part of the vestibule. These ROIs drawn on MRC for each time point were copied and pasted onto Images ♮1 and ♮2. We then used the histogram function of OsiriX to measure the numbers of all pixels in the ROI and the number of pixels with negative signal intensity values (i.e., endolymph) in the ROI.

The ratio of the area (%) of endolymphatic space in the whole lymphatic space (%EL) was defined as: %EL = (number of negative pixels for endolymph in the ROI divided by number of total pixels in the ROI) × 100.

In our recent volunteer study,[19] we observed significant enhancement of the perilymph at 1.5, 3, 4.5, and 6 hours after IV-SD-GBCM. Therefore, we generated and evaluated Images ♮1 and ♮2 at these time points.

Statistical analysis

To evaluate the change in the estimated area ratio of endolymph (%EL) over time after IV-SD-GBCM and the difference in image type in this ratio, we performed an analysis of variance (ANOVA) for a 2 × 4 repeated-measures design and a planned trend analysis. Factors were the 2 types of formed images (Images ♮1 and ♮2) and 4 time points after IV-SD-GBCM (1.5, 3, 4.5, and 6 hours). Here, if the null hypothesis in Mauchly's test of sphericity was rejected, we used the Greenhouse-Geisser epsilon, Huynh-Feldt epsilon, and lower-bound epsilon to adjust degrees of freedom of the F test statistics. We also performed pairwise comparison among those means of estimated %EL by the Bonferroni adjustment.

We used SPSS 17 software (SPSS Inc., Chicago, IL, USA) for all statistical analyses and adopted 5% as the significance level.

Results

Figure 1 shows examples of Images ♮1 and ♮2 at each time point.

Figure 2 shows the means (with standard deviations) of estimated %EL in cochlear images. Repeated-measures ANOVA showed a statistically significant difference in estimated %EL among the times after IV-SD-GBCM ($P < 0.001$ for the Greenhouse-Geisser epsilon, for the Huynh-Feldt epsilon, and for the lower-bound epsilon) and statistically significant linear and quadratic trends of time after IV-SD-GBCM ($P < 0.001$). However, there was no statistically significant difference between the 2 types of formed images ($P = 0.356$), but there was significant interaction between type of formed image and time after IV-SD-GBCM
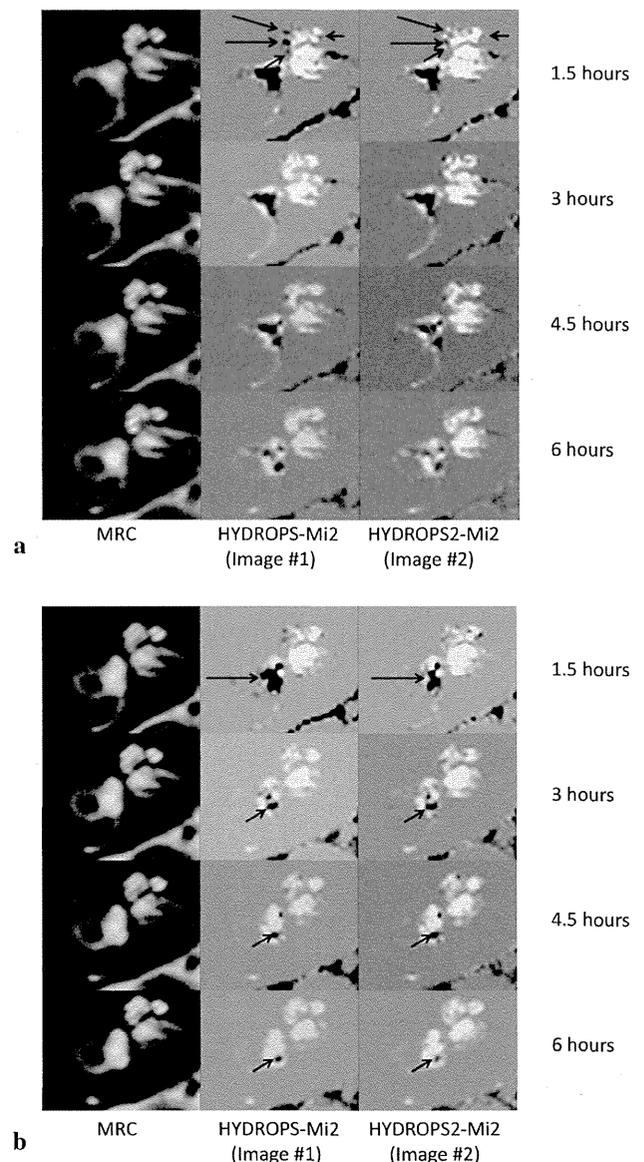

Fig. 1. A 53-year-old healthy male volunteer. (**a**) Slice for evaluation of cochlear endolymphatic size. The size of the black area in the cochlea (long arrows) is largest in the images obtained 1.5 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM). The black area (short arrow) extends to the perilymph of the scala tympani in the images obtained 1.5 hours after IV-SD-GBCM. Therefore, endolymphatic size is overestimated on the images obtained 1.5 hours after IV-SD-GBCM. (**b**) Slice for evaluation of vestibular endolymphatic size. The size of the black area in the vestibule (long arrows) is largest in the images obtained 1.5 hours after IV-SD-GBCM. Only the black area (short arrow) corresponding to the posterior ampulla can be recognized at all times. Therefore, endolymphatic size is thought to be overestimated on the images obtained at 1.5 hours after IV-SD-GBCM.
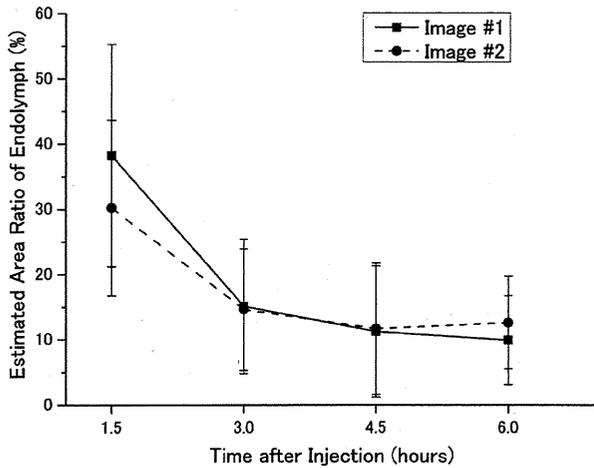
Fig. 2. Means (± standard deviation) of the estimated ratio of the endolymph to that of total lymph (%EL) for 1.5, 3, 4.5, and 6 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM) in 2 types of formed images in 16 cochleas of 8 volunteers. The %EL is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours. "Image ♮1," HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T_2-weighted magnetic resonance [MR] cisternography); "Image ♮2," HYDROPS2-Mi2 (HYDROPS2 image Multiplied with heavily T_2-weighted MR cisternography)
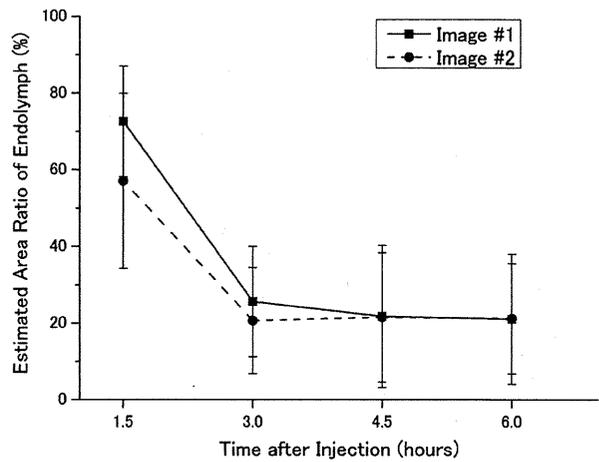

Fig. 3. Means (± standard deviation) of the estimated ratio of the endolymph to that of total lymph (%EL) for 1.5, 3, 4.5, and 6 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM) in 2 types of formed images in 16 vestibules of 8 volunteers. The %EL is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours. Image ♮1, HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T_2-weighted magnetic resonance [MR] cisternography); Image ♮2, HYDROPS2-Mi2 (HYDROPS2 image Multiplied with heavily T_2-weighted MR cisternography)

($P = 0.005$ for the Greenhouse-Geisser epsilon, $P = 0.003$ for the Huynh-Feldt epsilon, and $P = 0.027$ for the lower-bound epsilon) and a statistically significant linear trend of the interaction ($P = 0.002$). Thus, the estimated %EL of endolymph was significantly higher at 1.5 hours after IV-SD-GBCM than other times (these are also statistically significant [$P < 0.001$] from the pairwise comparison), almost the same after 3 hours, and showed no significant difference between the 2 types of formed images.

Figure 3 shows the means (with standard deviations [SD]) of estimated %EL in vestibular images. Repeated-measures ANOVA showed a statistically significant difference in the estimated %EL among the times after IV-SD-GBCM ($P < 0.001$) and statistically significant linear ($P < 0.001$), quadratic ($P < 0.001$), and cubic ($P = 0.001$) trends of time after IV-SD-GBCM. Further, there was a statistically significant difference between the 2 types of formed images ($P = 0.003$), a statistically significant linear trend of type of formed image ($P = 0.003$), a statistically significant interaction between type of formed image and time after IV-SD-GBCM ($P = 0.003$ for the Greenhouse-Geisser epsilon, $P = 0.002$ for the Huynh-Feldt epsilon, and $P = 0.012$ for the lower-bound epsilon in the

cochlear image), and statistically significant linear ($P = 0.006$) and quadratic ($P = 0.008$) trends of the interaction. Thus, the estimated %EL of the endolymph was significantly higher at 1.5 hours after IV-SD-GBCM than other times (these are also statistically significant [$P < 0.001$] from the pairwise comparison), almost the same after 4.5 hours, and showed no significant difference between the 2 types of formed images after 4.5 hours.

Discussion

In evaluating endolymphatic size, weak enhancement of the perilymph on PPI results in poor contrast between the perilymph and endolymph. Weak enhancement of the perilymph on PPI also results in poor suppression of the perilymph on PEI. Poor suppression of the perilymph on PEI results in overestimation of %EL in Image ♮1. Regarding the time course of perilymph enhancement in healthy volunteers, one previous study reported the strongest enhancement of labyrinthine lymph fluid 4 hours after IV-SD-GBCM among 0, 2, 4, and 6 hours after IV-SD-GBCM.[18]

Another recent volunteer study[19] showed significant perilymph enhancement beginning 1.5 hours after IV-SD-GBCM but significantly weaker enhancement at 1.5 hours than at 3, 4.5, and 6 hours

after IV-SD-GBCM, with no significant difference among 3, 4.5, and 6 hours. Significantly weaker enhancement of the perilymph at 1.5 hours or poor suppression of the perilymph on PEI might have yielded the larger %EL in Image ♯1 than Image ♯2.

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) after IT administration of GBCM[25] but not after IV-SD-GBCM, probably because of lower GBCM concentration in the perilymph. Recently, the fusion of gray-scale inverted PEI with native gray-scale PPI, that is, subtraction of PEI from PPI, has been reported to yield a 3D-real IR-like image even after IV-SD-GBCM. These HYDROPS images facilitate recognition of endolymphatic space by IV-SD-GBCM but require long scan time to obtain both PPI and PEI for processing.[23] An alternative processing technique, HYDROPS2, subtracts heavily T_2-weighted MRC from PPI to achieve images with similar contrast to HYDROPS in less scan time.[24]

The multiplication of heavily T_2-weighted MRC and HYDROPS, which we have termed HYDROPS-Mi2, has been reported to increase the contrast-to-noise ratio (CNR) between the endolymph and perilymph.[21] HYDROPS-Mi2 images showed a more than 200-fold increase in CNR, and the background signal became quite uniform. MRC can be used as a "CNR booster." On HYDROPS-Mi2 images, pixel values of the endolymph are negative, and those of the perilymph are positive. The absolute values of the endo- and perilymph are quite large due to the multiplication of MRC. Air and bone near the labyrinth show zero pixel values on HYDROPS-Mi2. MRC can also be multiplied as a CNR booster for HYDROPS2 images, and we have termed the generated image HYDROPS2-Mi2.[20]

In the present study, the measured size of the endolymphatic space is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours after IV-SD-GBCM. Measured values at 1.5 hours are surprisingly large for healthy subjects and unrealistic. In most volunteers, sufficient enhancement has not been achieved on the source images (PPI) obtained at 1.5 hours in the cochlear and vestibular perilymph. Therefore, the %EL was overestimated.

The subjective evaluation of the course of endolymphatic size over time after IV-SD-GBCM in patients with suspected Ménière's disease demonstrated no significant differences in grades of endolymphatic hydrops between 3.5 and 4 hours or between 4 and 4.5 hours after IV-SD-GBCM.[26]

No study has compared the semi-quantitative values of endolymphatic size at multiple time points after IV-SD-GBCM. Our present study results indicate that measured values of endolymphatic size are stable from 3 to 6 hours in the cochlea and from 4.5 to 6 hours in the vestibule.

We observed statistically significant interaction between type of formed image and time after IV-SD-GBCM for both the cochlea and vestibule. As the graphs in Figs. 2 and 3 demonstrate, this means that there is a trend for the plotted lines of Images ♯1 and ♯2 to cross each other at a certain time point. The time of crossing in the cochlea is between 3 and 4.5 hours and in the vestibule, around 4.5 hours. Thus, we can speculate that the measured %EL value at around 4.5 hours would be similar between Images ♯1 and ♯2. Acquisition takes longer for Image ♯1 than ♯2. Use of the value of Image ♯2 instead of that of Image ♯1 could shorten examination time. Further clinical study is necessary if the measured %EL is comparable between Images ♯1 and ♯2 even in patients with endolymphatic hydrops.

Currently, most clinical studies wait 4 hours after IV-SD-GBCM before initiating the MR scan.[13,15,16,21] The typical protocol takes approximately 40 min including patient set-up and localizing scan. Therefore, our current finding of 4.5 hours as the optimal waiting time would give additional confidence to ongoing clinical studies. However, serial data in patients with suspected endolymphatic hydrops is still needed to confirm optimal timing.

One study utilizing the IT method reported the normal range (mean $\pm$ 1.96 SD) of %EL as 8 to 26% in the cochlea and 20 to 41% in the vestibule for 45- to 55-year-old volunteers,[27] and another study reported the normal range as 10.2 to 25.8% in the cochlea and 13.3 to 40.7% in the vestibule in 20- to 30-year-old volunteers.[28] Mean values of our present results at 4.5 hours were 11.2% (Image ♯1) and 11.6% (Image ♯2) in the cochlea and 23.1% (Image ♯1) and 22.3% (Image ♯2) in the vestibule, values within the normal range shown utilizing the IT method. Although these previous measurements by the IT method were performed by manual tracing on 3D-FLAIR images, these previous results suggest that the measured results of the present study are reasonable. However, one ear was larger than this range in the cochlea on both Images ♯1 and ♯2, and 3 ears were larger than this range in the vestibule on both Images ♯1 and ♯2. Even in asymptomatic volunteers, enlargement of the endolymphatic space is sometimes seen, a finding consistent with results of a reported histological study performed in asymptomatic ears with endolymphatic hydrops.[29] As previously suggested, there

may be a population with asymptomatic endolymphatic hydrops.[30]

Our study has some limitations. We included a small number of only male volunteers within a limited age range. Age or gender dependency of endolymphatic size might be of interest for future research. Evaluation was done in area on a single slice not in volume. Further study with volumetric measurement should be conducted in the future. Most previous studies in patients employed gadodiamide as the GBCM; in the present study, we employed gadoteridol. No study has directly compared these 2 kinds of GBCM. However, a study that uses these 2 kinds of GBCM in different patients suggested that the contrast effect of the two might be similar in the perilymph.[3]

In conclusion, a time delay of 1.5 hours after IV-SD-GBCM is not sufficient to evaluate endolymphatic size. Measured size plateaus between 4.5 and 6 hours. At 4.5 to 6 hours, values do not differ between Images ♮1 and ♮2 in both the cochlea and vestibule. These data might be valuable for further clinical studies in inner ear pathology.

Acknowledgements

References

1. Naganawa S, Kawai H, Sone M, Nakashima T. Increased sensitivity to low concentration gadolinium contrast by optimized heavily T_2-weighted 3D-FLAIR to visualize endolymphatic space. Magn Reson Med Sci 2010; 9:73–80.
2. 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 T_2-weighted 3D-FLAIR. Magn Reson Med Sci 2010; 9:237–242.
3. Naganawa S, Yamazaki M, Kawai H, Sone M, Nakashima T. Contrast enhancement of the anterior eye segment and subarachnoid space: detection in the normal state by heavily T_2-weighted 3D FLAIR. Magn Reson Med Sci 2011; 10:193–199.
4. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Ménière's disease. Laryngoscope 2007; 117:415–420.
5. Nakashima T, Naganawa S, Teranishi M, et al. Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Ménière's disease. Acta Otolaryngol 2010; 130:338–343.
6. Pyykko I, Nakashima T, Yoshida T, Zou J, Naganawa S. Ménière's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. BMJ Open 2013; 3.
7. Pyykko I, Zou J, Poe D, Nakashima T, Naganawa S. Magnetic resonance imaging of the inner ear in Ménière's disease. Otolaryngol Clin North Am 2010; 43:1059–1080.
8. Fiorino F, Pizzini FB, Barbieri F, Beltramello A. Magnetic resonance imaging fails to show evidence of reduced endolymphatic hydrops in gentamicin treatment of Ménière's disease. Otol Neurotol 2012; 33:629–633.
9. Fukuoka H, Takumi Y, Tsukada K, et al. Comparison of the diagnostic value of 3 T MRI after intratympanic injection of GBCA, electrocochleography, and the glycerol test in patients with Ménière's disease. Acta Otolaryngol 2012; 132:141–145.
10. Gurkov R, Flatz W, Ertl-Wagner B, Krause E. Endolymphatic hydrops in the horizontal semicircular canal: a morphologic correlate for canal paresis in Ménière's disease. Laryngoscope 2013; 123:503–506.
11. Kitahara T, Maekawa C, Kizawa K, Kamakura T, Horii A, Inohara H. Endolymphatic sac tumor with overexpression of V2 receptor mRNA and inner ear hydrops. Acta Otolaryngol 2011; 131:951–957.
12. Katayama N, Yamamoto M, Teranishi M, et al. Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. Acta Otolaryngol 2010; 130:917–923.
13. Uno A, Imai T, Watanabe Y, et al Changes in endolymphatic hydrops after sac surgery examined by Gd-enhanced MRI. Acta Otolaryngol 2013.
14. Yamamoto M, Teranishi M, Naganawa S, et al. Relationship between the degree of endolymphatic hydrops and electrocochleography. Audiol Neurootol 2010; 15:254–260.
15. Yoshida T, Teranishi M, Kato M, et al. Endolymphatic hydrops in patients with tinnitus as the major symptom. Eur Arch Otorhinolaryngol 2013; 270:3043–3048.
16. Kato M, Sugiura M, Shimono M, et al. Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Ménière's disease. Acta Otolaryngol 2013; 133:123–129.
17. Kato K, Yoshida T, Teranishi M, et al. Peak width in multifrequency tympanometry and endolymphatic hydrops revealed by magnetic resonance imaging. Otol Neurotol 2012; 33:912–915.
18. Naganawa S, Komada T, Fukatsu H, Ishigaki T, Takizawa O. Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol 2006; 16:733–737.
19. Naganawa S, Suzuki K, Yamazaki M, Sakurai Y. Serial scans in healthy volunteers following intrave-

nous administration of gadoteridol: time course of contrast enhancement in various cranial fluid spaces. Magn Reson Med Sci 2014; 13:7–13.

20. Naganawa S, Suzuki K, Nakamichi R, et al. Semi-quantification of endolymphatic size on MR imaging after single-dose intravenous injection of gadodiamide: Comparison between two types of processing strategies. Magn Reson Med Sci 2013; 12:261–269.

21. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Ménière's Disease after Intravenous Administration of Single-dose Gadodiamide: Utility of Multiplication of MR Cisternography and HYDROPS Image. Magn Reson Med Sci 2013; 12:63–68.

22. 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 2012; 11:145–150.

23. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Ménière's disease after intravenous administration of single-dose gadodiamide: utility of subtraction images with different inversion time. Magn Reson Med Sci 2012; 11:213–219.

24. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Ménière's disease by subtraction of MR cisternography from positive perilymph image. Magn Reson Med Sci 2012; 11:303–309.

25. 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.

26. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière's disease after single-dose intravenous gadolinium-based contrast medium: timing of optimal enhancement. Magn Reson Med Sci 2012; 11:43–51.

27. Liu F, Huang W, Meng X, Wang Z, Liu X, Chen Q. Comparison of noninvasive evaluation of endolymphatic hydrops in Ménière's disease and endolymphatic space in healthy volunteers using magnetic resonance imaging. Acta Otolaryngol 2012; 132: 234–240.

28. Liu F, Huang W, Wang Z, et al. Noninvasive evaluation of endolymphatic space in healthy volunteers using magnetic resonance imaging. Acta Otolaryngol 2011; 131:247–257.

29. Merchant SN, Adams JC, Nadol JB Jr. Pathophysiology of Ménière's syndrome: are symptoms caused by endolymphatic hydrops? Otol Neurotol 2005; 26: 74–81.

30. Nakashima T, Sone M, Teranishi M, et al. A perspective from magnetic resonance imaging findings of the inner ear: Relationships among cerebrospinal, ocular and inner ear fluids. Auris Nasus Larynx 2012; 39: 345–355.

REVIEW

Visualization of endolymphatic hydrops with MR imaging in patients with Ménière's disease and related pathologies: current status of its methods and clinical significance

Shinji Naganawa · Tsutomu Nakashima

Abstract Ménière's disease is an inner ear disorder characterized by vertigo attacks, fluctuating low-frequency hearing loss, ear fullness, and tinnitus. Endolymphatic hydrops has long been thought to be the pathological basis for Ménière's disease. Some patients have inner ear symptoms that do not match the diagnostic guidelines for Ménière's disease, and these are also thought to be related to endolymphatic hydrops. The diagnosis of endolymphatic hydrops is usually made based on clinical symptoms with some assistance from otological functional tests. Recently, the objective diagnosis of endolymphatic hydrops by MR imaging has become possible and many research results have been reported regarding the imaging methods, evaluation methods, the correlation between imaging results and functional otological tests and the correlation between imaging findings and clinical symptoms. In this article we summarize the development of current imaging methods, evaluation techniques and clinical reports based on a review of the literature. We also attempt to characterize the current significance and future directions of MR imaging of endolymphatic hydrops.

Keywords Magnetic resonance imaging · Endolymphatic hydrops · Temporal bone disease · Ménière's disease

Introduction

Ménière's disease is an inner ear disorder characterized by spontaneous attacks of vertigo, fluctuating low-frequency hearing loss, aural fullness, and tinnitus. Endolymphatic hydrops has long been held to be the pathological basis for Ménière's disease [1, 2]. Some patients have inner ear symptoms that do not match the diagnostic guidelines for Ménière's disease, and these are also thought to be related to endolymphatic hydrops [3–6]. Endolymphatic hydrops is a pathological anatomical finding in which the structures bounding the endolymphatic space are distended by an enlargement of endolymphatic volume. In the 1995 consensus statement of the committee on hearing and equilibrium of the American Association of Otolaryngology-Head and Neck Surgery (AAO-HNS) [7], Ménière's disease is defined as "the idiopathic syndrome of endolymphatic hydrops." At the same time, however, these guidelines state that the diagnosis of "definite" Ménière's disease is made by clinical criteria, whereas a diagnosis of "certain" Ménière's disease can only be confirmed by histological demonstration of endolymphatic hydrops in postmortem temporal bone specimens.

Although image-based diagnosis of endolymphatic hydrops may be a key to understanding inner-ear diseases such as Ménière's disease or fluctuating sensorineural hearing loss, imaging of endolymphatic hydrops had not been fully established for living human subjects as of 2007, when Nakashima et al., visualized endolymphatic hydrops by intratympanic gadolinium-based contrast media (GBCM) administration (IT-Gd) [1]. The development of MR imaging methods over the last few years has enabled the visualization of endolymphatic hydrops in living human subjects, and can now also be performed via intravenous GBCM administration (IV-Gd) [8]. Various

S. Naganawa (✉)
Department of Radiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Shouwa-ku, Nagoya 466-8550, Japan
e-mail: naganawa@med.nagoya-u.ac.jp

T. Nakashima
Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine, Nagoya, Japan

🌀 Springer

methods in endolymphatic hydrops imaging (EHI), contrast material administration and evaluation criteria for endolymphatic hydrops have been reported [8–15]. The clinical utility of MR imaging has also been reported by multiple research institutions that have compared the results of MR imaging with clinical symptoms or otological tests [6, 16–23]. In this review, we describe the development of current techniques in MR imaging methods and summarize the reported clinical results based on a review of the literature. We also aimed to outline the current significance and the future directions of MR imaging of endolymphatic hydrops.

Development of MR methods for the visualization of endolymphatic hydrops by various contrast administration

Separate visualization of endolymph and perilymph

The composition of endolymph, with a high potassium and low sodium concentration, resembles that of the cytosol, in contrast with the composition of perilymph, which is more similar to that of the extracellular medium, with low potassium and high sodium concentrations. However, clinical imaging of the endolymphatic space has not been achieved despite these differences in chemical composition. Reissner's membrane, which separates the endolymph and perilymph, is too thin to be visualized with clinical MR scanners [1].

IT-Gd

Initial techniques

In guinea pigs, intratympanically administered gadodiamide (Omniscan®, Gd-DTPA-BMA) was shown to be distributed throughout the perilymphatic space of the labyrinth [24]. In this study which also included human patients, 2 patients with sudden hearing loss were intratympanically administered non-diluted Gd-DTPA-BMA and T1-weighted imaging was performed at 1.5 T. In the images obtained, the scala media (cochlear duct, endolymphatic space) was visualized as the filling defect [24]. The osmolality of non-diluted Omniscan® is higher than blood plasma, so dilution is recommended for increased safety. Due to this dilution, a more sensitive pulse sequence is necessary. In 2007, Nakashima et al. [1] reported the clear visualization of endolymphatic hydrops in patients with Ménière's disease by intratympanic administration of diluted gadolinium contrast material (GBCM) using three-dimensional fluid attenuated inversion recovery (3D-FLAIR) at 3 T. This is thought to be the first in vivo

visualization of endolymphatic hydrops in patients [18]. Many subsequent reports repeated this combination of 3D-FLAIR and diluted IT-Gd [18, 25–29].

In most studies, the tympanic membrane is punctured with a thin needle and GBCM, diluted 8-fold, is administered. Some studies have also reported using fivefold [30] and 16-fold dilutions [31]. The volume of injected solutions was 0.3–0.6 ml. Patients are asked to remain still for about 30 min after injection. MR imaging is typically performed 24 h after IT-Gd [1].

Initially, 3D-FLAIR using a conventional turbo spin echo sequence was used; however, faster sequences such as 3D-FLAIR with a variable flip angle turbo spin echo sequence have been recently utilized [32]. Three-dimensional imaging with variable flip angle turbo spin echo sequence is referred to as SPACE (sampling perfection with application-optimized contrasts using different flip angle evolutions) or VISTA (volumetric isotropic turbo spin echo acquisition), depending on the scanner vendor [33]. In 3D-FLAIR images obtained after IT-Gd, the perilymph shows high levels of signal due to the distribution of GBCM; in contrast, the endolymph without GBCM distribution shows a low-level signal, similar to the surrounding bone and air [31, 34, 35].

Positive endolymphatic image (PEI)

To demonstrate that the filling defect in the endolymphatic space observed with 3D-FLAIR after IT-Gd is not due in part to a volume artifact of bone or air, the inversion time of the 3D-FLAIR was shortened to suppress the signal of the perilymph. Instead, the signal from the endolymph increased while the signal from surrounding bone and air remained low [35]. Based on this "positive endolymphatic image (PEI)", the confidence in MR visualization of endolymphatic hydrops was increased. A similar technique has also been applied to an IV-Gd technique [13].

3D-real inversion recovery technique (3D-real IR)

As described above, 3D-FLAIR can differentiate the endolymphatic space from the perilymphatic space, but not from the surrounding bone and air. To separately visualize endolymph, perilymph and bone in a single image, 3D inversion-recovery turbo spin echo with real reconstruction (3D-real IR) was suggested [34]. 3D-real IR could separate the signals from the perilymphatic space (positive value), endolymphatic space (negative value) and bone (near zero) by setting the inversion time between the null point of GBCM-containing perilymphatic fluid and that of the endolymphatic fluid without GBCM. This technique, as well as 3D-FLAIR, is widely used by various institutions with the IT-Gd technique. However, 3D-real IR is not as

sensitive to low concentrations of GBCM as 3D-FLAIR, therefore, 3D-FLAIR is still necessary in cases of poor contrast distribution [31, 36].

2D-real IR

3D-real IR can provide thinner slices than 2D-real IR; however, the 3D method usually requires a longer scanning time. Typically, 3D real IR takes approximately 15 min. To shorten this lengthy scan time, 2D-real IR was tested with a scan time of 6 min and results showed that endolymphatic hydrops in Ménière's disease could be evaluated with either 2D-real IR or 3D-real IR [37]. The shorter scan time of 2D-real IR offers the potential to scan multiple images with various inversion times to adapt to the various degrees of contrast distribution in the inner ear labyrinth even at 1.5 T [38]. However, volumetrically separate visualization of the endolymphatic/perilymphatic space after IT-Gd in patients with Ménière's disease has only been reported with 3D-real IR sequences [39].

IT-Gd through the Eustachian tube

For intratympanic administration of GBCM, many studies punctured the tympanic membrane, although some studies utilized an alternative Eustachian tube approach [10, 40]. This method is described as a non-invasive procedure; however, most institutes still use tympanic membrane puncture as the route for intratympanic administration, due to the technical simplicity.

Wait time after IT-Gd before MR scanning

Initial MR scans were serially repeated to determine the optimal timing after IT-Gd. The vestibule began to show enhancement 1–2 h after IT-Gd and the basal turn of the cochlea was enhanced after 7 h [1, 24]. Currently, 24 h is the accepted optimal scan time after IT-Gd for EHI by most institutions [3, 17–19, 30, 38]. In most patients, IT-Gd disappears from the labyrinth after 6–7 days [1, 41].

Safety and contrast effect of IT-Gd

After IT-Gd, with an eightfold dilution, it is estimated that the concentration of GBCM within the perilymph is 1×10^{-4} mol/L, which is a 5000-fold dilution of the original solution [41]. To date, there have not been any reports of adverse effects on the inner ear by IT-Gd in human patients. In isolated cochlear outer hair cells, morphological changes were observed in 24 % (6/25) and 3 % (1/33) of cells after direct application of 1/8 and 1/16 diluted gadoteridol (Gd HP-DO3A, ProHance®), respectively. The degree of hair cell damage was significantly lower after

application of 1/16 diluted gadoteridol compared with 1/8 diluted gadoteridol ($p < 0.05$) [29]. However, the direct application of 1/8 or 1/16 diluted gadoteridol to hair cells is a substantially higher concentration than the amount of GBCM that would be present in the perilymph after IT-Gd. Moreover, the GBCM concentration in the endolymph surrounding the hair cells is much lower than in the perilymph. Therefore, the safety of IT-Gd is presumed to be quite high. In humans, some researchers performed IT-Gd in healthy ears without any adverse effects [10, 27, 40], and the use of IT-Gd diluted fivefold has also been reported without any adverse effects in patients [30]. A prospective IT-Gd study in 65 patients with probable or definite Ménière's disease showed no significant deterioration of hearing function 1 week after administration of eightfold diluted IT-Gd. The potential long-term adverse effects of IT-Gd should still be investigated, although there have been no clinical reports thus far [42].

One study was conducted to compare gadopentetate dimeglumine (Gd-DTPA, Magnevist®) and gadodiamide (Gd-DTPA-BMA, Omniscan®) in IT-Gd, and no significant difference in contrast enhancement was reported [43].

Permeability of the round window membrane

Intratympanically administered drugs are thought to be absorbed mainly through round window membrane. Individual differences in the permeability of the round window membrane after IT-Gd have been reported [44]. Round window permeability was absent in 5 % of ears, and 13 % of ears showed poor permeability. In order to predict poor contrast distribution before beginning long MR scans, it has been suggested that perilymph enhancement should be estimated using fast T1-mapping with a dual flip angle 3D spoiled gradient echo sequence [36]. In cases of poor contrast distribution in the perilymph after IT-Gd, a more sensitive pulse sequence using heavily T2-weighted 3D-FLAIR might help [36, 45].

Recently, absorption through the annular ligament of the oval window membrane has been suggested as an alternate route for intratympanically administered drug distribution to the inner ear labyrinth, although this route can be blocked by the significant endolymphatic hydrops in vestibule [30]. Impaired labyrinthine enhancement in some patients is one limitation of the IT-Gd method that should be taken into consideration [44].

IV-Gd

Dose of GBCM

In an animal study, a 12.5-times higher dose than normal was administered intravenously to guinea pigs; this

Ⓐ Springer

resulted in a preferential enhancement of the perilymph allowing the visualization of endolymphatic hydrops in T1-weighted images at 1.5 T [2]. In human volunteers, lymph fluid enhancement was observed with 3D-FLAIR at 3 T, and peaked 4 h after single dose IV-Gd (IV-SD-GBCM). In humans, intravenously injected GBCM becomes distributed to the perilymph as well as to the fluid within the anterior portion of the eye, the subarachnoid space surrounding the optic nerve, Meckel's cave, and the fundus of the internal auditory canal 4 h after IV-SD-GBCM [46]. However, GBCM does not get distributed to the endolymph. Another study using human volunteers which utilized a triple dose of IV-Gd and T1-weighted imaging at 3 T, reported the visualization of endolymphatic hydrops; however, it was noted that precise definition of the scala media (the cochlear duct, endolymphatic space) could not be achieved [47]. In other studies using 3D-FLAIR at 3 T and a double dose of IV-Gd [14, 48], visualization of endolymphatic hydrops was achieved 4 h after IV-Gd. However, double or triple doses of IV-Gd might cause nephrogenic systemic fibrosis in patients with impaired renal function; therefore, a method of IV-SD-GBCM which could enable the wider-spread use of EHI was desired.

In 2010, visualization of endolymphatic hydrops by IV-SD-GBCM was accomplished using a high-sensitivity heavily T2-weighted 3D-FLAIR sequence at 3T [8].

Variations in image processing using the IV-Gd method: PEI, HYDROPS and HYDROPS2

After the report of IV-SD-GBCM visualization of endolymphatic hydrops, [8] various techniques for MR imaging and processing have been proposed to make images more robust and easy to interpret. The use of a positive endolymphatic image (PEI) was proposed based on a concept similar to IT-Gd [13, 35]. With this method, the PEI is subtracted from the positive perilymphatic image (hT2w-3D-FLAIR) and is referred to as a "HYDROPS" (Hybrid of the reversed image of the positive endolymph signal and native image of the positive perilymph signal) image [12]. HYDROPS images provide similar contrast to 3D-real IR after IT-Gd enabling separation between the endolymph, perilymph and bone in a single type of image. HYDROPS2 imaging was subsequently proposed which shortened the scan time and produced similar contrast as HYDROPS. HYDROPS2 images are generated by the subtraction of MR cisternography from the positive perilymphatic image [11]; scan time is 40 % shorter for HYDROPS2 than for HYDROPS imaging.

HYDROPS-Mi2

To further increase the contrast-to-noise ratio (CNR) between the endolymph and perilymph in a HYDROPS image, MR cisternography was multiplied onto the HYDROPS image. This was named HYDROPS-Mi2 (HYDROPS image multiplied by T2). The average CNR between endolymph and perilymph in generated images increased more than 200 times compared to that of basic HYDROPS images [49] (Fig. 1). With this increased CNR, separate volumetric image presentations of endolymph and perilymph were made possible even in images obtained by IV-SD-GBCM. Such three-dimensional visualization will contribute to our understanding of the pathophysiology of Ménière's disease [50].

Wait time after IV-Gd administration

Various studies were conducted to determine the optimal wait time for EHI after IV-Gd [51–54]. The window of time for EHI was estimated to be relatively broad, between 3 and 6 h, with an optimal time around 4 h after IV-Gd. While in most reports regarding EHI by IV-SD-GBCM, imaging was performed at 3T, HYDROPS images can be obtained at 1.5 T 4 h after IV-SD-GBCM [55]. This is expected to lead to a broader use of EHI in the clinical setting.

Advantages and disadvantages of the IV-Gd and IT-Gd methods are summarized in Table 1 [9, 31, 56, 57]. The typical scan parameters used recently with the IV-Gd method 4 h after IV-SD-GBCM are shown in Table 2 [58, 59].

Types of gadolinium contrast materials

No study has directly compared the effects of various GBCM for EHI in the same subjects. For IV-Gd, most reports utilized gadodiamide [11, 52, 58, 60], while some used gadoteridol [14, 48, 61]. Both types of GBCM give similar findings regarding endolymphatic hydrops 4 h after the administration of IV-Gd, and there appears to be no major differences in the effects on perilymph contrast. Further study is required to confirm the similarities and differences between the various GBCMs for EHI, as the size of the molecules, osmolality and electrical charge are different among the GBCMs.

EHI without GBCM

It is also possible for non-contrast enhanced images to allow the separate visualization of endolymph/perilymph in some conditions. Endolymphatic fluid gives a high signal due to hemorrhaging [62] or reflux of fluid containing a high protein concentration from enlarged endolymphatic sacs [63]. In contrast, perilymphatic fluid shows a high signal in cases of vestibular schwannoma [64]. Under these conditions, the endolymphatic space can be identified without GBCM.
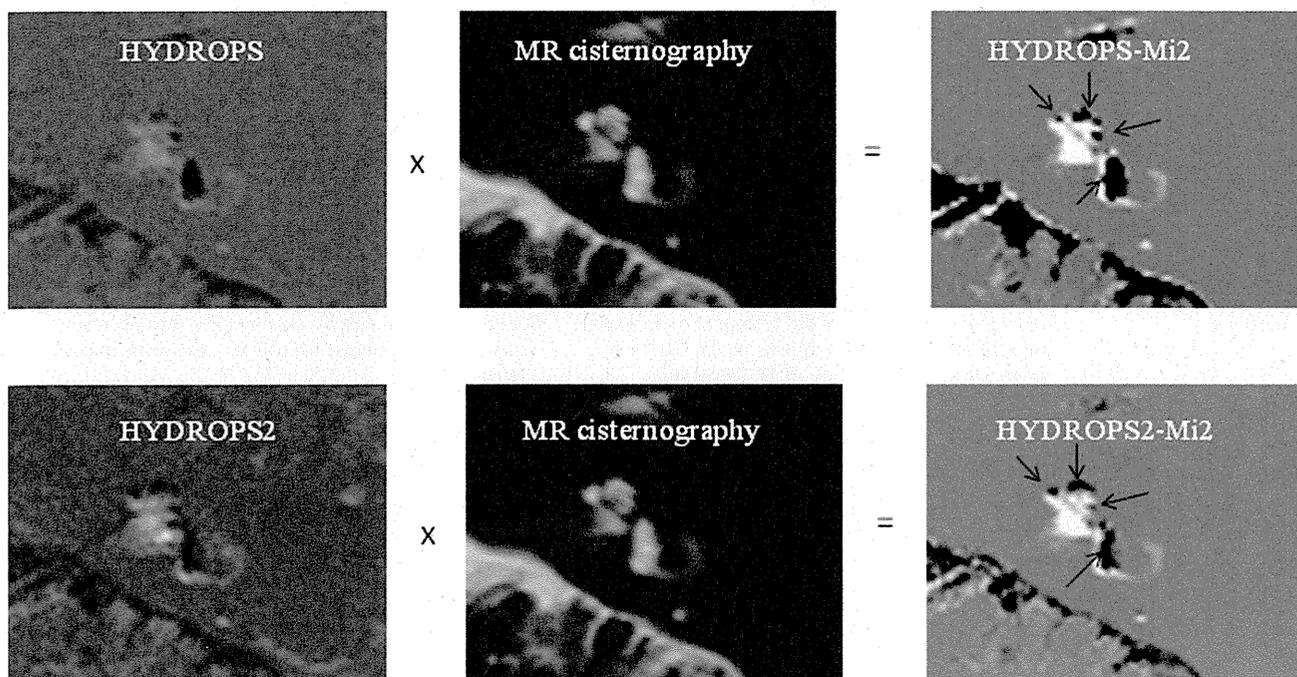
Fig. 1 A 72-year-old man with a clinical diagnosis of probable Ménière's disease in the left ear. Images were obtained 4 h after IV-SD-GBCM. A conceptual diagram of the image generated by HYDROPS-Mi2 and HYDROPS2-Mi2 is shown. Images in the *upper row* indicate the generation of the HYDROPS-Mi2 image. The HYDROPS image, a subtraction of the positive endolymphatic image (not shown) from the positive perilymphatic image (heavily T2-weighted 3D-FLAIR, not shown), is multiplied by T2-weighed MR cisternography. Note that *black areas* (*arrows*) represent the endo-lymphatic space in the labyrinth and white areas represent the perilymphatic space in the HYDROPS-Mi2 image. The contrast between the endolymphatic and perilymphatic space is very strong, while the background signal is uniform in the HYDROPS-Mi2. *Lower images* indicate the generation of the HYDROPS2-Mi2 image. The HYDROPS2 image, a subtraction of the T2-weighed MR cisternography from the positive perilymphatic image (heavily T2-weighted 3D-FLAIR, not shown), is multiplied by T2-weighted MR cisternography. Note that *black areas* (*arrows*) represent the endolymphatic space in labyrinth and white areas represent the perilymphatic space in the HYDROPS2-Mi2 image similar to that shown for HYDROPS-Mi2. The contrast between the endolymphatic and perilymphatic space is very strong, while the background signal is quite uniform in the HYDROPS2-Mi2 similar to that of HYDROPS-Mi2

Direct puncture of the endolymphatic sac

There is yet another method to visualize the endolymphatic space, whereby direct injection of GBCM into the endo-lymphatic sac during surgery is used for EHI [15]. Contrast enhancement of the endolymphatic space was maintained for more than one week. While this is an invasive proce-dure, the possibility of injecting substances into the endo-lymphatic space might open up new prospects for the treatment of inner ear disorders.

Intratympanic and intravenous injection of GBCM (IT + IV double contrast)

Although the IT-Gd method allows greater enhancement of the perilymph, many patients are reluctant to receive IT-Gd in asymptomatic ears. Iida et al. [65] attempted to evaluate endolymphatic space size on both the left and right sides without the need for IT injection in asymptomatic ears. They performed IT-Gd in one ear 24 h prior to the MR scan then IV-SD-GBCM 4 h before the MR scan. This enabled the prediction of drug distribution after intratym-panic administration in one ear and the evaluation of the degree of endolymphatic hydrops in the other ear with minimal invasiveness. HYDROPS2 can replace 3D-real IR with the IT + IV protocol. HYDROPS2 imaging can evaluate both the IV-only side and the IT + IV side simultaneously [66] (Fig. 2).

Development of evaluation methods

Subjective method

Various grading methods for the degree of EHI have been proposed. The first grading system, proposed by Nakashi-ma et al. [67], divided endolymphatic hydrops grades into three categories: none, mild and significant. The presence of endolymphatic hydrops is characterized as enlarged negative-signal spaces within the labyrinth using 3D-

Table 1 Features of the IT-Gd and IV-Gd method

	IT-Gd	IV-Gd
Side for evaluation	Injected side only	Both sides simultaneously
Invasiveness	Puncture of tympanic membrane	Regular intravenous injection
Usage of GBCM	Off-label use	Clinical use
Waiting time	24 h	4 h
Contrast effect	Usually stronger than IV-Gd	Usually less intense than IT-Gd
Contrast uniformity	Stronger in basal turn of the cochlea	More uniform throughout the cochlea
Side effects	Scarring after puncture of the tympanic membrane, no side effects reported to date for IT-Gd itself, however long term safety of IT-Gd is still unknown	Rare reports of shock by anaphylaxis, rare occurrence of nephrogenic systemic fibrosis in cases with imparied renal function
Dose of GBCM	0.3–0.6 ml of eightfold diluted GBCM	Typically 0.2 ml/kg body weight of GBCM (single dose)
Core pulse sequence	3D-FLAIR, 3D-real IR, occasionally 2D-FLAIR and 2D-real IR	Heavily T2-weighted 3D-FLAIR
Additional information	Permeability of round window membrane	Blood-labyrinthine barrier
Contra indication	Severe otitis media	Allergy to GBCM, impaired renal function
Success rate	Approximately 80–90 %	Approximately 95 %
Causes of failure	Poor contrast enhancement of labyrinth in some cases	Claustrophobia, gross motion, metal artifact
Common caution	In both the IT-Gd and IV-Gd method, GBCM is administered prior to the MR scans. Screening for MR examination, such as claustrophobia, metal substances in the body and cooperativeness should be throughly checked before GBCM administration	

GBCM gadolinium based contrast media, *IT-Gd* intratympanic GBCM administration, *IV-Gd* intravenous GBCM administration, *FLAIR* fluid-attenuated inversion recovery, *Real IR* inversion recovery with real reconstruction, *2D* two dimensional, *3D* three dimensional

FLAIR or 3D-real IR after IT-Gd. The cochlea and vestibule are graded separately as follows: if the endolymph of the cochlear duct (CD) is larger than that of the scala vestibuli, the endolymphatic hydrops is deemed to be significant. If there is no bulging of the CD and the CD is slit-shaped or triangular, endolymphatic hydrops is deemed absent. Mild endolymphatic hydrops is intermediate between these two. If the endolymphatic area of the vestibule is more than one half of the total vestibular area, it is described as significant endolymphatic hydrops. If the area is <1/3 the total, there is no endolymphatic hydrops. A mild designation is intermediate between the two. This grading scale directly evaluates the size of the endolymph, and can be applied to EHI by IV-Gd. The main limitation of this grading system is that the slice level for evaluation has not been precisely defined.

Gurkov et al. [18] proposed another subjective classification. With this method, the cochlea and vestibule are analyzed separately, and the respective degree of hydrops is graded on a 4-point Likert scale (0: no hydrops, 1: mild hydrops, 2: marked hydrops, 3: extreme hydrops). Examples of each grade of cochlear hydrops are given in figures in the literature; however, the distinction between grades 3 and 4 is unclear. Moreover, they did not precisely define the slice level for evaluation. This classification is a modification of the previously proposed 3-point scale [67].

Other classifications separated the labyrinth into 7 parts and graded the enhancement of parts as not visible, partially visible and completely visible using 3D-FLAIR [25]. Although this scoring system is reported to be accurate for the diagnosis of MD, impaired GBCM distribution in some parts of the labyrinth is sometimes encountered after IT-Gd. The presence of non-visible parts does not directly indicate the presence of endolymphatic hydrops.

Semi-quantitative method

Liu et al. [10] reported a semi-quantitative method by manual tracing. In this method, the endolymphatic space was evaluated using 3D-FLAIR after IT-Gd. In the basal turn of the cochlea, the cross-sectional area of the endolymphatic space and the fluid space (sum of the endolymphatic and perilymphatic space) was measured and the ratio of the area of the endolymphatic space to that of the fluid space was evaluated in images parallel to the modiolus of the cochlea. In the vestibule, the sectional area of the endolymphatic space (sum of the utricle and saccule) and the fluid space (sum of the endolymphatic and perilymphatic spaces) was measured and the ratio of the area of the endolymphatic space to that of the fluid space was evaluated in images parallel to the longitudinal axis of the vestibule. Using 3D-FLAIR, the border between the

Table 2 Typical pulse sequence parameters at 3 T using 32-channel head coil for the MR scan 4 h after IV-SD-GBCM and image processing methods

Sequence name	Type	Repetition time (ms)	Echo time (ms)	Inversion time (ms)	Flip angle (°)	Section thickness (mm)	Pixel size (mm)	Number of slices	Echo train length	Field of view (mm)	Matrix size	Number of excitation	Scan time (min)
MR cisternography (MRC)	SPACE with restore pulse	4400	544	NA	90/initial 180 decrease to constant ‹120	1	0.5 × 0.5	104	173	150 × 180	322 × 384	1.8	3
Heavily T2 weighted 3D-FLAIR (PPI)	SPACE with inversion pulse	9000	544	2250	90/initial 180 decrease to constant 120	1	0.5 × 0.5	104	173	150 × 180	322 × 384	2 or 4	7 or 14
Heavily T2 weighted 3D-inversion recovery (PEI)	SPACE with inversion pulse	9000	544	2050	90/initial 180 decrease to constant 120	1	0.5 × 0.5	104	173	150 × 180	322 × 384	2 or 4	7 or 14

GRAPPA × 2 for all sequences

All sequences use slab-selective excitation mode, frequency selective fat suppression pre-pulse; MRC uses restore magnetization pulse at the end of the echo train

Each 3D slab is set in an identical axial orientation

HDROPS (HYbriD of reversed image of positive endolymph signal and native image of positive perilymph signal): PPI − PEI

HYDROPS2 (HYbriD of reversed image of MR cisternography and positive perilymph signal by heavily T2-weighted 3D-FLAIR): PPI − 0.05 × MRC

HYDROPS-Mi2 (HYDROPS image multiplied with heavily T2-weighted MR cisternography): HYDROPS × MRC

HYDROPS2-Mi2 (HYDROPS2 image multiplied with heavily T2-weighted MR cisternography): HYDROPS2 × MRC

PPI positive perilymphatic image, *PEI* positive endolymphatic image, *SPACE* sampling perfection with application-optimized contrasts using different flip angle evolutions, *IV-SD-GBCM* intravenous administration of single dose gadolinium based contrast media
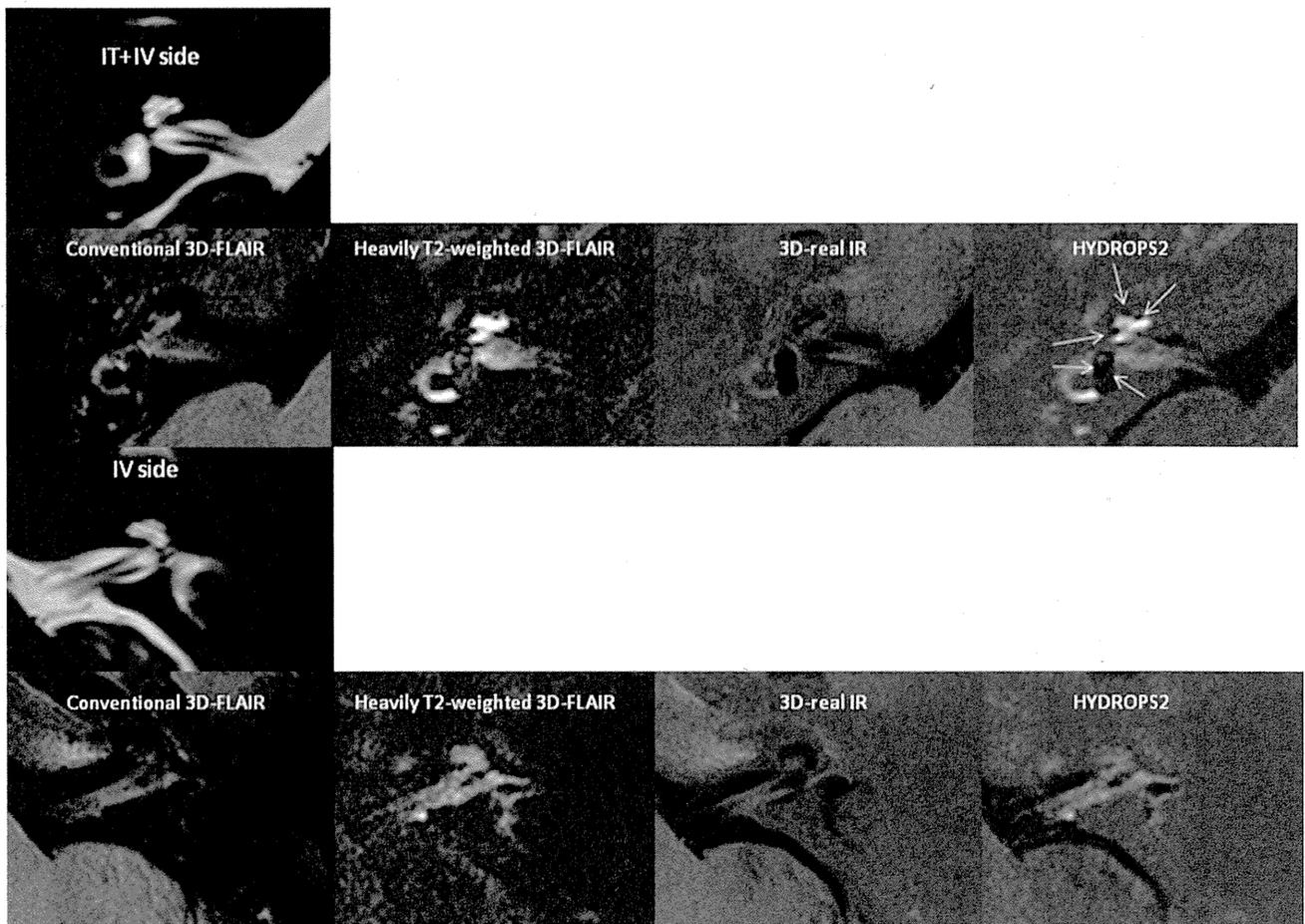
Fig. 2 A 42-year-old man with a clinical diagnosis of definite Ménière's disease of the right ear. Images were obtained 24 h after IT-Gd in the right ear and 4 h after IV-SD-GBCM. The right ear shows the combined IT + IV effect while the left ear shows only the IV-Gd effect. Note that only on the IT + IV side is the conventional 3D-FLAIR and 3D-real IR sufficient to show enhancement of the perilymph in order to distinguish the endolymphatic space; however, heavily T2-weighted 3D-FLAIR and HYDROPS2 allows the differentiation between the perilymphatic and endolymphatic space in both the IV side and IT + IV side. Significant endolymphatic hydrops (*arrows*) is seen in both the cochlea and vestibule on the right side, but no endolymphatic hydrops is observed in the *left* cochlea. Absence of endolymphatic hydrops in the *left* vestibule is confirmed in lower-level slices (not shown)

cochlear duct (endolymph) and surrounding bone is unclear making manual tracing of each cochlear duct in the 3D-FLAIR image time consuming and susceptible to operator bias. This manual tracing method of the endolymphatic space was also employed in another study [27].

Less observer-dependent semi-quantitative method

With the development of EHI by IV-SD-GBCM, the number of patients that could be examined by MR increased. Given this, a more reliable, less observer-dependent and less time consuming method for evaluation was desired. For this purpose, high CNR by HYDROPS-Mi2 is utilized for semi-automated quantification of endolymphatic size. HYDROPS-Mi2 allows the segregation of endolymph and perilymph using the signal intensity threshold setting and area ratio of endolymph against the total lymphatic space can be easily calculated semi-automatically. Inter-observer variability with this method is reported to be quite small. To further reduce inter-observer variability, the slice level for evaluation has been defined in detail for MR cisternography (MRC) as follows [58]:

"Before starting the contouring of the cochlea or vestibule on MRC, set the image window level and width to 400/1000".

"For the cochlear ROI, select the slice on which the cochlear modiolus is visually largest. If the size of the modiolus is comparable on 2 or more slices, choose the slice with the largest height of the modiolus. When contouring the cochlea on MRC, exclude the modiolus when drawing the ROI".

"For the vestibular ROI, select the lowest slice where the lateral semicircular canal ring is visualized more than

240°, and exclude the semicircular canal and ampulla when drawing the ROI for the vestibule on MRC."

Reduced scan time for the less observer-dependent semi-quantitative method

Reduced scan time for HYDROPS-Mi2 imaging has been proposed as HYDROPS2-Mi2 [58]. The HYDROPS2-Mi2 image is generated by multiplying the MRC and HYDROPS2 images. In both HYDROPS-Mi2 and HYDROPS2-Mi2, the aim of multiplying the MRC image onto the HYDROPS and HYDROPS2 images is to zero the signal intensity value of bony structures that may be included in the region of interest (ROI), i.e., the osseous spiral lamina, interscalar septum and bony wall of the labyrinth [49, 58]. Without multiplication, such bony structures might show non-zero negative signal intensity values due to the low signal-to-noise ratio (SNR) of the HYDROPS and HYDROPS2 images, which would result in overestimation of the size of the endolymph area. Acquisition of source images takes 31 min for HYDROPS-Mi2 images and 17 min for HYDROPS2-Mi2 images. HYDROPS2-Mi2 also allows the segregation of endo-lymph and perilymph by the signal intensity threshold setting and the area ratio of endolymph against the total lymphatic space (%EL) can be easily calculated. The area ratio of the endolymphatic space against the total lymphatic space by HYDROPS-Mi2 and by HYDROPS2-Mi2 are well correlated, although HYDROPS-Mi2 showed slightly overestimated %EL values [58].

Normal range of endolymphatic size

Another important issue is to set up a normal range for %EL. In a previous histological study, the %EL in 5 control subjects was 9–12 % in the cochlea and 22–26 % in the vestibule [68].

In a living human study performed using the IT-Gd method, the normal range (mean ± 1.96 SD) for %EL in 45 to 55 year-old volunteers was reported to be 8–26 % in the cochlea and 20–41 % in the vestibule [40]. In 20 to 30 year-old volunteers, it was 10.2–25.8 % in the cochlea and 13.3–40.7 % in the vestibule using the IT method [10].

Correlation between EHI and various otological tests

Histological confirmation of endolymphatic hydrops is impossible to obtain in living patients with Ménière's or related diseases, therefore, in order to increase the clinical significance of EHI, the accumulation of cases in which correlations have been made between EHI findings and clinical symptoms, as well as with results from various

conventional functional otological tests, is greatly needed. Various functional otological tests have been utilized to diagnose endolymphatic hydrops, however an ideal test has not been developed. The diagnostic guidelines set by AAO-HNS do not include functional otological tests. To date, most reports regarding clinical results of EHI have been performed using the IT-Gd method, however, some reports using IV-Gd are appearing.

Electrocochleography

It has been reported that the summating potential/action potential (SP/AP) ratio from electrocochleography is increased in patients with significant endolymphatic hydrops, as identified by MRI, except in 2 patients with a relatively short history of the disease [69]. An increased SP/AP ratio is believed to be a marker of endolymphatic hydrops, and it has been suggested that the SP/AP ratio is related not only to the degree of endolymphatic hydrops in EHI but also to the persistence of endolymphatic hydrops [69].

In patients with clinically and electrocochleographically confirmed definite Ménière's disease, the degree of endo-lymphatic hydrops severity in EHI correlates significantly with impairment of hearing function and saccular function [70]. EHI is reported to be more useful for the diagnosis of endolymphatic hydrops compared with the glycerol test and electrocochleography [19].

Vestibular-evoked myogenic potential (VEMP)

Vestibular-evoked myogenic potential (VEMP) is now widely used to examine otolith function, and saccular function in particular. VEMP may be reduced or abolished in patients with endolymphatic hydrops in the vestibule. Vestibular endolymphatic hydrops in EHI is significantly associated with the disappearance of VEMP [21]. However, another study has reported that the absence of VEMP did not correlate with vestibular hydrops in EHI [20]. Further study is necessary to confirm the relationship between VEMP findings and EHI findings.

Caloric test

Caloric testing is used to evaluate the vestibular function of the ears. It is widely used as one of the most important functional tests of the vestibular system. It measures vestibular function in the lateral semicircular canal (LSC) by giving the external auditory canal thermal stimulation. Using the IT-Gd method, no significant relationship between the caloric response and the degree of endolymphatic hydrops in the vestibule, the cochlea or the ampulla of the lateral semicircular canal was shown [22]. Another

study failed to show a significant relationship between the degree of endolymphatic hydrops and the caloric test [71], while a different study showed only a trend towards a correlation between endolymphatic hydrops and the caloric response [18].

Glycerol test

Ingestion of glycerol is believed to cause a transient reduction in hearing loss in the early stages of Ménière's disease. Twenty patients with 'definite' unilateral Ménière's disease underwent IT-Gd. A positive result was observed in 11 patients (55 %) with the glycerol test and in 12 patients (60 %) by electrocochleography. The incidence of positive findings when evaluating the same patients with both the glycerol test and electrocochleography increased to 75 %. In contrast, nineteen of 20 (95 %) patients showed positive results using EHI by MRI at 3T [19].

Multifrequency tympanometry

Multifrequency tympanometry was also reported to be useful for the detection of endolymphatic hydrops. A prospective study was performed to investigate the relationship between the peak width generated by multifrequency tympanometry and the degree of endolymphatic hydrops by EHI. In 128 ears with a normal tympanic membrane, 19 ears had definite Ménière's disease, 5 ears had probable Ménière's disease, and 26 ears had possible Ménière's disease. Sixteen ears were clinically diagnosed as having delayed endolymphatic hydrops. Forty-four ears had other cochlear or vestibular symptoms, such as idiopathic sudden sensorineural hearing loss, acute low-tone sensorineural hearing loss, fluctuating hearing loss, and floating sensation. Eighteen asymptomatic ears were contralateral to ears with unilateral inner-ear diseases. All patients underwent EHI using the IT-Gd or IV-Gd method. Broad peak width in multifrequency tympanometry is associated with significant endolymphatic hydrops. However, the peak width was not significantly different between cases of mild and absent endolymphatic hydrops [16].

Clinical significance

Observations of temporal changes in the degree of endolymphatic hydrops in serial EHI

The degree of endolymphatic hydrops decreased in EHI using the IT-Gd method when the hearing level improved or vertigo attacks subsided [6, 72]. Moreover, it has been shown that after sac surgery, endolymphatic hydrops was reduced and symptoms went into remission in some cases, although the suppression of vertigo did not always result from the reduced endolymphatic hydrops. This study was conducted with either the IT-Gd or IV-Gd method [73]. The effect of drug therapy on endolymphatic hydrops has also been monitored with EHI [28].

Endolymphatic hydrops and duration of clinical symptoms

The increased prevalence and severity of endolymphatic hydrops with the duration of Ménière's disease indicates that endolymphatic hydrops is a progressive degenerative phenomenon. The frequent abnormality in the vestibule and, secondarily, in the cochlea is in line with some histopathological investigations. It remains to be determined if hydropic changes are related to specific signs and symptoms of Ménière's disease [26].

Gentamicin

Intratympanic ototoxic agents such as gentamicin have become a widely accepted means of managing vertigo in patients with Ménière's disease while preserving residual hearing [74]. IT-Gd is expected to show the distribution of intratympanically injected drug [44]; however, the possibility of a reduced effect of intratympanically administered gentamicin in the presence of severe endolymphatic hydrops, owing to diffusion obstacles along the perilymphatic compartments, has not been confirmed [75]. Intratympanic gentamicin administration itself does not improve endolymphatic hydrops [17].

Atypical Ménière's disease

In patients with atypical Ménière's disease, endolymphatic hydrops has also been detected by EHI [5, 6, 27]. To investigate images of the endolymphatic space in patients with atypical Ménière's disease (cochlear and vestibular Ménière's disease), 64 patients were divided into two groups. The first group included 36 patients who had fluctuating hearing loss without vertigo, and were candidates for cochlear Ménière's disease (CMD). The second group included 28 patients who had recurrent vertigo without hearing loss, and were candidates for vestibular Ménière's disease (VMD). The VMD group had a significant vestibular predominance in endolymphatic hydrops distribution whereas the CMD group showed no significant regional predominance of endolymphatic hydrops. The patients with atypical Ménière's disease had endolymphatic hydrops in both the cochlea and the vestibule [5].

Sudden deafness

Even amongst patients with sudden deafness, some have been shown to have endolymphatic hydrops by EHI [76]. In cases of sudden deafness and vertigo, more than half of the patients showed endolymphatic hydrops in the cochlea and/or the vestibule of the affected ears. Thus, there may be some relationship between endolymphatic hydrops and idiopathic sensorineural hearing loss with vertigo [3].

In IV-Gd studies, perilymph enhancement is stronger on the ipsilateral side ear than on the contralateral side ear. The signal intensity ratio (SIR) between the cochlea and cerebellum in EHI by IT-Gd may be a good indicator of disruption of the blood-labyrinthine barrier [61].

Delayed endolymphatic hydrops (DELH)

DELH has previously been diagnosed based on clinical history, hearing and vestibular examinations. DELH is classified into three types: ipsilateral, contralateral and bilateral; these classifications indicate the side with long standing hearing loss. Ipsilateral DELH occurs in the ear with a profound hearing loss, contralateral DELH in the ear with better hearing and bilateral DELH in both ears. Endolymphatic hydrops was observed in all patients in images generated by IT-Gd. Imaging diagnosis of the endolymphatic hydrops may add a new dimension to the diagnosis and treatment of DELH [4]. Endolymphatic hydrops in patients with ipsilateral DEHL has also recently been reported by IV-SD-GBCM [77].

Non-symptomatic endolymphatic hydrops

With the development of the EHI method with IV-SD-GBCM, many patients without typical Ménière's disease symptoms have been examined. Based on this, many subjects with non-symptomatic endolymphatic hydrops have been identified [56]. Recent findings indicate that just as the prevalence of asymptomatic glaucoma is greater than that of symptomatic glaucoma, there are also many cases of asymptomatic endolymphatic hydrops. It is assumed that the asymptomatic endolymphatic hydrops that precedes Ménière's disease is found more frequently by EHI using MRI than with other techniques [57].

Vestibular migraine

A recent study showed that some patients with vestibular migraine have cochlear and vestibular endolymphatic hydrops. Therefore, EHI might be indicated not only for inner ear diseases, but also for vestibular migraine [78]. Fluid homeostasis might be a key to deepening the understanding of hydrocephalus, glaucoma, migraine and Ménière's disease as a group [56].

Clinical significance of EHI

Firm evidence of the clinical utility of EHI has yet to be established. Based on EHI data from more than 200 patients and clinical data from more than 300 patients, Ménière's disease often shows bilateral endolymphatic hydrops and comprises a continuum from a monosymptomatic disease to the typical symptom complex of the disease [57]. The time delay between hearing loss and vertigo was more than 5 years in 20 % of patients. Thus, it is suggested that EHI by IV-Gd should be carried out in patients with sensorineural hearing loss, vertigo and tinnitus, to verify the inner ear pathology. This may lead to better management of the condition [57] as early detection of endolymphatic hydrops and early intervention might improve the prognosis of patients with Ménière's disease.

For wider spread use of EHI, easier, standardized and more reliable evaluation strategies need to be established. If this is made possible, EHI might be included in the diagnostic guidelines for Ménière's disease in the near future.

Conclusions

The objective diagnosis of endolymphatic hydrops with EHI is now feasible with clinically and easily applicable MR methods even at 1.5 T using IV-SD-GBCM. This technique will rapidly spread throughout the clinical field for the evaluation of patients with vertigo attacks, fluctuating hearing loss and ear fullness. Target diseases might include not only inner ear disorders such as Ménière's disease, but also more common neurological diseases such as migraine.

From the results reported in the literature, all patients with Ménière's disease have endolymphatic hydrops in EHI; however, not all subjects that show endolymphatic hydrops by EHI present with the typical symptoms of Ménière's disease. The mechanism of vertigo attack should be clarified in the future. The imaging methods and evaluation strategies of EHI are still under development; however, standardization of the EHI method is necessary in order to conduct larger scale multi-institutional studies to establish "evidence based medicine" for Ménière's disease.

🖄 Springer

References

1. Nakashima T, Naganawa S, Sugiura M, Teranishi M, Sone M, Hayashi H, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. Laryngoscope. 2007;117(3):415–20.
2. Niyazov DM, Andrews JC, Strelioff D, Sinha S, Lufkin R. Diagnosis of endolymphatic hydrops in vivo with magnetic resonance imaging. Otol Neurotol. 2001;22(6):813–7.
3. Chen X, Zhang XD, Gu X, Fang ZM, Zhang R. Endolymphatic space imaging in idiopathic sudden sensorineural hearing loss with vertigo. Laryngoscope. 2012;122(10):2265–8.
4. Kasai S, Teranishi M, Katayama N, Sugiura M, Nakata S, Sone M, et al. Endolymphatic space imaging in patients with delayed endolymphatic hydrops. Acta Otolaryngol. 2009;129(11):1169–74.
5. Kato M, Sugiura M, Shimono M, Yoshida T, Otake H, Kato K, et al. Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Meniere's disease. Acta Otolaryngol. 2013;133(2):123–9.
6. Miyagawa M, Fukuoka H, Tsukada K, Oguchi T, Takumi Y, Sugiura M, et al. Endolymphatic hydrops and therapeutic effects are visualized in 'atypical' Meniere's disease. Acta Otolaryngol. 2009;129(11):1326–9.
7. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg. 1995;113(3):181–5.
8. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Meniere's disease with single-dose intravenous gadolinium-based contrast media using heavily T(2)-weighted 3D-FLAIR. Magn Reson Med Sci. 2010;9(4):237–42.
9. Naganawa S, Nakashima T. Cutting edge of inner ear MRI. Acta Otolaryngol Suppl. 2009;560:15–21.
10. Liu F, Huang W, Wang Z, Chen Q, Liu X, Li S, et al. Noninvasive evaluation of endolymphatic space in healthy volunteers using magnetic resonance imaging. Acta Otolaryngol. 2011;131(3):247–57.
11. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Meniere's disease by subtraction of MR cisternography from positive perilymph image. Magn Reson Med Sci. 2012;11(4):303–9.
12. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Meniere's disease after intravenous administration of single-dose gadodiamide: utility of subtraction images with different inversion time. Magn Reson Med Sci. 2012;11(3):213–9.
13. 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. 2012;11(2):145–50.
14. Nakashima T, Naganawa S, Teranishi M, Tagaya M, Nakata S, Sone M, et al. Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Meniere's disease. Acta Otolaryngol. 2010;130(3):338–43.
15. Colletti V, Mandala M, Carner M, Barillari M, Cerini R, Pozzi Mucelli R, et al. Evidence of gadolinium distribution from the endolymphatic sac to the endolymphatic compartments of the human inner ear. Audiol Neurootol. 2010;15(6):353–63.
16. Kato K, Yoshida T, Teranishi M, Sano R, Otake H, Sone M, et al. Peak width in multifrequency tympanometry and endolymphatic hydrops revealed by magnetic resonance imaging. Otol Neurotol. 2012;33(6):912–5.
17. Fiorino F, Pizzini FB, Barbieri F, Beltramello A. Magnetic resonance imaging fails to show evidence of reduced endolymphatic hydrops in gentamicin treatment of Meniere's disease. Otol Neurotol. 2012;33(4):629–33.
18. Gurkov R, Flatz W, Louza J, Strupp M, Krause E. In vivo visualization of endolymphatic hydrops in patients with Meniere's disease: correlation with audiovestibular function. Eur Arch Otorhinolaryngol. 2011;268(12):1743–8.
19. Fukuoka H, Takumi Y, Tsukada K, Miyagawa M, Oguchi T, Ueda H, et al. Comparison of the diagnostic value of 3 T MRI after intratympanic injection of GBCA, electrocochleography, and the glycerol test in patients with Meniere's disease. Acta Otolaryngol. 2012;132(2):141–5.
20. Seo YJ, Kim J, Choi JY, Lee WS. Visualization of endolymphatic hydrops and correlation with audio-vestibular functional testing in patients with definite Meniere's disease. Auris Nasus Larynx. 2013;40(2):167–72.
21. Katayama N, Yamamoto M, Teranishi M, Naganawa S, Nakata S, Sone M, et al. Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. Acta Otolaryngol. 2010;130(8):917–23.
22. Kato M, Teranishi M, Katayama N, Sone M, Naganawa S, Nakashima T. Association between endolymphatic hydrops as revealed by magnetic resonance imaging and caloric response. Otol Neurotol. 2011;32(9):1480–5.
23. Yoshida T, Teranishi M, Kato M, Otake H, Kato K, Sone M, et al. Endolymphatic hydrops in patients with tinnitus as the major symptom. Eur Arch Otorhinolaryngol. 2013;270(12):3043–8.
24. Zou J, Pyykko I, Bjelke B, Dastidar P, Toppila E. Communication between the perilymphatic scalae and spiral ligament visualized by in vivo MRI. Audiol Neurootol. 2005;10(3):145–52.
25. Fang ZM, Chen X, Gu X, Liu Y, Zhang R, Cao DR, et al. A new magnetic resonance imaging scoring system for perilymphatic space appearance after intratympanic gadolinium injection, and its clinical application. J Laryngol Otol. 2012;126(5):454–9.
26. Fiorino F, Pizzini FB, Beltramello A, Barbieri F. Progression of endolymphatic hydrops in Meniere's disease as evaluated by magnetic resonance imaging. Otol Neurotol. 2011;32(7):1152–7.
27. Fukuoka H, Tsukada K, Miyagawa M, Oguchi T, Takumi Y, Sugiura M, et al. Semi-quantitative evaluation of endolymphatic hydrops by bilateral intratympanic gadolinium-based contrast agent (GBCA) administration with MRI for Meniere's disease. Acta Otolaryngol. 2010;130(1):10–6.
28. Gurkov R, Flatz W, Keeser D, Strupp M, Ertl-Wagner B, Krause E. Effect of standard-dose Betahistine on endolymphatic hydrops: an MRI pilot study. Eur Arch Otorhinolaryngol. 2013;270(4):1231–5.
29. Katahira N, Tanigawa T, Tanaka H, Nonoyama H, Ueda H. Diluted gadoteridol [ProHance(R)] causes mild ototoxicity in cochlear outer hair cells. Acta Otolaryngol. 2013;133(8):788–95.
30. Shi H, Li Y, Yin S, Zou J. The predominant vestibular uptake of gadolinium through the oval window pathway is compromised by endolymphatic hydrops in Meniere's disease. Otol Neurotol. 2014;35(2):315–22.
31. Nakashima T, Naganawa S, Katayama N, Teranishi M, Nakata S, Sugiura M, et al. Clinical significance of endolymphatic imaging after intratympanic gadolinium injection. Acta Otolaryngol Suppl. 2009;560:9–14.
32. Naganawa S, Satake H, Iwano S, Fukatsu H, Sone M, Nakashima T. Imaging endolymphatic hydrops at 3 tesla using 3D-FLAIR with intratympanic Gd-DTPA administration. Magn Reson Med Sci. 2008;7(2):85–91.
33. Naganawa S, Kawai H, Fukatsu H, Ishigaki T, Komada T, Maruyama K, et al. High-speed imaging at 3 Tesla: a technical and clinical review with an emphasis on whole-brain 3D imaging. Magn Reson Med Sci. 2004;3(4):177–87.
34. 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(5):920–4.

35. Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid at 3 T after intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. AJNR Am J Neuroradiol. 2008;29(4):724–6.

36. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Estimation of perilymph enhancement after intratympanic administration of Gd-DTPA by fast T1-mapping with a dual flip angle 3D spoiled gradient echo sequence. Magn Reson Med Sci. 2013;12(3):223–8.

37. Naganawa S, Sone M, Yamazaki M, Kawai H, Nakashima T. Visualization of endolymphatic hydrops after intratympanic injection of Gd-DTPA: comparison of 2D and 3D real inversion recovery imaging. Magn Reson Med Sci. 2011;10(2):101–6.

38. Grieve SM, Obholzer R, Malitz N, Gibson WP, Parker GD. Imaging of endolymphatic hydrops in Meniere's disease at 1.5 T using phase-sensitive inversion recovery: (1) demonstration of feasibility and (2) overcoming the limitations of variable gadolinium absorption. Eur J Radiol. 2012;81(2):331–8.

39. Naganawa S, Ishihara S, Iwano S, Sone M, Nakashima T. Three-dimensional (3D) visualization of endolymphatic hydrops after intratympanic injection of Gd-DTPA: optimization of a 3D-real inversion-recovery turbo spin-echo (TSE) sequence and application of a 32-channel head coil at 3T. J Magn Reson Imaging. 2010;31(1):210–4.

40. Liu F, Huang W, Meng X, Wang Z, Liu X, Chen Q. Comparison of noninvasive evaluation of endolymphatic hydrops in Meniere's disease and endolymphatic space in healthy volunteers using magnetic resonance imaging. Acta Otolaryngol. 2012;132(3):234–40.

41. Pyykko I, Zou J, Poe D, Nakashima T, Naganawa S. Magnetic resonance imaging of the inner ear in Meniere's disease. Otolaryngol Clin North Am. 2010;43(5):1059–80.

42. Louza J, Krause E, Gurkov R. Audiologic evaluation of Meniere's disease patients one day and one week after intratympanic application of gadolinium contrast agent: our experience in sixty-five patients. Clin Otolaryngol. 2013;38(3):262–6.

43. Suzuki H, Teranishi M, Naganawa S, Nakata S, Sone M, Nakashima T. Contrast-enhanced MRI of the inner ear after intratympanic injection of meglumine gadopentetate or gadodiamide hydrate. Acta Otolaryngol. 2011;131(2):130–5.

44. Yoshioka M, Naganawa S, Sone M, Nakata S, Teranishi M, Nakashima T. Individual differences in the permeability of the round window: evaluating the movement of intratympanic gadolinium into the inner ear. Otol Neurotol. 2009;30(5):645–8.

45. Naganawa S, Kawai H, Sone M, Nakashima T. Increased sensitivity to low concentration gadolinium contrast by optimized heavily T2-weighted 3D-FLAIR to visualize endolymphatic space. Magn Reson Med Sci. 2010;9(2):73–80.

46. Naganawa S, Yamazaki M, Kawai H, Sone M, Nakashima T. Contrast enhancement of the anterior eye segment and subarachnoid space: detection in the normal state by heavily T2-weighted 3D FLAIR. Magn Reson Med Sci. 2011;10(3):193–9.

47. Carfrae MJ, Holtzman A, Eames F, Parnes SM, Lupinetti A. 3 Tesla delayed contrast magnetic resonance imaging evaluation of Meniere's disease. Laryngoscope. 2008;118(3):501–5.

48. Tagaya M, Yamazaki M, Teranishi M, Naganawa S, Yoshida T, Otake H, et al. Endolymphatic hydrops and blood-labyrinth barrier in Meniere's disease. Acta Otolaryngol. 2011;131(5):474–9.

49. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Meniere's disease after intravenous administration of single-dose gadodiamide: utility of multiplication of MR cisternography and HYDROPS image. Magn Reson Med Sci. 2013;12(1):63–8.

50. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Three-dimensional visualization of endolymphatic hydrops after intravenous administration of single-dose gadodiamide. Magn Reson Med Sci. 2013;12(2):147–51.

51. Zou J, Li M, Zhang Y, Zheng G, Chen D, Chen S, et al. Transport augmentation through the blood-inner ear barriers of guinea pigs treated with 3-nitropropionic acid and patients with acute hearing loss, visualized with 3.0 T MRI. Otol Neurotol. 2011;32(2):204–12.

52. Sano R, Teranishi M, Yamazaki M, Isoda H, Naganawa S, Sone M, et al. Contrast enhancement of the inner ear in magnetic resonance images taken at 10 min or 4 h after intravenous gadolinium injection. Acta Otolaryngol. 2012;132(3):241–6.

53. Naganawa S, Komada T, Fukatsu H, Ishigaki T, Takizawa O. Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol. 2006;16(3):733–7.

54. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Meniere's disease after single-dose intravenous gadolinium-based contrast medium: timing of optimal enhancement. Magn Reson Med Sci. 2012;11(1):43–51.

55. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière's disease after intravenous administration of single-dose gadodiamide at 1.5T. Magn Reson Med Sci. 2013;12(2):137–9.

56. Nakashima T, Sone M, Teranishi M, Yoshida T, Terasaki H, Kondo M, et al. A perspective from magnetic resonance imaging findings of the inner ear: relationships among cerebrospinal, ocular and inner ear fluids. Auris Nasus Larynx. 2012;39(4):345–55.

57. Pyykko I, Nakashima T, Yoshida T, Zou J, Naganawa S. Meniere's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. BMJ Open. 2013;3(2). doi:10.1136/bmjopen-2012-001555.

58. Naganawa S, Suzuki K, Nakamichi R, Bokura K, Yoshida T, Sone M et al. Semi-quantification of endolymphatic size on MR imaging after intravenous injection of single-dose gadodiamide: comparison between two types of processing strategies. Magn Reson Med Sci. 2013.

59. Naganawa S, Suzuki K, Yamazaki M, Sakurai Y, Ikeda M. Time course of endolymphatic size measurement in healthy volunteers following intravenous administration of gadoteridol. Magn Reson Med Sci. (in press).

60. Tanigawa T, Tamaki T, Yamamuro O, Tanaka H, Nonoyama H, Shiga A, et al. Visualization of endolymphatic hydrops after administration of a standard dose of an intravenous gadolinium-based contrast agent. Acta Otolaryngol. 2011;131(6):596–601.

61. Tagaya M, Teranishi M, Naganawa S, Iwata T, Yoshida T, Otake H, et al. 3 Tesla magnetic resonance imaging obtained 4 h after intravenous gadolinium injection in patients with sudden deafness. Acta Otolaryngol. 2010;130(6):665–9.

62. Naganawa S, Ishihara S, Iwano S, Sone M, Nakashima T. Detection of presumed hemorrhage in the ampullar endolymph of the semicircular canal: a case report. Magn Reson Med Sci. 2009;8(4):187–91.

63. Naganawa S, Sone M, Otake H, Nakashima T. Endolymphatic hydrops of the labyrinth visualized on noncontrast MR imaging: a case report. Magn Reson Med Sci. 2009;8(1):43–6.

64. Naganawa S, Kawai H, Sone M, Nakashima T, Ikeda M. Endolymphatic hydrops in patients with vestibular schwannoma: visualization by non-contrast-enhanced 3D FLAIR. Neuroradiology. 2011;53(12):1009–15.

65. Iida T, Teranishi M, Yoshida T, Otake H, Sone M, Kato M, et al. Magnetic resonance imaging of the inner ear after both intratympanic and intravenous gadolinium injections. Acta Otolaryngol. 2013;133(5):434–8.

66. Naganawa S, Yamazaki M, Kawai H, Bokura K, Iida T, Sone M et al. MR imaging of Ménière's disease by both intratympanic and intravenous injection of gadolinium using HYDROPS2. Magn Reson Med Sci. (in press).

67. Nakashima T, Naganawa S, Pyykko I, Gibson WP, Sone M, Nakata S, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol Suppl. 2009;560:5–8.

68. Teranishi M, Yoshida T, Katayama N, Hayashi H, Otake H, Nakata S, et al. 3D computerized model of endolymphatic hydrops from specimens of temporal bone. Acta Otolaryngol Suppl. 2009;560:43–7.

69. Yamamoto M, Teranishi M, Naganawa S, Otake H, Sugiura M, Iwata T, et al. Relationship between the degree of endolymphatic hydrops and electrocochleography. Audiol Neurootol. 2010;15(4):254–60.

70. Gurkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E. In vivo visualized endolymphatic hydrops and inner ear functions in patients with electrocochleographically confirmed Meniere's disease. Otol Neurotol. 2012;33(6):1040–5.

71. Fiorino F, Pizzini FB, Beltramello A, Barbieri F. MRI performed after intratympanic gadolinium administration in patients with Meniere's disease: correlation with symptoms and signs. Eur Arch Otorhinolaryngol. 2011;268(2):181–7.

72. Sone M, Naganawa S, Teranishi M, Nakata S, Katayama N, Nakashima T. Changes in endolymphatic hydrops in a patient with Meniere's disease observed using magnetic resonance imaging. Auris Nasus Larynx. 2010;37(2):220–2.

73. Uno A, Imai T, Watanabe Y, Tanaka H, Kitahara T, Horii A, et al. Changes in endolymphatic hydrops after sac surgery examined by Gd-enhanced MRI. Acta Otolaryngol. 2013; 133(9):924–9.

74. Bauer PW, MacDonald CB, Cox LC. Intratympanic gentamicin therapy for vertigo in nonserviceable ears. Am J Otolaryngol. 2001;22(2):111–5.

75. Fiorino F, Pizzini FB, Barbieri F, Beltramello A. Variability in the perilymphatic diffusion of gadolinium does not predict the outcome of intratympanic gentamicin in patients with Meniere's disease. Laryngoscope. 2012;122(4):907–11.

76. Horii A, Osaki Y, Kitahara T, Imai T, Uno A, Nishiike S, et al. Endolymphatic hydrops in Meniere's disease detected by MRI after intratympanic administration of gadolinium: comparison with sudden deafness. Acta Otolaryngol. 2011;131(6):602–9.

77. Nonoyama H, Tanigawa T, Tamaki T, Tanaka H, Yamamuro O, Ueda H. Evidence for bilateral endolymphatic hydrops in ipsilateral delayed endolymphatic hydrops: preliminary results from examination of five cases. Acta Otolaryngol. 2013 [Epub ahead of print].

78. Gurkov R, Kantner C, Strupp M, Flatz W, Krause E, Ertl-Wagner B. Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms. Eur Arch Otorhinolaryngol. 2013 [Epub ahead of print].

TECHNICAL NOTE

MR Imaging of Ménière's Disease after Combined Intratympanic and Intravenous Injection of Gadolinium using HYDROPS2

Shinji Naganawa[1]*, Masahiro Yamazaki[1], Hisashi Kawai[1], Kiminori Bokura[1],

Tatsuo Iida[2], Michihiko Sone[2], and Tsutomu Nakashima[2]

[1]Department of Radiology, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Shouwa-ku, Nagoya 466–8550, Japan
[2]Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine

Endolymphatic hydrops (EH) in Ménière's disease is currently evaluated by 3-dimensional (3D)-real inversion recovery (IR) sequence after intratympanic (IT) administration of gadolinium (Gd) or by heavily T_2-weighted (hT_2W)-3D-fluid-attenuated IR (FLAIR) sequence after intravenous (IV) injection of Gd. Unilateral IT injection is usually performed. We employed a method in which we simultaneously administered contrast into one ear intravenously (IV side) and into the other ear both intravenously and intratympanically (IT + IV side) to evaluate EH in 10 patients with Ménière's disease. We then compared a HYDROPS2 image obtained by subtracting magnetic resonance cisternography from hT_2W-3D-FLAIR with an image obtained by 3D-real IR and found that we could evaluate EH in all ears on the HYDROPS2 image but only in the IT + IV side on the 3D-real IR image.

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

Introduction

Visualization of endolymphatic hydrops (EH) in patients with clinically suspected Ménière's disease (MD) is currently performed by 3-dimensional inversion recovery with real reconstruction (3D-real IR) imaging after intratympanic (IT) administration of gadolinium-based contrast material (GBCM)[1,2] or by heavily T_2-weighted (hT_2W)-3D fluid-attenuated inversion-recovery (FLAIR) sequence after intravenous (IV) administration of single-dose GBCM.[3–6] The IT method usually provides higher contrast than the IV method and can predict the intralabyrinthine distribution of intratympanically injected gentamicin and steroids.[7,8] However, IT administration of GBCM is off-label use and requires puncture of the tympanic membrane.[9] Many patients with unilateral disease are reluctant to receive IT administration of GBCM in asymptomatic or ears with better hearing,[10] so unilateral IT injec-

tion is usually performed even in cases when bilateral EH is suspected. Furthermore, in some patients, impaired permeability of the round window membrane prevents sufficient concentration of GBCM to visualize EH using the IT method.[11] Intravenous administration permits simultaneous evaluation of both ears but requires sufficiently sensitive pulse sequences to detect very low GBCM concentration.[12]

Imaging parameters for the IT and IV methods differ. To simulate drug distribution in one ear and evaluate EH in the other, we have begun to administer contrast materials using a method that combines IT and IV administration (IT + IV). That is, we administer contrast only intravenously in one ear (IV side) and both intravenously and intratympanically in the other (IT + IV side). We have previously detailed the combined IT and IV administration of contrast and the difference in contrast enhancement between the IV and IT + IV sides.[10]

For the IT method, the use of 3D-real IR images was proposed, and their use allowed separate visualization of the endolymph, perilymph, and bone

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