and air pixels are near zero, with far less noise than HYDROPS images, and the perilymph and endolymph show similar very high signal intensity. The signal intensity values of perilymph and endolymph on heavily T2-weighted MRC images are far larger than on HYDROPS images. Therefore, to further increase the CNR between the endo- and perilymph of HYDROPS images, we propose the multiplication of heavily T2-weighted MRC images to HYDROPS images. We named this processed image HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted MR cisternography).

In this study, we compared CNR values between the endo- and perilymph on HYDROPS images and those on HYDROPS-Mi2 images obtained 4 hours after IV administration of single-dose GBCM.

**Materials and Methods**

**Patients**

Ten patients with clinically suspected Ménière’s disease (4 men, 6 women, aged 17 to 68 years) were included in this study. All patients had undergone 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 (methylamide) (gadodiamide: Gd-DTPA-BMA; Omniscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. All patients also had an estimated glomerular filtration rate (eGFR) value exceeding 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): eGFR (mL/min/1.73 m²) = 194 × Cr^{-1.094} × Age^{-0.287} (if female, × 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, results of 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. Four hours after IV-SD-GBCM, all patients underwent heavily T2-weighted MR cisternography (MRC) for anatomical reference of total lymph fluid, hT2W-3D-FLAIR with inversion time of 2250 ms (PPI), and hT2W-3D-IR with inversion time of 2050 ms (PEI) according to the clinical protocol of our hospital for evaluating endolymphatic hydrops. Parameters were set as previously reported.2

Detailed scan parameters for MRC follow. For heavily T2-weighted MRC 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 180° flip angle rapidly decreased to constant 120° flip angle for the turbo-spin-echo refocusing echo train; echo train length, 173 with restore magnetization pulse (fast recovery pulse); matrix size, 322 × 384; 96 axial slices with 1.0-mm-thick 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 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 180° flip angle rapidly decreased to constant 120° flip angle for the turbo-spin-echo refocusing echo train; echo train length, 173; matrix size, 322 × 384; 104 axial 1.0-mm-thick slices covering the labyrinth with FOV, 15 × 18 cm; acquired using GRAPPA parallel imaging with acceleration factor of 2; NEX, 4; and scan time, 14.5 min. Shorter inversion time (2050 ms) was employed for PEI than for PPI (2250 ms). MRC, PPI, and PEI employed identical FOV, matrix size, and slice thickness to make the comparison easier.

**Image processing**

HYDROPS images were generated on the scanner console by subtracting the PEI from the PPI. Generated HYDROPS images were saved and transferred to a PACS server as a separate series.
Negative signal value was allowed for subtraction results. HYDROPS-Mi2 images were generated on a free DICOM viewer (OsiriX image software, ver. 3.0.2. 32 bit; downloadable at http://www.osirix-viewer.com/index.html). HYDROPS and MRC images were transferred by CD-ROM to a MacBook personal computer (Apple Computer, Inc., Cupertino, CA, USA) with OsiriX software, which allowed easy pixel-by-pixel multiplication of HYDROPS and MRC images in a few seconds. Figure 1 is a conceptual diagram of the image processing.

**Image analysis**

For quantitative evaluation, we measured the CNR between the perilymph and endolymph for HYDROPS and HYDROPS-Mi2 images. We measured CNR in the vestibule, where the endolymphatic space is usually larger than in the cochlea, allowing the reduction of partial volume averaging effect. An experienced neuroradiologist manually placed circular regions of interest (ROI) of 1.2-mm diameter on the OsiriX viewer, first on the HYDROPS image and then copied to the HYDROPS-Mi2 image.

On the HYDROPS image, the ROI for the vestibular endolymph was set in the center of the area of low signal in the utricle of the vestibule at the slice level of the superior vestibular nerve. The ROI for the vestibular perilymph was set in the area of high signal surrounding the utricle. When endolymph occupies the entire vestibule, an ROI was also set in the area of high signal of 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 then copied from the HYDROPS im-

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**Fig. 1.** Conceptual diagram for the processing of HYDROPS (HYbriD of R
versed image Of Positive endolymph signal and native image of positive peri-
ymph Signal) and HYDROPS-Mi2 (HYDROPS image Multiplied with heavily
T_2-weighted MR cisternography) images. Images of a 31-year-old woman with
bilateral Ménière’s disease. (a) The HYDROPS image is generated by subtract-
ing the PEI (positive endolymph image) from the PPI (positive perilymph im-
age) and allows image presentation like that with 3-dimensional inversion recov-
ery sequence with ‘‘real’’ reconstruction (3D-real IR). (b) The HYDROPS-Mi2
image is generated by the pixel-by-pixel multiplication of magnetic resonance
cisternography (MRC; heavily T_2-weighted MRC) and the HYDROPS image.
On this slice level, significant endolymphatic hydrops is visualized in the vesti-
bule.
Fig. 2. An example of region of interest (ROI) setting for quantitative analysis. A HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted MR cisternography) image from a 53-year-old woman with bilateral Ménière’s disease. The black circle indicates the ROI for the perilymph and the white circle, the ROI for the endolymph.

age onto the HYDROPS-Mi2 image (Fig. 2). CNR was defined as the difference in signal intensity between the perilymph and endolymph divided by the SD of the air signal. We used Student’s t-test to compare the average CNR of the HYDROPS image and HYDROPS-Mi2 image. \(P < 0.05\) was considered a statistically significant difference.

For the HYDROPS and HYDROPS-Mi2 images, the neuroradiologist subjectively scored the presence of misregistration artifact as positive (present) or negative (absent). The apparent double contour of the labyrinth was considered positive for misregistration.

The medical ethics committee of our institution approved this retrospective study, and informed consent was waived.

### Results

In the quantitative analysis, the average CNR ± standard deviation (SD) of HYDROPS image was 56.0 ± 20.5 and of HYDROPS-Mi2 image, 11533.7 ± 7425.9 (\(P < 0.0001\)). In all ears, the CNR was larger for HYDROPS-Mi2 than HYDROPS images. Table summarizes the patients and CNR results of each ear.

In the qualitative analysis, no misregistration artifact was noted in any ear.

Figure 3 presents representative images of a pa-

### Table. Patients and contrast-to-noise ratios (CNR)

| Patient # | Age | Sex | Side | CNR between endo- and perilymph |
|-----------|-----|-----|------|---------------------------------|
|           |     |     |      | HYDROPS-Mi2                     | HYDROPS                        |
| 1         | 38  | f   | r    | 6572.7                         | 32.3                           |
| 2         | 17  | f   | l    | 6900.9                          | 26.1                           |
| 3         | 58  | m   | r    | 12352.2                         | 45.3                           |
| 4         | 58  | m   | l    | 14035.3                         | 48.1                           |
| 5         | 31  | f   | r    | 29768.4                         | 105.9                          |
| 6         | 53  | f   | l    | 3888.4                          | 34.3                           |
| 7         | 60  | f   | l    | 7290.3                          | 35.0                           |
| 8         | 68  | m   | r    | 422.3                           | 63.3                           |
| 9         | 47  | m   | l    | 11956.1                         | 72.0                           |
| 10        | 60  | f   | r    | 12834.4                         | 84.4                           |
|           |     |     |      | 11533.7                         | 56.0                           |
| SD        | 15.8|     |      | 7425.9                          | 20.5                           |

SD, standard deviation
Fig. 3. Representative images from a 68-year-old man with bilateral Ménière’s disease. Significant endolymphatic hydrops of the cochlea and mild endolymphatic hydrops of the vestibule are seen in the patient’s right ear. (a) HYDROPS (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image and (b) HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted MR cisternography) image. On both images, the dilated endolymphatic space is black, the perilymph, white, and surrounding bone, gray. Note that the signal of the bone and cerebellum is far more uniform on the HYDROPS-Mi2 image than the HYDROPS image and that the range of gray-scale signal values is far wider on the HYDROPS-Mi2 image.

Discussion

Development of the HYDROPS image has facilitated the recognition of endolymphatic space on a single kind of image even after clinically feasible IV administration of single-dose GBCM, and HYDROPS-Mi2 images further have improved the CNR between the endo- and perilymph. HYDROPS-Mi2 demonstration of an average increase in CNR 200 times greater than that of HYDROPS images further facilitated recognition of endolymphatic hydrops. On both HYDROPS and HYDROPS-Mi2 images, the signal of perilymph is positive, of endolymph, negative, and of surrounding bone, near zero. Image contrast resembles that of 3D-real IR images obtained after IT administration of GBCM. The largely increased CNR between endo- and perilymph on HYDROPS-Mi2 images might permit automatic segmentation of the endolymphatic space for area and volume quantification in the future and possibly be used to improve spatial resolution or shorten scan time.

A potential risk using HYDROPS-Mi2 images is the increased chance of misregistration caused by patient motion. HYDROPS images are generated by subtracting the PEI from the PPI, and HYDROPS-Mi2, by multiplying the HYDROPS and MRC. Thus, the processing of HYDROPS-Mi2 images might double the chance of misregistration. In this study, we noted no misregistration or motion between scans for any patient. Scan time is relatively long for PPI and PEI, 14.5 min each, but only 2.9 min for MRC. Future experience with more patients should likely demonstrate some misregistration between the 3 scans. In those circumstances, a simple image registration technique for rigid body might be applicable because the labyrinth is in the rigid skull.

Our study has some limitations. We applied parallel imaging and estimated noise in the air area, but use of parallel imaging and multi-channel phased array coil is reported to result in uneven noise distribution across the image. However, we measured CNR to compare that ratio between HYDROPS and HYDROPS-Mi2 images in each subject. Signal in the inner ear and of noise in the air area in the lower corner of image were estimated in the identical place in a subject, and those places differed little among subjects. Therefore, though our method of measuring CNR is not ideal, we believe it is reasonable for our study purpose. This preliminary study is also limited because we did not include healthy subjects and cannot, therefore, conclude that the HYDROPS-Mi2 images improve recognition of the endolymphatic space in patients without endolymphatic hydrops.

On HYDROPS-Mi2 images, increased CNR might lead to overdiagnosis of endolymphatic hydrops, and we cannot confirm its diagnosis by histology in living subjects. Therefore, in the fu-
ture, we should evaluate inter- and intraobserver variability in diagnosing endolymphatic hydrops in more cases among more observers to establish the clinical significance of HYDROPS-Mi2 images. The validity of the diagnosis using HYDROPS-Mi2 image should be evaluated by correlating clinical symptoms and otological test results in larger numbers of patients.

Conclusions

On average, CNR was more than 200 times greater on HYDROPS-Mi2 images than HYDROPS images. Further clinical study is warranted to justify the routine use of HYDROPS-Mi2 images.

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