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Magnetic resonance imaging of endolymphatic hydrops: a comparison of methods with and without gadolinium-based contrast agent administration

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ABSTRACT

In the evaluation of endolymphatic hydrops (EH) using magnetic resonance (MR) imaging, hybrid of reversed image of positive endolymph signal and native image of perilymph signal multiplied with heavily T2-weighted MR cisternography (HYDROPS-Mi2) imaging with the intravenous administration of a gadolinium-based contrast agent (IV-GBCA) has been utilized. Recently, MR cisternography (MRC) without GBCA has been proposed as a potential alternative method. However, the feasibility of EH evaluation by MRC without GBCA has not been established. The present study aimed to compare HYDROPS-Mi2 imaging with IV-GBCA to MRC without IV-GBCA for the evaluation of EH. In 40 ears of 20 patients with clinically suspected EH, MRC at pre-IV-GBCA and HYDROPS-Mi2 images from 4 h post-IV-GBCA were analyzed. The saccular height on the MRC (SH-MRC) was measured. The percentage of the volume of the endolymphatic space within the whole lymphatic space of the vestibule on the HYDROPS-Mi2 image (%EL_{volume}-HYD) was measured. The correlation between the SH-MRC and %EL_{volume}-HYD was calculated. The receiver operating characteristic (ROC) of the SH-MRC and %EL_{volume}-HYD for the clinical diagnosis of EH was evaluated. The Spearman's rank correlation coefficient between the SH-MRC and %EL_{volume}-HYD was 0.102. The areas under the ROC curve were 0.570 for the SH-MRC, and 0.926 for the %EL_{volume}-HYD. In conclusion, there was no significant correlation between the MRC without IV-GBCA and the HYDOROPS-Mi2 with IV-GBCA in the evaluation of EH.

Keywords: magnetic resonance imaging, gadolinium, endolymphatic hydrops, Meniere's disease

Abbreviations:
bSSFP: balanced steady-state free-precession

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EH: endolymphatic hydrops
FLAIR: fluid-attenuated inversion recovery
GBCA: gadolinium-based contrast agent
hT2w: heavily T2-weighted
HYDROPS: HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal
HYDROPS-Mi2: HYDROPS-Multiplied with hT2w MRC
IV: intravenous administration
MR: magnetic resonance
MRC: MR cisternography
%EL_{volume}-HYD: percentage of the volume of the endolymphatic space within the whole lymphatic space of vestibule measured on HYDROPS-Mi2
ROC: receiver operating characteristic
ROI: region of interest
SH-MRC: saccular height on MRC
3D: three-dimensional

INTRODUCTION

Meniere's disease is a neurological disorder of the inner ear with symptoms that include attacks of vertigo, hearing loss, tinnitus, and aural fullness.[1] Endolymphatic hydrops (EH) in the inner ear has been considered as a pathological finding of Meniere's disease.[1] The presence of EH has been clinically evaluated using magnetic resonance (MR) imaging after the intravenous administration of a gadolinium-based contrast agent (IV-GBCA).[1-3] Intravenously administered GBCAs cross the blood-perilymph barrier, but do not cross the blood-endolymph and perilymph-endolymph barriers.[4] The amount of intravenously administered GBCA that penetrates into the perilymph is too small to detect using conventional T1-weighted imaging.[2,5] A heavily T2-weighted three-dimensional fluid-attenuated inversion recovery (hT2w-3D-FLAIR) sequence can detect subtle T1 shortening such as in fluid with very small concentrations of GBCA, and hence has been applied for the evaluation of EH with MR imaging.[3,5] A HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal (HYDROPS) and a HYDROPS-Mi2 (HYDROPS-Multiplied with hT2w MRC) sequence enables separate visualization of the endolymph, perilymph, and surrounding bony structures.[6,7] This separate visualization of the endo- and perilymph reduces the difficulty of the EH evaluation.[2,6,7] A Nakashima grade has been proposed as the criterion for the diagnosis of EH on MR imaging.[8] A quantitative evaluation of the endolymphatic space by volumetric measurement has also been reported.[9] MR imaging with GBCA administration has thus been applied clinically for the qualitative and quantitative evaluation of EH.[1,2,8,9]

Recently, several studies for the evaluation of EH using MR imaging without GBCA administration have been reported.[10-12] They have proposed that MR cisternography (MRC) permits the direct evaluation of the vestibular endolymphatic space through anatomical identification.[10-12] One of the studies suggested that the utricular endolymph has a lower signal intensity than the vestibular perilymph on MRC without IV-GBCA.[10] The other studies assessed vestibular EH by measuring the height and width of the saccule on MRC without IV-GBCA.[11,12] The saccule was defined as the region bounded by the utricular macula and the lateral membranous walls of the saccule for the measurement of the saccular size.[11,12]

The evaluation of EH using MRC without GBCA administration has clinical implications. In our hospital, we routinely perform the evaluation of EH at 4 h post-IV-GBCA administration, and

prior to the IV-GBCA, we obtain an MRC as the anatomical reference image. When our reviewing the MRC, we were able to distinguish the utricular macula, however the lateral membranous wall of the saccule or the vestibular endolymph was unclear. At least, there did not seem to be any displacement of the utricular macula in our MRC with or without EH. Therefore, we hypothesized that an MRC without GBCA might not be suitable to evaluate the endolymphatic space. To our knowledge, there are no reports directly comparing EH evaluation methods with and without IV-GBCA. The purpose of present study was to compare the evaluation of EH using HYDROPS-Mi2 (with IV-GBCA) and MRC (without IV-GBCA).

MATERIALS AND METHODS

Patients and materials

Forty ears from consecutive 20 patients with clinically suspected EH who underwent MR imaging from November, 2017 through November, 2018 were enrolled in the present study (men: 9, women: 11, ages: 21 to 70-year-old, median: 53.5-year-old). The patient with severe motion artifact was an exclusion criterion. The estimated glomerular filtration rate of all patients at pre-administration of GBCA exceeded 60 ml/min/1.73m^2. The medical ethics committee of our institution approved this retrospective cross-sectional study with a waiver of written informed consent from the patients (2021-0461). The present study was conducted in compliance with the Declaration of Helsinki in 1964 and its later amendments. All MR imaging was performed using a 3-tesla MR scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) with a 32-channel phased-array head coil. The contrast agent administered to patients in the present study was a macrocyclic GBCA (Gd-HP-DO3A: ProHance; Eisai, Tokyo, Japan). A single dose of GBCA defined as 0.1 mmol/kg body-weight was administered. A DICOM viewer (OsiriX version 5.8 32 bit; Pixmeo SARL, http://www.osirix-viewer.com/) was used for image processing and analysis. Statistical analyses were performed with free statistical software (R software version 3.6.1; The R Foundation, https://www.r-project.org/).

MR imaging

MRC and hT2w-3D-FLAIR images were obtained. All imaging sequences were based on hT2w-3D-fast spin echo imaging with a variable refocusing flip angle. The cross section of the slab for all imaging was the axial plane parallel to the anterior commissure - posterior commissure line and through the bilateral internal auditory canal in the axial plane. The slab center of all imaging was set at the level of the internal auditory canal. At pre-IV-GBCA, MRC of the whole lymphatic space was obtained for anatomical reference. A repetition time of 2500 ms, echo time of 400 ms, voxel size of 0.50 × 0.50 × 0.5 mm, and slab thickness of 80 mm were applied. At 4 h post-IV-GBCA, MRC, hT2w-3D-FLAIR with an inversion time of 2250 ms as the positive perilymph image, and hT2w-3D-FLAIR with an inversion time of 2050 ms as the positive endolymph image were obtained to generate the HYDROPS-Mi2 image. The parameters were set according to a previously reported study.[6] A repetition time of 4400 ms for the MRC, a repetition time of 9000 ms for the positive perilymph image and positive endolymph image, an echo time of 544 ms, voxel size of 0.51 × 0.51 × 1.0 mm, and a slab thickness of 104 mm were applied. The detailed parameters of all imaging are summarized in Table 1. The HYDROPS-Mi2 images were generated according to the previous study as follows.[7]

HYDROPS = positive perilymph image - positive endolymph image

HYDROPS-Mi2 = HYDROPS × MRC

On the HYDROPS-Mi2 images, no misregistration artifacts greater than 1 mm were confirmed

Table 1 Pulse sequence parameters

	Pre-IV-GBCA	4 h Post-IV-GBCA		
	MRC	MRC	positive perilymph image	positive endolymph image
Pulse sequence type	SPACE	SPACE	SPACE with inversion pulse	SPACE with inversion pulse
Repetition time/Echo time (ms)	2500 / 400	4400 / 544	9000 / 544	9000 / 544
Inversion time (ms)	NA	NA	2250	2050
Band width (Hz/Px)	422	434	434	434
Flip angle (degree)	90 / initial 180 decrease to constant 120	90 / initial 180 decrease to constant 120	90 / constant 180	90 / constant 180
Echo train length	181	173	173	173
Matrix	320 × 320	324 × 384	324 × 384	324 × 384
Slice thickness (mm) / Slices	0.5 / 80	1.0 / 104	1.0 / 104	1.0 / 104
Resolution (mm)	0.50 × 0.50	0.51 × 0.51	0.51 × 0.51	0.51 × 0.51
Field of view (mm)	160 × 160	196 × 165	196 × 165	196 × 165
Parallel imaging / Accel. factor	GRAPPA / 2	GRAPPA / 2	GRAPPA / 2	GRAPPA / 2
Fat saturation	NA	CHESS	CHESS	CHESS
Number of excitations	1.5	1.8	2	2
Acquisition time (min)	5.2	3.3	7.4	7.4

CHESS: chemical shift selective saturation
GRAPPA: generalized auto-calibrating partially parallel acquisition
IV-GBCA: intravenous administration of gadolinium-based contrast agent
MRC: magnetic resonance cisternography
NA: not applicable
SPACE: sampling perfection with application-optimized contrasts using different flip angle evolutions

in any patients.

Image analysis

A clinical diagnosis of EH had been made by an experienced neuroradiologist (SN) subjectively, according to the Nakashima grade.[8]

Two radiological technologists with 18 years (TO) and 8 years (YN) of experience in MR imaging performed all image analyses. The distance between the utricular macula and the vestibular edge of the osseous spiral lamina was measured as the saccular height on the MRC (SH-MRC) obtained at pre-IV-GBCA. The measurement protocol was described below.

1. The MRC was reformatted to the coronal plane perpendicular to the anterior commissure-posterior commissure line.
2. The reformatted coronal image through the inferior vestibular nerve was used for the measurement.
3. The distance between the middle of the utricular macula and the vertically inferior osseous

spiral lamina was measured.

The SH-MRC ie, the shift of the utricular macula, was regarded as an indicator of the degree of vestibular EH using MRC without IV-GBCA in the present study. An example of the measurement of the SH-MRC is indicated in Fig. 1.

The percentage of the volume of the endolymphatic space within the whole lymphatic space of the vestibule was measured on the HYDROPS-Mi2 images ($\%EL_{volume}$-HYD), according to previously a reported study.[9]

1. The regions of interest (ROIs) were manually drawn along the boundary of the vestibule excluding the ampulla of the semicircular canal on all slices of the MRC obtained at 4 h post-IV-GBCA.
2. The ROIs of the MRC were copied and pasted onto the HYDROPS-Mi2 image.
3. The number of voxels in all ROIs represented the whole-lymph volume and were counted on the HYDROPS-Mi2 image.
4. The number of voxels with a negative signal intensity in all ROIs represented the endolymph volume and were counted on the HYDROPS-Mi2 image.
5. The $\%EL_{volume}$-HYD was calculated as follows.

   $\%EL_{volume}$-HYD = (endolymph volume/whole lymph volume) × 100

The $\%EL_{volume}$-HYD was regarded as an indicator of the degree of vestibular EH with IV-GBCA in the present study.

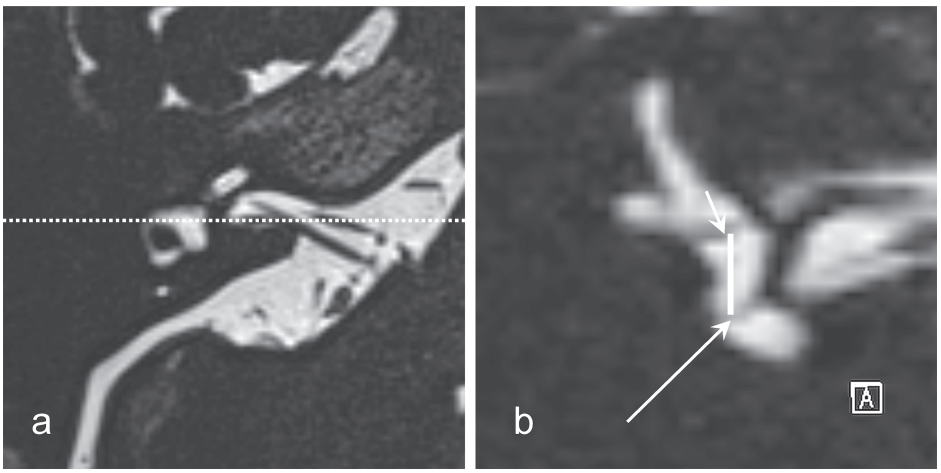

Fig. 1 An example of the measurement of the saccular height

Magnetic resonance cisternography was reformatted to the coronal plane perpendicular to the anterior commissure-posterior commissure line (dotted line) (a). The reformatted coronal images through the inferior vestibular nerve were used for the measurement (b). The distance between the middle of the utricular macula (short arrow) and the vertically inferior osseous spiral lamina (long arrow) was measured as the saccular height (line).

Statistical analyses

The inter-observer reliability was evaluated using an intraclass correlation coefficient (2, 1). The averaged value from the two observers was used for the statistical analyses. The correlation between the SH-MRC and $\%EL_{volume}$-HYD was evaluated by a Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curve of the SH-MRC and $\%EL_{volume}$-HYD were plotted to assess the consistency of the SH-MRC and $\%EL_{volume}$-HYD compared to our

clinical diagnosis of EH by the Nakashima grade using the area under the ROC curve. The ears were classified into EH-negative and EH-positive groups using a cut-off value determined by the maximum value of the Youden index of the ROC curve of the $\%EL_{volume}$-HYD. A Mann-Whitney U test was used to compare the SH-MRC between the EH-negative and EH-positive groups. We defined 5% as a threshold for statistical significance.

RESULTS

There were no patients with severe motion artifact that would be an exclusion criterion. The intraclass correlation coefficients (2, 1) between the measurements of the two observers were 0.900 for the SH-MRC and 0.979 for the $\%EL_{volume}$-HYD. There was no significant correlation between the SH-MRC and $\%EL_{volume}$-HYD (Fig. 2). The Spearman's rank correlation coefficient between the SH-MRC and $\%EL_{volume}$-HYD was 0.102 (P = 0.532). In the ROC analysis for the SH-MRC, the area under the ROC curve was 0.570 (95% confidence level: 0.378-0.762) (Fig. 3a). In the ROC analysis for the $\%EL_{volume}$-HYD, the area under the ROC curve was 0.926 (95% confidence level: 0.850-1.000) (Fig. 3b). The maximum value of the Youden index analyzed by

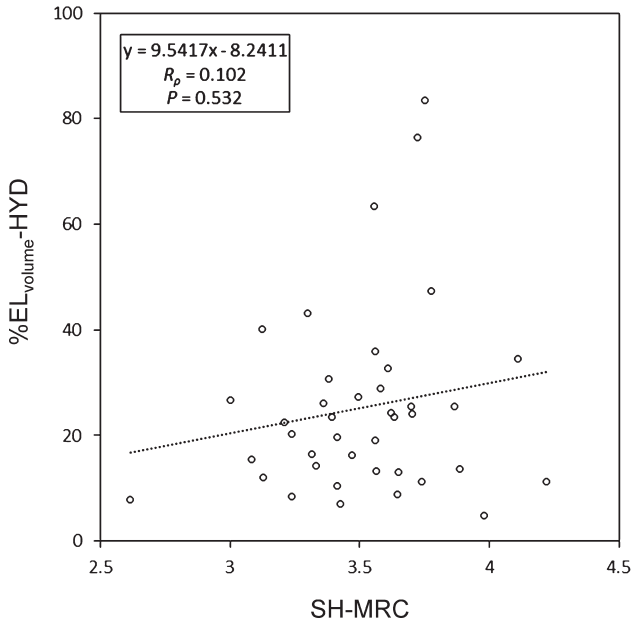

Fig. 2 Relationship between SH-MRC and $\%EL_{volume}$-HYD

Scatterplots of the degree of endolymphatic hydrops showing the relationship between the SH-MRC without an IV-GBCA and the $\%EL_{volume}$-HYD with IV-GBCA. There was no significant correlation between the SH-MRC and $\%EL_{volume}$-HYD. The Spearman's rank correlation coefficient between the SH-MRC and $\%EL_{volume}$-HYD was 0.102 (P = 0.532).

IV-GBCA: intravenous administration of gadolinium-based contrast agent

$\%EL_{volume}$-HYD: percentage of the volume of the endolymphatic space within the whole lymphatic space of vestibule measured on HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal-Multiplied with heavily T2-weighted magnetic resonance cisternography

SH-MRC: saccular height on magnetic resonance cisternography

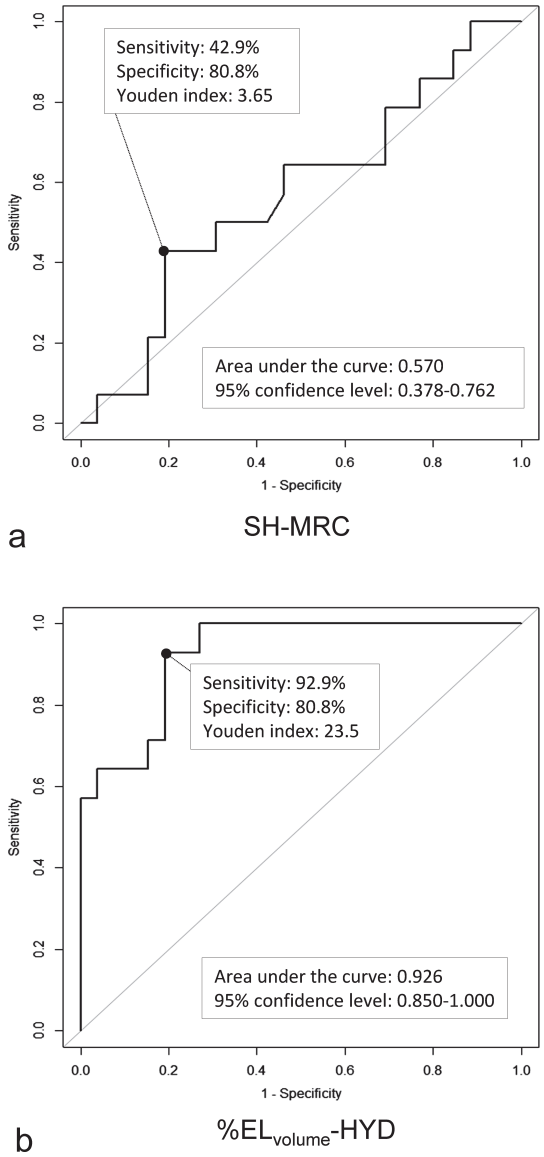

Fig. 3 Diagnostic performance of SH-MRC and $\%EL_{volume}$-HYD

ROC curve for the clinical diagnosis of EH from the SH-MRC without an IV-GBCA (a), and the $\%EL_{volume}$-HYD with IV-GBCA (b). In the ROC analysis for the SH-MRC, the area under the ROC curve was 0.570 (95% confidence level: 0.378-0.762), for the $\%EL_{volume}$-HYD, the area under the ROC curve was 0.926 (95% confidence level: 0.850-1.000). The maximum value of the Youden index analyzed by the ROC curve of $\%EL_{volume}$-HYD was 23.5 (sensitivity: 92.9%, specificity: 80.8%).

EH: endolymphatic hydrops

IV-GBCA: intravenous administration of gadolinium-based contrast agent

$\%EL_{volume}$-HYD: percentage of the volume of the endolymphatic space within the whole lymphatic space of vestibule measured on HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal-Multiplied with heavily T2-weighted magnetic resonance cisternography

ROC: receiver operating characteristic

SH-MRC: saccular height on magnetic resonance cisternography

the ROC curve of the $\%EL_{volume}$-HYD was 23.5 (sensitivity: 92.9%, specificity: 80.8%). The number of ears divided by the cut-off value was 14 ears in the EH-negative group and 14 ears in the EH-positive group. The median of the SH-MRC was 3.48, with a range of 2.62 to 4.22 in the EH-negative group. The median of the SH-MRC was 3.59, with a range of 3.13 to 4.11 in the EH-positive group. There was no significant difference in the SH-MRC between the EH-negative and EH-positive groups (P = 0.478) (Fig. 4). Representative images obtained in the present study are indicated in Fig. 5.

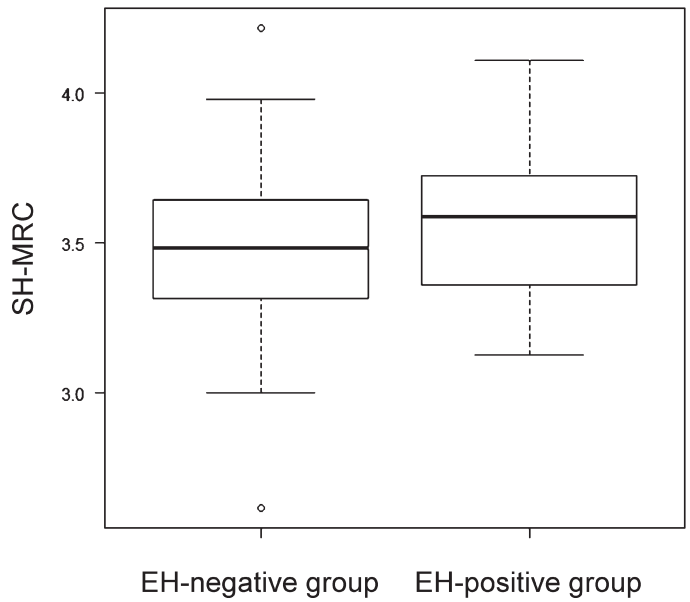

Fig. 4 Comparison between the SH-MRC of the EH-negative and EH-positive groups
A box-and-whisker plot showing the SH-MRC without an intravenous administration of gadolinium-based contrast agent in the EH-negative group and EH-positive groups. The lower side of the rectangle shows the first quartile (25th percentile value) and the upper side is the 75th percentile value. The thick horizontal line in the rectangle shows the median. The horizontal line under the whisker indicates the 10th percentile value, and the horizontal line above the whisker shows the 90th percentile value. There was no significant difference in the SH-MRC between EH-negative and EH-positive groups (P = 0.478).
EH: endolymphatic hydrops
SH-MRC: saccular height on magnetic resonance cisternography

DISCUSSION

In the present study, highly reproducible results between the two observers were found in both the SH-MRC without IV-GBCA and the $\%EL_{volume}$-HYD with IV-GBCA. There was no significant correlation between the SH-MRC without IV-GBCA and the $\%EL_{volume}$-HYD with IV-GBCA. The $\%EL_{volume}$-HYD with IV-GBCA showed higher agreement to our clinical diagnosis of EH using the Nakashima grade compared to the SH-MRC without IV-GBCA. There was no difference in the SH-MRC without IV-GBCA between the EH-negative and EH-positive groups.

A method to evaluate EH by the lateral membranous wall of the saccule on MRC without IV-GBCA has been reported.[11,12] The MRC in these studies was acquired using a balanced

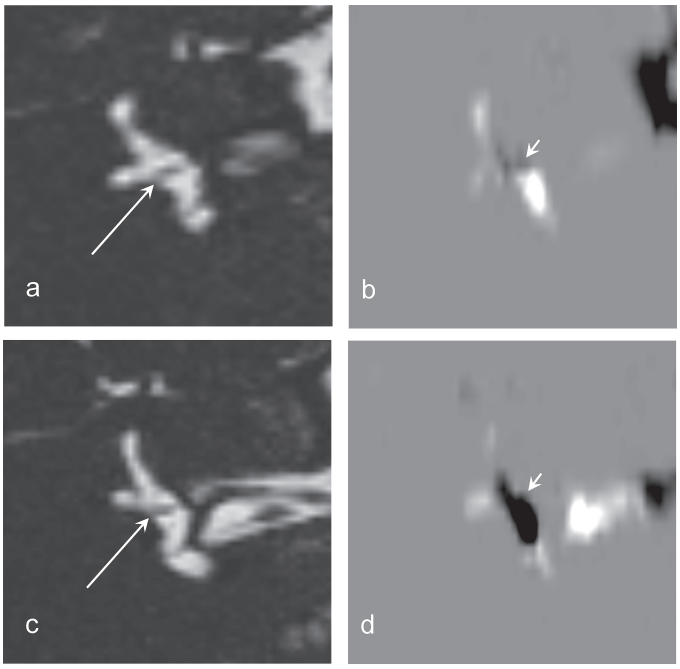

Fig. 5 Representative images with and without EH
Representative images from a 37-year-old man with no EH; MRC obtained at pre- IV-GBCA (a); a HYDROPS-Mi2 image obtained at 4 h post-IV-GBCA (b), and a 55-year-old woman with significant EH; MRC obtained at pre-IV-GBCA (c); a HYDROPS-Mi2 image obtained at 4 h post-IV-GBCA(d). Black areas in HYDROPS-Mi2 images (short arrows, b, d) indicate endolymphatic space. There was no displacement of the utricular macula (long arrows) due to the presence of EH.
EH: endolymphatic hydrops
HYDROPS-Mi2: HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal-Multiplied with heavily T2-weighted MRC
IV-GBCA: intravenous administration of gadolinium-based contrast agent
MRC: magnetic resonance cisternography

steady-state free-precession (bSSFP) sequence.[11,12] The bSSFP sequence has a risk of a banding artifact with low signal due to the B_0 field inhomogeneity.[13] Previously reported studies have suggested that a fast spin echo sequence without banding artifact is more appropriate than the bSSFP sequence for MRC of the inner ear imaging.[14,15] Recently, a machine learning-based trial to automatically diagnose Meniere's disease by training the differences of imaging findings between patients with Meniere's disease and controls on MRC without IV-GBCA was reported.[16] Because the fast spin echo-based MRC and bSSFP-based MRC were mixed in their study,[16] a concern about the bias for their results due to low-signal banding artifacts of bSSFP-based MRC has been mentioned.[17] A previous study compared a bSSFP-based MRC without IV-GBCA to a 3D-FLAIR with IV-GBCA for the evaluation of EH.[18] In that study, the degree of EH assessed by the MRC was less specific for Meniere's disease symptoms than that obtained with the 3D-FLAIR images.[18] Additionally, a poor inter-rater agreement was reported for the measurement of the saccular size using MRC without IV-GBCA in that study.[18] Since the membrane separating the endolymph and perilymph is much thinner than the resolution of routine clinical MR imaging (0.5 × 0.5 × 0.5 mm in this study),[1,19] the lateral membranous wall of the saccule would be obscured by partial volume effects. The structures, which were thought to be the lateral membranous walls of saccule

in these studies,[11,12,18] might be banding artifacts associated with the bSSFP sequence. Because we were actually unable to clearly distinguish the lateral membranous wall of the saccule using the MRC based on a fast spin echo sequence, we measured the distance between the utricular macula and the osseous spiral lamina in the present study. There was no displacement of the utricular macula due to the presence of EH. Therefore, we concluded that MRC without IV-GBCA is not suitable for the evaluation of EH.

A previously reported study suggested that vestibular EH had a lower signal intensity than the perilymph on MRC without IV-GBCA.[10] However, it has also been reported that a difference in the fluid-composition between the endo- and perilymph was insufficient to produce enough contrast to visualize individually the endo- and perilymph on MRC without IV-GBCA.[2,20] In some exceptions, the endolymphatic spaces have been visualized on MR imaging without IV-GBCA.[21-23] The endolymph had a higher signal intensity than the perilymph on 3D-FLAIR images without IV-GBCA for a condition in which the endolymph contained blood components.[21] With enlarged endolymphatic sac and duct syndrome, the endolymph of the inner ear receives an influx of fluid containing highly proteinaceous or hemorrhagic components from the endolymphatic sac, and can have a high signal intensity on 3D-FLAIR images.[22] In contrast, it has been reported that the perilymphatic space had a higher signal intensity than the endolymphatic space in non-contrast 3D-FLAIR images in cases of vestibular schwannoma.[23] Outside of these exceptions, it is necessary to produce contrast between the endo- and perilymphatic spaces by IV-GBCA, for visualization of EH.

The present study has a few limitations. A small number of patients were evaluated. The drawing of the ROI was performed manually, although measurements from two observers indicated high agreement. The cochlear endolymph was not evaluated. Since the cochlear duct is a small structure compared to the saccule,[1] it was considered that cochlear endolymph could not be visualized with MRC.

CONCLUSION

There was no significant correlation between the MRC without GBCA administration and the HYDOROPS-Mi2 with GBCA administration in the evaluation of EH. It was concluded that MRC without GBCA administration cannot apply for accurate evaluation of the degree of EH.

DISCLOSURE STATEMENT

None of the authors have any conflicts of interest regarding the present study.

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