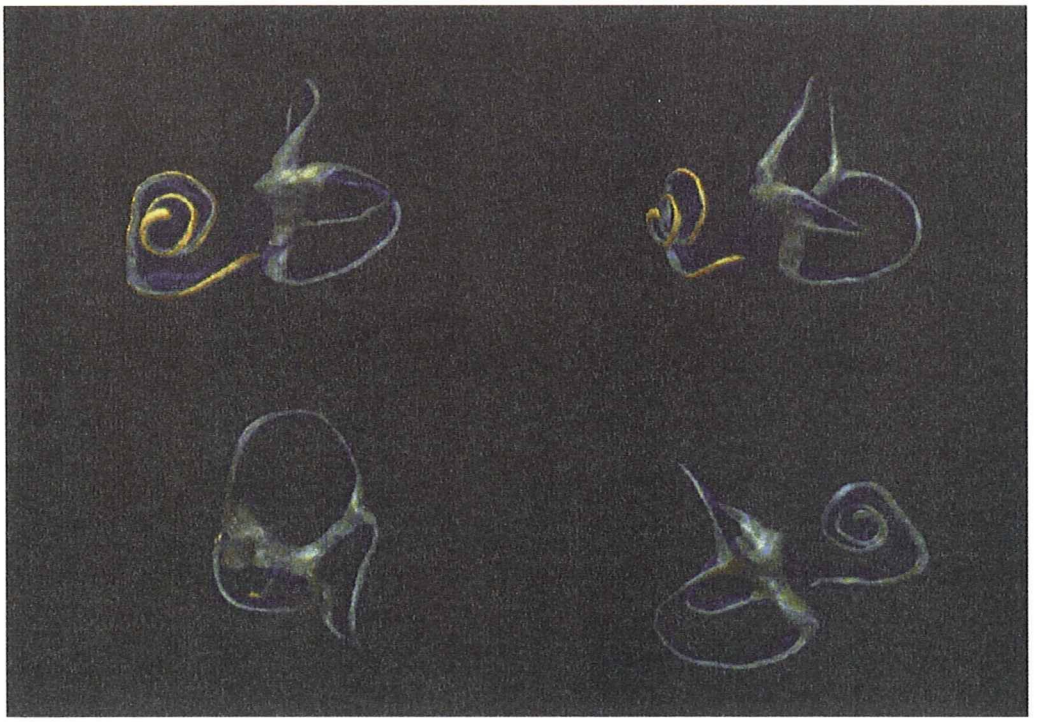

Figure 6. A 3D model of the inner ear of case 3 (a control). Blue area indicates perilymphatic space and yellow area indicates endolymphatic space. The endolymphatic space is not enlarged in either the cochlea or the vestibule.

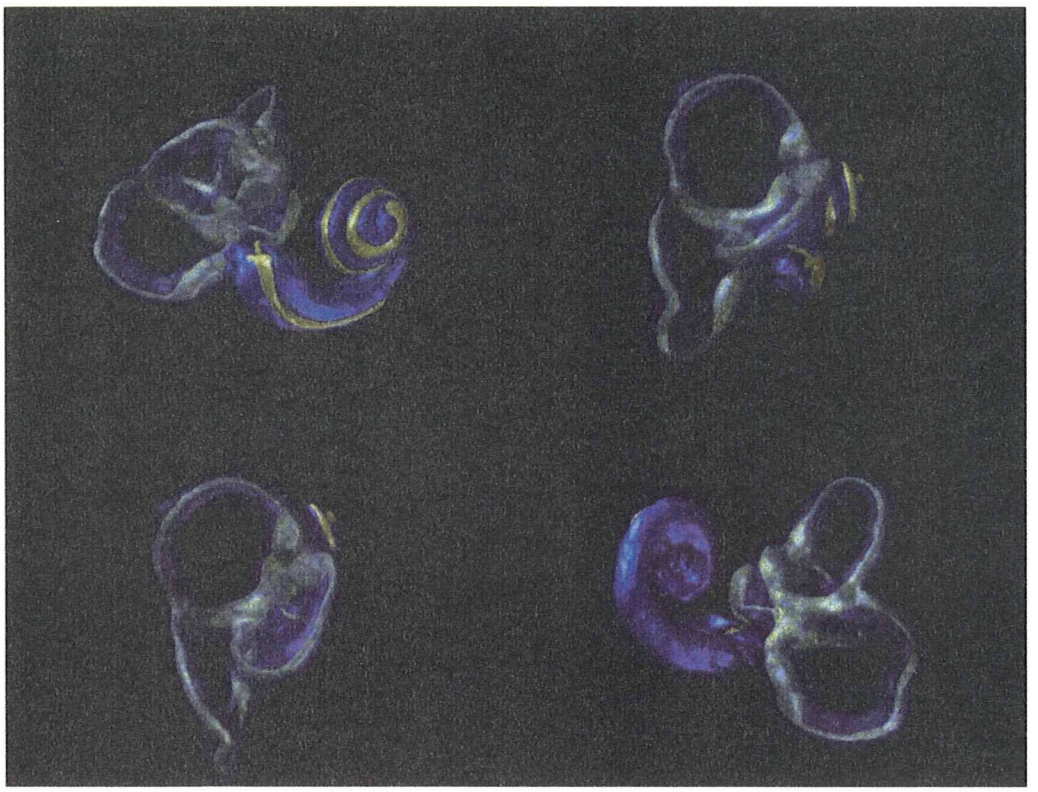

Figure 7. A 3D model of the inner ear of case 7 (a control). Blue area indicates perilymphatic space and yellow area indicates endolymphatic space.

Discussion

Using image-analytical software we have succeeded, for the first time to our knowledge, in making a 3D model of the inner ear and measuring the volumes of perilymphatic and endolymphatic spaces from sections obtained at autopsy in patients who had endolymphatic hydrops. A 3D model of endolymphatic and perilymphatic spaces enabled us to obtain the volumes of each space and gave us useful information about the composition of the inner ear with endolymphatic hydrops. It helps us understand endolymphatic and perilymphatic structures three-dimensionally in various parts of the inner ear because we can observe these from every point of view [1–3].

We conclude that a 3D model of endolymphatic and perilymphatic spaces will enable us to acquire the volumes of each space for further analysis and understanding of the fundamental physiology of these spaces in the hearing apparatus, and may provide possible clinical guidance in diagnostic or therapeutic tasks. It will give us useful information regarding the 3D structures of various parts of the inner ear and the composition of the inner ear with endolymphatic hydrops.

Acknowledgements

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORIGINAL ARTICLE

Grading of endolymphatic hydrops using magnetic resonance imaging

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Abstract

Conclusion: Grading of endolymphatic hydrops in the vestibule and the cochlea using magnetic resonance imaging (MRI) is proposed (2008 Nagoya scale). *Objective:* To standardize the evaluation of endolymphatic hydrops in both the vestibule and the cochlea using MRI. *Patients and methods:* The endolymphatic space was evaluated after intratympanic gadolinium injection using three-dimensional fluid attenuated (3D-FLAIR) MRI and three-dimensional real inversion recovery (3D-real IR) MRI. *Results:* A simple three-stage grading system was acceptable for hydrops in both the vestibule and the cochlea: none, mild, and significant. In the vestibule, the grading was determined by the ratio of the area of endolymphatic space to the vestibular fluid space (sum of the endolymphatic and perilymphatic spaces). Patients with no hydrops have a ratio of one-third or less, those with mild hydrops have between one-third and a half, and those with significant hydrops have a ratio of more than 50%. In the cochlea, patients classified as having no hydrops show no displacement of Reissner's membrane; those with mild hydrops show displacement of Reissner's membrane but the area of the endolymphatic space does not exceed the area of the scala vestibuli; and in those with significant hydrops the area of the endolymphatic space exceeds the area of the scala vestibuli.

Keywords: *Membranous labyrinth, endolymphatic space, cochlea, vestibule, gadolinium*

Introduction

Successful visualization of endolymphatic hydrops has been reported in patients with inner ear diseases using advanced magnetic resonance imaging (MRI) with intratympanic gadolinium (Gd) injection [1–3]. Endolymphatic imaging after intravenous Gd injection has also been reported [4,5]. Because endolymphatic space imaging has started to be used or is being planned in many hospitals, standardization of the evaluation of endolymphatic hydrops is necessary.

Patients and methods

In Nagoya University Hospital, endolymphatic imaging was performed after intratympanic Gd injection in more than 70 patients with inner ear diseases. The details of the method are as described previously [1–3]. Briefly, Gd diluted eightfold with saline was injected intratympanically. One day after the injection, inner ear scans were taken using a 3 Tesla MR unit with three-dimensional fluid attenuated (3D-FLAIR) MRI and three-dimensional real inversion recovery (3D-real IR) MRI.

With assistance from the Ministry of Health, Labor and Welfare in Japan, two of the authors (I.P. and W.P.G.) visited Nagoya University for 1 week and investigated endolymphatic imaging performed on three patients. In these patients, meglumin gadopentate (Magnevist®; Bayer HealthCare Pharmaceuticals, Leverkusen, Germany) diluted eightfold with saline (0.5 ml) was injected intratympanically. All authors observed the endolymphatic space in the vestibule and the cochlea of the MRI from the electronic medical records and discussed the images and clinical symptoms.

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To determine the grading of endolymphatic hydrops, the endolymphatic and perilymphatic spaces were outlined. The ratio of the area of the endolymphatic space to that of the fluid space in the vestibule was calculated using computer software (Adobe Photoshop CS3 Extended; Adobe Systems Inc., San Jose, CA, USA). For reference, the ratio of the endolymphatic space area to that of the fluid space in the vestibule was also calculated for four temporal bone specimens from patients without inner ear diseases.

Results

A scheme for grading endolymphatic hydrops is proposed for the vestibule and the cochlea, respectively. This is shown in Table I. An example of significant hydrops is shown in Figures 1 and 2. Examples of each grade are shown in the next paper in this Supplement.

In the vestibule, when the area ratio of endolymphatic space to the vestibular fluid space exceeds one-third, it is judged as endolymphatic hydrops. When the endolymphatic space exceeds 50% of fluid area in the vestibule, it is classified as significant hydrops. In temporal bone specimens from patients without inner ear diseases, the area ratio of endolymphatic space to the vestibular fluid ranged from 26.5% to 39.4% (mean 33.2%).

For the cochlea, the grading of endolymphatic hydrops has been determined as described in Table I. When the grade of endolymphatic hydrops differs between the basal and upper turns, we recommend reporting a higher grade of endolymphatic hydrops in the cochlea.

Table I. Grading of endolymphatic hydrops using MRI.

Grade of hydrops	Vestibule (area ratio*)	Cochlea
None	≤33.3%	No displacement of Reissner's membrane
Mild	>33.3%, ≤50%	Displacement of Reissner's membrane Area of cochlear duct ≤ area of the scala vestibuli
Significant	>50%	Area of the cochlear duct exceeds the area of the scala vestibuli

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

Discussion

In the vestibule, an endolymphatic area one-third that of the vestibular fluid space was determined as the border between normal and mild hydrops. This value might be slightly lower compared to the value of the area ratio obtained from the temporal bone specimens. However, the area ratio did not exceed 40% in any temporal bone specimen. We adopted this one-third ratio as a simple index in this study. In future, volume percentage of endolymphatic space should be calculated using more advanced MRI.

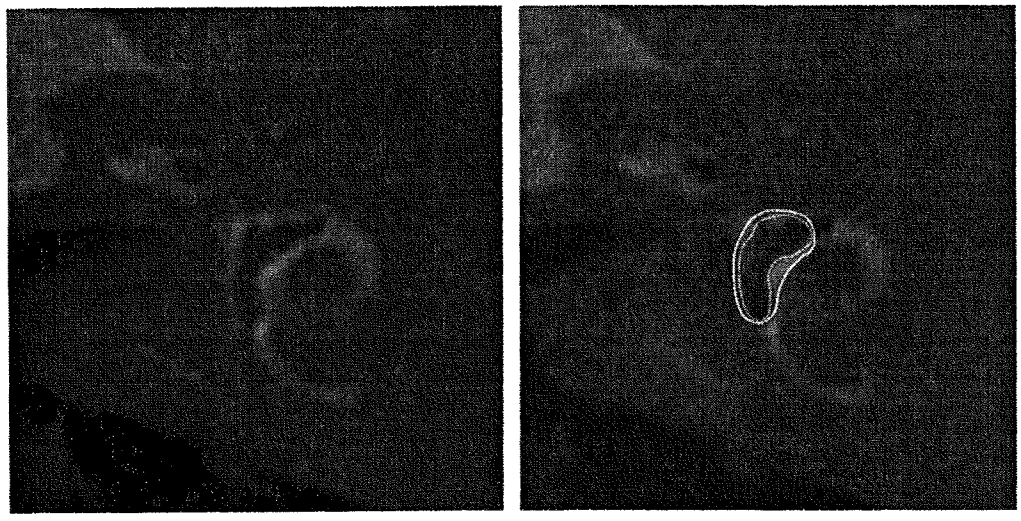

Figure 1. 3D-real IR MRI in a 57-year-old male patient with left Ménière's disease. Original MRI (left side) and line drawings on the MRI (right side). In this MRI, the lateral and posterior semicircular canals are also seen. Dotted line indicates endolymphatic space and solid line indicates the fluid space in the vestibule. Area ratio of the endolymphatic space to the vestibular fluid space is 67.5% (i.e. significant hydrops in the vestibule).

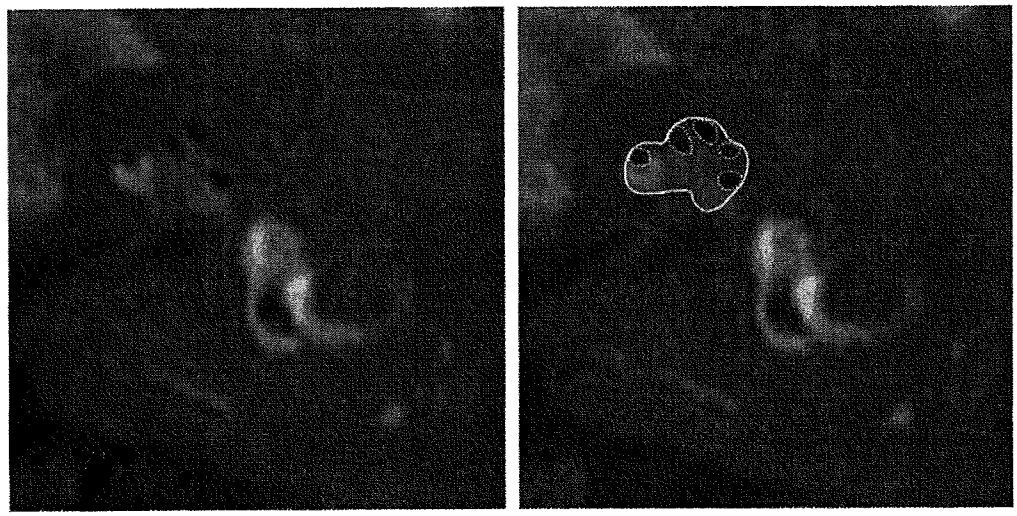

Figure 2. 3D-real IR MRI of the next section of Figure 1. Original MRI (left side) and line drawings of the cochlea on the MRI (right side). Dotted lines indicate endolymphatic spaces of cochlear turns. Solid line indicates fluid area of the cochlea. It it clear that the endolymphatic space (cochlear duct) is larger than the area of the scala vestibuli in the upper turns (i.e. significant hydrops in the cochlea).

In MRI, the cochlear endolymphatic space is divided into cochlear turns, and each space is small. However, the section that includes the modiolus (mid-modiolar section) is the most suitable region for evaluating the endolymphatic space. Not only the mid-modiolar section, but also other sections that include the cochlea help in the evaluation of the endolymphatic space in the cochlea. However, it is occasionally difficult to evaluate the endolymphatic space in all cochlear turns.

When there is collapse of the endolymphatic space, it is not recognized in MRI scans. Moreover, if there is rupture of Reissner's membrane, Gd may enter the endolymphatic space. In this study, collapse of an endolymphatic hydrops in the cochlea was suspected in one patient and collapse of an endolymphatic hydrops in the vestibule was suspected in another patient. In one patient with a large vestibular aqueduct syndrome, rupture of Reissner's membrane was suspected after deterioration in their hearing level. In this patient, Gd was seen in the endolymph of the endolymphatic sac and duct. Accordingly, classification as 'no hydrops' does not always mean 'normal'.

Conclusion

Seventy years have passed since Hallpike and Yamakawa demonstrated endolymphatic hydrops in temporal bone specimens in patients with Ménière's disease. Today, we can image endolymphatic hydrops using advanced MRI technology in living patients. For the standard evaluation of endolymphatic hydrops, we propose a simple three-stage grading of endolymphatic hydrops in the vestibule and the cochlea. The new technology has also enabled us to see pathological conditions in patients with inner ear diseases such as idiopathic sudden sensorineural hearing loss and viral labyrinthitis. Further advancement of MRI is expected to allow more detailed imaging of pathology in patients with inner ear diseases.

Acknowledgements

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORIGINAL ARTICLE

Clinical significance of endolymphatic imaging after intratympanic gadolinium injection

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Abstract

Conclusion: Using three-dimensional real inversion recovery (3D-real IR) and three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI), various degrees of endolymphatic hydrops were observed in the basal and upper turns of the cochlea and in the vestibular apparatus after intratympanic gadolinium (Gd) injection. MRI may contribute to our understanding of inner ear diseases and may be a useful addition to intratympanic drug therapy in the management of inner ear diseases. *Objective:* To evaluate 3D-real IR MRI and 3D-FLAIR MRI with clinical symptoms and signs in patients with inner ear disease. *Patients and methods:* Gd was diluted in saline and injected intratympanically in 73 patients with inner ear disease. The endolymphatic space was evaluated with 3-Tesla MRI at 1 day after the intratympanic Gd injection. *Results:* 3D-real IR MRI was generally better than 3D-FLAIR MRI in discriminating between the perilymphatic space and endolymphatic space in the cochlear turns and in the vestibular apparatus. However, when Gd concentration was insufficient in the perilymph, it was more difficult to visualize the Gd with 3D-real IR MRI than with 3D-FLAIR MRI. Endolymphatic hydrops was observed using MRI in patients with 'probable' Ménière's disease based on the criteria.

Keywords: *Membranous labyrinth, magnetic resonance imaging, MRI, endolymphatic space, perilymphatic space*

Introduction

Endolymphatic hydrops can be visualized using three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) after gadolinium (Gd), diluted eightfold with saline, is injected in patients with inner ear disease [1,2]. Gd enters the perilymphatic space through the round window membrane and can then delineate the perilymphatic and endolymphatic spaces.

This clinical endolymphatic imaging has two purposes. One is to investigate the relationship between clinical symptoms and endolymphatic hydrops. According to the criteria of the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS) guidelines [3], histopathological confirmation is necessary to diagnose 'certain' Ménière's disease in addition to 'definite' Ménière's disease. In addition, the diagnosis can be made when endolymphatic hydrops is observed with MRI in patients with 'probable' or 'possible' Ménière's disease. Thus, visualization of endolymphatic hydrops may be vital for making a new diagnosis of Ménière's disease. Investigation of the relationship between the endolymphatic image and functional tests such as electrocochleography and vestibular-evoked myogenic potential may deepen our understanding of inner ear diseases [1].

Another purpose of this clinical imaging is to investigate the permeability of the round window membrane and to observe drug distribution inside the inner ear. Intratympanic gentamicin administration is now used widely in the treatment of intractable Ménière's disease [4–6], and intratympanic steroid

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administration is used to treat sudden sensory hearing loss [7–10]. The number of papers on intratympanic drug therapy for the treatment of inner ear diseases is increasing. Intratympanic drug administration therapy depends on the permeability of the round window membrane. However, the permeability of the round window membrane is diminished in some patients [11,12]. Confirming that an intratympanically applied drug actually reaches the inner ear and investigating its distribution inside the inner ear are important when using intratympanic drug therapy to treat inner ear diseases.

MRI of the endolymphatic and perilymphatic spaces following intratympanic Gd injection may play an essential role in the management of inner ear diseases. However, the toxicity of Gd to the inner ear must be considered. Kakigi et al. [13] reported no remarkable effects on the stria vascularis after Gd diluted eightfold with saline was injected into the tympanic cavity of guinea pigs, although a higher concentration had adverse effects. In the present study, we used Gd diluted 16-fold with saline and compared the MRI with that obtained with Gd diluted 8-fold.

We recently developed three-dimensional real inversion recovery (3D-real IR) MRI to discriminate between the perilymphatic space and endolymphatic space, and between the endolymphatic space and the surrounding bone [14]. Improvements in software and hardware used in MRI may help to reduce the amount of injected Gd and improve the quality of the images. In the present study, we compared the results of 3D-FLAIR MRI and 3D-real IR MRI applied using the 8-fold and 16-fold Gd dilutions.

Patients and methods

The subjects for this investigation included 73 patients with inner ear disease. They had idiopathic sudden sensorineural hearing loss, Ménière's disease, delayed endolymphatic hydrops, fluctuating hearing loss without vertigo, or acute hearing deterioration with large vestibular aqueduct syndrome. Most of the patients were candidates for intratympanic steroid therapy or intratympanic gentamicin therapy. Using a 3-Tesla MRI unit, 3D-FLAIR, T1, and CISS (heavily T2) MRI was applied in all patients. 3D-real IR MRI was also used in 60 patients. The method of MRI was described previously [1,2,14].

Gadodiamide hydrate (Gd-DTPA-BMA: Omniscan®) or gadopentetate dimeglumine (Gd-DTPA: Magnevist®) diluted with saline was injected intratympanically. Fifty-four patients received gadodiamide hydrate and 19 patients received gadopentetate dimeglumine. In each drug group, the Gd was diluted 16-fold with saline in three patients. In the other patients, the drug was diluted eightfold with saline.

The method of intratympanic injection was the same as described previously [1]. To make the solution for the intratympanic injection, we opened a 5 ml or 10 ml commercially available Gd syringe used for intravenous injection. Because the chelator surrounding the free Gd is apt to separate after the syringe is opened, we opened the syringe immediately before it was used for the intratympanic injection.

The protocol of the study was approved by the Ethics Review Committee of Nagoya University School of Medicine (approval numbers 369, 369-2, 369-3, and 369-4). All patients gave their informed consent to participation in this study. Their written informed consent was attached to the electronic medical record after permission was given by each patient.

Results

Enhancement was fainter with the 16-fold dilution than with the 8-fold dilution, although the degree of endolymphatic hydrops could be evaluated with the 16-fold dilution. This tendency was observed with both gadodiamide hydrate and gadopentetate dimeglumine. We used the eightfold dilution in the other patients.

3D-real IR MRI was generally better than 3D-FLAIR MRI for visualizing the endolymphatic space because the 3D-real IR MRI could discriminate the perilymphatic space from the surrounding bone. However, when the Gd concentration was not sufficient in the perilymph, it was more difficult to visualize the Gd using 3D-real IR MRI than using 3D-FLAIR MRI. Example results of 3D-FLAIR MRI and 3D-real IR MRI are shown in Figure 1a and b. The degree of endolymphatic hydrops could be evaluated more accurately using both 3D-real IR and 3D-FLAIR MRI. Figures 2 and 3 reveal different degrees of endolymphatic hydrops in various parts of the inner ear.

In patients with severe endolymphatic hydrops and almost no perilymphatic space recognized in the vestibule, the Gd movement toward the semicircular canals was disturbed (Figure 4). This disturbance occurred because Gd passage was restricted through the perilymphatic space. The

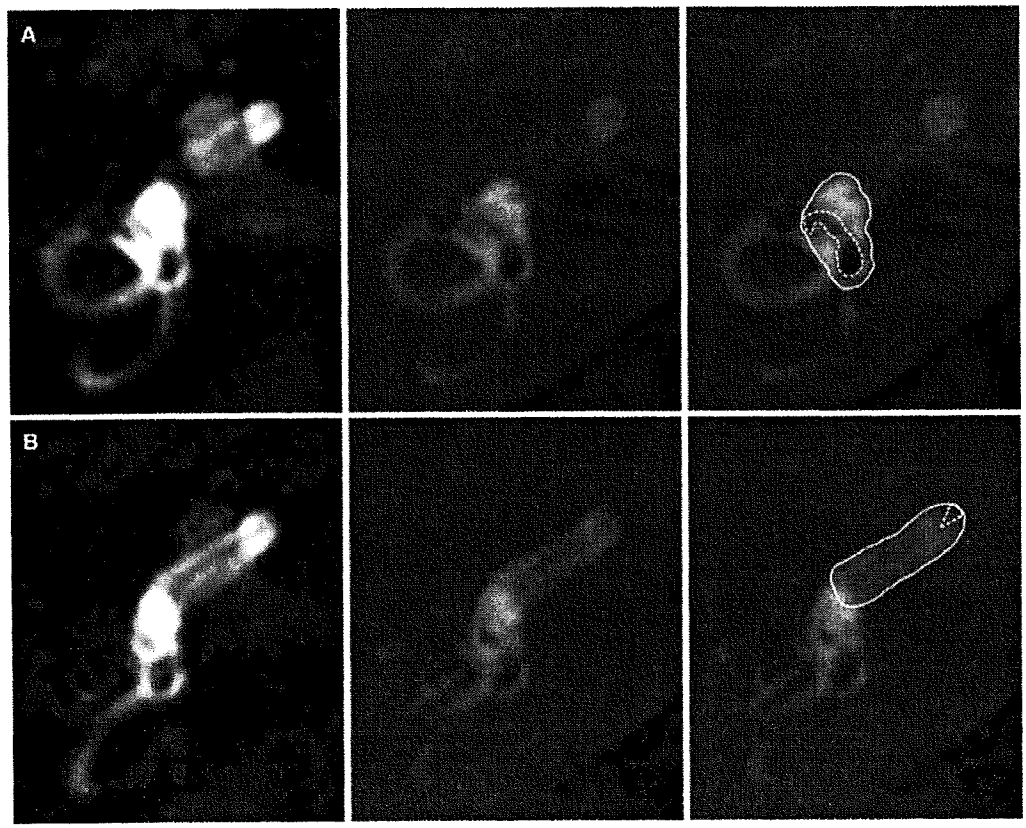

Figure 1. Images in (A) and (B) are consecutive sections of MRI in a 57-year-old woman who had right sudden deafness. 3D-FLAIR MRI (left side), 3D-real IR MRI (center), and the line drawings (right side) are shown. The 3D-real IR MRI is fainter than the 3D-FLAIR MRI. In 3D-real IR MRI, Gd is observed only in the basal turn in the cochlea. In the line drawings in (A), the area ratio of endolymphatic space (dotted circle) to total fluid space (solid line) in the vestibule is 25.2% (no vestibular hydrops). In (B), endolymphatic space is barely visible in the basal turn of the cochlea (dotted line).

effect of intratympanic gentamicin therapy was poor in two patients who showed this restricted passage toward the semicircular canal and who had received intratympanic gentamicin therapy.

Significant endolymphatic hydrops was observed in two patients with 'probable' Ménière's disease according to the 1995 AAOHNS criteria. An example is shown in Figure 5. This patient had frequent

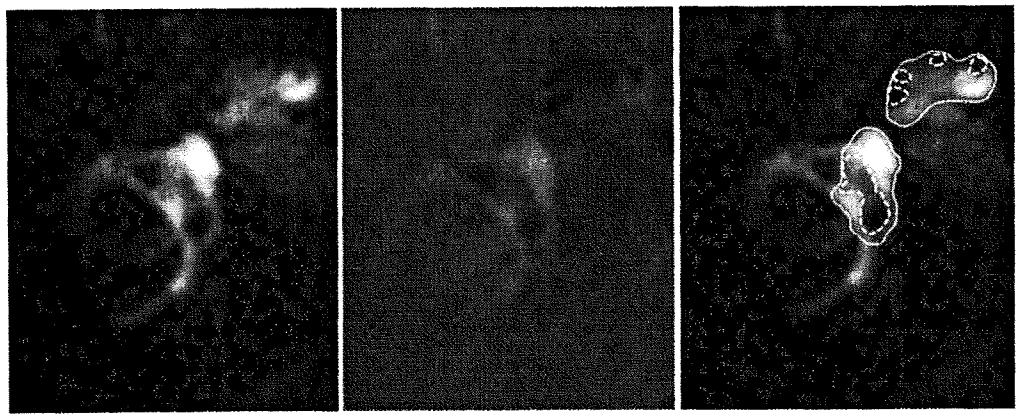

Figure 2. MRI in a 45-year-old man with right Ménière's disease. 3D-FLAIR MRI (left side), 3D-real IR MRI (center), and line drawing of the endolymphatic hydrops (right side). In the vestibule, the area ratio of endolymphatic space (dotted circle) to total fluid space (solid line) is 35.4% (mild vestibular hydrops). In the cochlea, endolymphatic hydrops is observed but the size is smaller than the size of the scala vestibuli (mild cochlear hydrops).

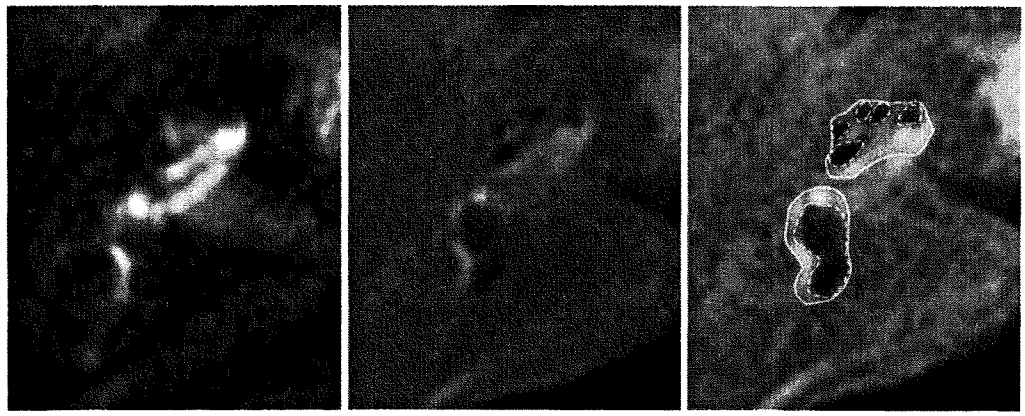

Figure 3. MRI in a 60-year-old woman with right Ménière's disease. 3D-FLAIR MRI (left side), 3D-real IR MRI (center), line drawing of the endolymphatic hydrops (right side). In the vestibule, the area ratio of endolymphatic space (dotted circle) to total fluid space (solid line) is 58.6% (significant vestibular hydrops). In the cochlea, endolymphatic hydrops (shown by dotted lines) is observed and the size is larger than the size of the scala vestibuli (significant cochlear hydrops).

nonrotatory vertigo with sensorineural hearing loss lasting 7 years but had experienced only one definitive episode of rotatory vertigo.

Discussion

The Gd concentration in the perilymph after intratympanic administration of the eightfold Gd dilution was estimated to be 0.1 mmol/L, which is a 5000 times concentration of the original Gd fluid [15]. Thus, the Gd concentration was 625 times less in the perilymph than in the intratympanic Gd fluid. Its slight penetration through the round window membrane may be associated with anatomic characteristics of the human round window membrane. The average thickness of the human round window membrane is 70 μm, which is much thicker than that of experimental animals [16]. Kakigi et al. [13] reported edema of the stria vascularis and a decreased endocochlear potential after the original Gd fluid (gadodiamide hydrate) was injected into the tympanic cavity of guinea pigs. In humans, no side effect was recognized even after the original Gd fluid was injected intratympanically [17]. In the present study, we observed no adverse effects such as hearing deterioration or vertigo in the 73 patients. We used Gd diluted 16-fold with saline and compared the MRI results to those obtained with Gd diluted 8-fold. We found that Gd in the perilymph looked fainter when the 16-fold dilution was used. We conclude that the eightfold dilution is better for MRI.

Free Gd (Gd^{3+} ions) at a concentration of 10^{-5} mol/L is toxic to isolated hair cells [18]. The chelator surrounds the free Gd to suppress its toxicity. It has been reported that 10^{-17} of the number of gadodiamide hydrate exists as free Gd if the number of free

Figure 4. 3D-FLAIR MRI in a 47-year-old man with Ménière's disease. Visualization of the semicircular canals was not obvious. Because there were extremely large endolymphatic hydrops in the vestibule, Gd movement towards the semicircular canals was disturbed.

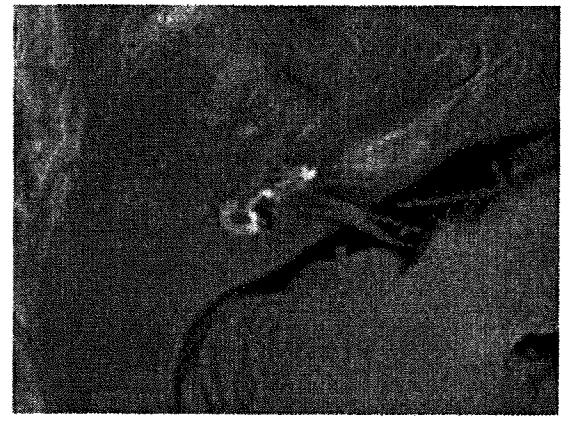

Figure 5. 3D-real IR MRI in a 42-year-old man who had 'probable' Ménière's disease. He had frequent nonrotatory vertigo lasting 7 years but had experienced only one definitive episode of rotatory vertigo. This 3D-real IR MRI reveals endolymphatic hydrops in the vestibule and cochlea.

Gd and the ligand (DTPA-BMA) are maintained at the same levels. The number of free Gd is far less in gadopentetate dimeglumine. In terms of toxicity, gadopentetate dimeglumine may be better than gadodiamide hydrate. Animal experiments and analysis of MRI are needed to determine the best Gd fluid.

Gd entered the perilymph from the tympanic cavity, and the perilymph and endolymph could be discriminated with MRI. 3D-real IR MRI gave a clearer image of the endolymphatic space than 3D-FLAIR MRI. However, more Gd was needed in the perilymph in 3D-real IR than in 3D-FLAIR MRI. When the Gd concentration was not sufficient in the perilymph, we evaluated the endolymphatic space with 3D-FLAIR MRI. Both 3D-real IR MRI and 3D-FLAIR MRI may be needed to evaluate the endolymphatic space accurately. 3D-FLAIR MRI was better for evaluating the permeability of the round window after intratympanic Gd administration and the signals in the inner ear in patients with sudden sensorineural hearing loss.

We observed significant endolymphatic hydrops using MRI in patients with 'probable' Ménière's disease. These patients had only one definitive episode of vertigo although they complained of dizziness frequently with sensorineural hearing loss. Our study confirmed that they had Ménière's disease. In patients with 'possible' Ménière's disease, MRI will be also useful for deciding on the diagnosis of Ménière's disease. MRI will contribute to more accurate diagnosis of Ménière's disease. In delayed endolymphatic hydrops, it is occasionally difficult to diagnose endolymphatic hydrops using functional tests such as electrocochleography and the glycerol test because of profound hearing loss. MRI is suitable for diagnosing endolymphatic hydrops in such ears.

MRI after intratympanic Gd administration is associated with intratympanic drug therapy for the treatment of inner ear diseases. It was possible to investigate the permeability of the round window and to observe how the drug distributes inside the inner ear. In 13% of patients, the movement of Gd through the round window was poor [19] from [unpublished observations]. Patients with severe endolymphatic hydrops in the vestibule showed poor Gd movement through the perilymph from the basal turn of the cochlea toward the semicircular canals (Figure 6). In these patients, intratympanic gentamicin therapy may not be suitable for the treatment of vertigo attacks. Our results suggest that MRI after intratympanic Gd administration is useful for predicting the suitability of intratympanic drug therapy in the treatment of inner ear diseases.

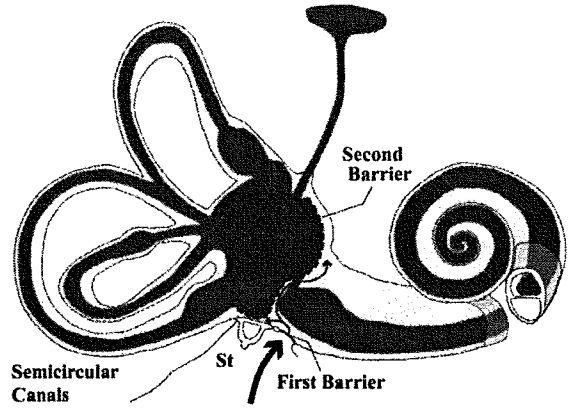

Figure 6. A schematic view of Gd movement from the tympanic cavity toward the semicircular canals. The round window membrane is the first barrier. Extremely large endolymphatic hydrops becomes the second barrier (shown in dotted line). St, stapes.

Conclusion

1. 3D-real IR MRI was generally better for visualizing the endolymphatic space than 3D-FLAIR MRI after intratympanic Gd injection. However, when Gd concentration was not sufficient in the perilymph, it was more difficult to visualize the Gd in 3D-real IR MRI than in 3D-FLAIR MRI. 3D-real IR MRI and 3D-FLAIR MRI allowed the observation of various degrees of endolymphatic hydrops in the basal and upper turns of the cochlea and in the vestibular apparatus after Gd injection.
2. We tried the 16-fold dilution of the original Gd fluid as the intratympanic injection fluid and compared the MRI to that obtained with an 8-fold dilution. Gd looked faint in the perilymph after the 16-fold dilution. At present, the eightfold dilution seems to be best for MRI.
3. We used gadodiamide hydrate (Omniscan®) and gadopentetate dimeglumine (Magnevist®) as the Gd fluid. Because the proportion of free Gd (Gd^{3+} ions) differs between drugs, animal experiments are needed to determine the toxicity of each drug in the inner ear.
4. We demonstrated significant endolymphatic hydrops using MRI in patients with 'probable' Ménière's disease, diagnosed according to the AAOHNS criteria. MRI may be used to change the criteria for the diagnosis of Ménière's disease.
5. Using MRI after intratympanic Gd injection allows one to observe the intratympanic distribution of drug inside the inner ear. Severe endolymphatic hydrops in the vestibule compressed the route of Gd passage through the perilymphatic space, and limited Gd movement

from the basal turn of the cochlea toward the semicircular canals.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORIGINAL ARTICLE

Cutting edge of inner ear MRI

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Abstract

Conclusion: Recent advances in clinical MR imagers, such as the 3-Tesla, multi-channel phased-array coil and novel pulse sequences, allow the evaluation of subtle alterations in the inner ear fluid environments and breakdown of the blood–labyrinthine barrier. Intratympanic injection of Gd-DTPA allows the imaging detection of endolymphatic hydrops in patients. *Objectives:* To describe the current status of inner ear MRI and future directions for imaging. *Materials and methods:* Based on our experiences and literature research, a brief review of the history and recent developments of inner ear MRI is presented. *Results:* The 3D-FLAIR technique can detect abnormalities that could not be visualized previously in many inner ear diseases, such as sudden deafness, otosclerosis, lupus erythematosus, mumps, and Ramsay-Hunt syndrome. Imaging techniques, indications, and findings for the visualization of endolymphatic hydrops after intratympanic injection of Gd-DTPA are also discussed. This procedure enabled the visualization of endolymphatic hydrops in vivo. Newly developed 3D-real IR techniques and utilities of 32 channel coil are also presented.

Keywords: *Magnetic resonance imaging, MRI, 3D imaging, advanced imaging techniques, temporal bone disease*

Introduction

Magnetic resonance (MR) imaging (MRI) of the inner ear has been used mainly to detect conditions such as vestibular schwannoma in the internal auditory canal and the cerebellopontine angle, inner ear malformation, and labyrinthine hemorrhage. Because of its small size, MRI of the inner ear is challenging. High spatial resolution is mandatory, although respiratory and cardiac motion is not a serious problem in this area. Thus, MRI of the inner ear has been a good testing field for new technical developments in MR scanning.

The widespread application of 3-Tesla scanners in clinical fields, and the development of new pulse sequences and the multi-channel phased-array coil opened a new world of inner ear MRI. The subtle alterations of inner ear fluid composition are now detectable using three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MRI. The blood–labyrinthine barrier can now be assessed using contrast-enhanced 3D-FLAIR MRI. Visualization of endolymphatic hydrops has also become possible with intratympanic injection of Gd-DTPA.

This paper describes the current status and future prospects of inner ear MRI.

History

Gd-DTPA-enhanced thin-sliced 2D-T1-weighted images by spin echo sequence (3 mm thick) has long been the method of choice to evaluate sensorineural hearing loss [1,2].

From the mid-1990s, MR cisternography without Gd-DTPA has been used to detect vestibular schwannoma. MR cisternography is also useful for evaluating inner ear malformations and for cochlear implant presurgical screening of the patency of the perilymphatic space [3,4]. Constructive interference in the steady state (CISS) and various kinds of 3D-turbo spin-echo (TSE)-type sequences were employed for this purpose [5–7]. Technical developments shortened the scan time for MR cisternography to within 90 s while keeping high spatial resolution and sufficient signal-to-noise ratio [8]. CISS-type sequences and 3D-TSE-type sequences have some advantages and disadvantages [7]. The CISS-type sequence is

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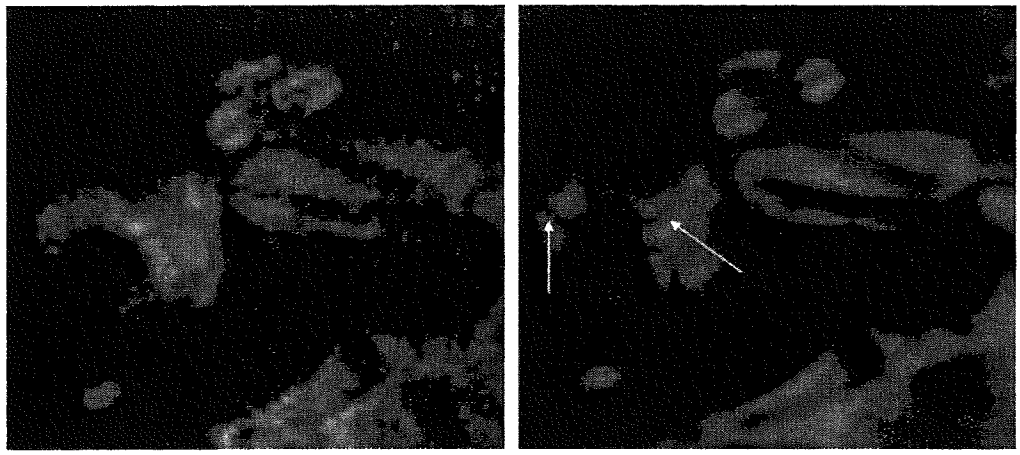

Figure 1. Images of a normal subject. High spatial resolution T2-weighted image at 3 Tesla. Spatial resolution is 0.3 × 0.3 × 0.5 mm. The left image was obtained with a 3D-turbo spin-echo sequence and the right image was obtained with 3D-CISS. On 3D-CISS, band-like artifacts (arrows) are prominent because of magnetic field inhomogeneity, and the vestibule appears deformed.

usually faster and can provide a higher signal-to-noise ratio than 3D-TSE. The CISS-type sequence is also sensitive to the T1-shortening effect, such as Gd-DTPA enhancement or higher protein concentration. However, 3D-CISS shows an interference-banding artifact caused by local magnetic field inhomogeneity, and deformity of the vestibule near the oval window is always seen on 3D-CISS (Figure 1).

Current status

Precontrast-enhanced 3D-FLAIR

Recently, with the development of the 3-Tesla scanner and fast imaging protocols such as SPACE, 3D-FLAIR of a thickness of < 1 mm became clinically feasible [9,10]. MR cisternography visualizes mainly the morphological anatomy of fluid-filled organs, and 3D-FLAIR allows the assessment of subtle alterations in the inner ear fluid composition. 3D-FLAIR is far more sensitive than 3D-CISS and T1-weighted images in this feature (Figure 2). Use of 3D-FLAIR has been reported in diagnosing various inner ear disorders such as sudden deafness [11,12], lupus erythematosus [13], mumps [14], invasion of middle ear cholesteatoma [15], and Ramsay Hunt syndrome [16].

Intravenous contrast-enhanced 3D-FLAIR

After the intravenous injection of Gd-DTPA, 3D-FLAIR can visualize the status of the blood–labyrinthine barrier. Even in healthy subjects, cochlear fluid is enhanced 4 h after intravenous injection of Gd-DTPA [9]. Increased permeability of the blood–labyrinthine barrier has been reported in sudden deafness [11,12], invasion of middle ear cholesteatoma [15] (Figure 3), and Ramsay Hunt syndrome [16].

Triple-dose intravenous Gd-DTPA administration and non-FLAIR sequence have been used to visualize endolymphatic hydrops in patients with Ménière's disease [17], although the resultant images were not clear or convincing.

Intratympanic injection of Gd-DTPA

Animal studies

Round window application of Gd-DTPA has been tried in animals [18,19]. In these studies, intratympanic round window application enhanced the

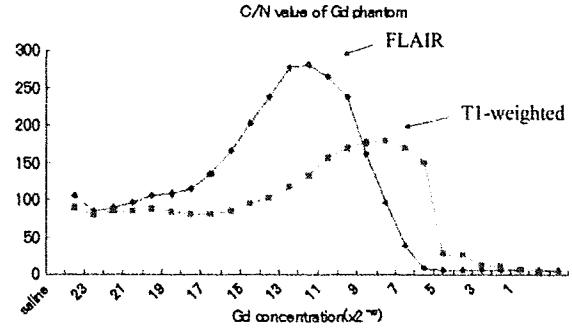

Figure 2. Sensitivity to low concentration of Gd-DTPA solution evaluated in a phantom study. The contrast-to-noise ratio by FLAIR and T1-weighted image are plotted against various diluted Gd-DTPA solution phantoms. FLAIR shows higher sensitivity to lower concentrations of Gd-DTPA solution than the T1-weighted image. However, the sensitivity of FLAIR to higher concentrations of Gd-DTPA is lower than for the T1-weighted image.

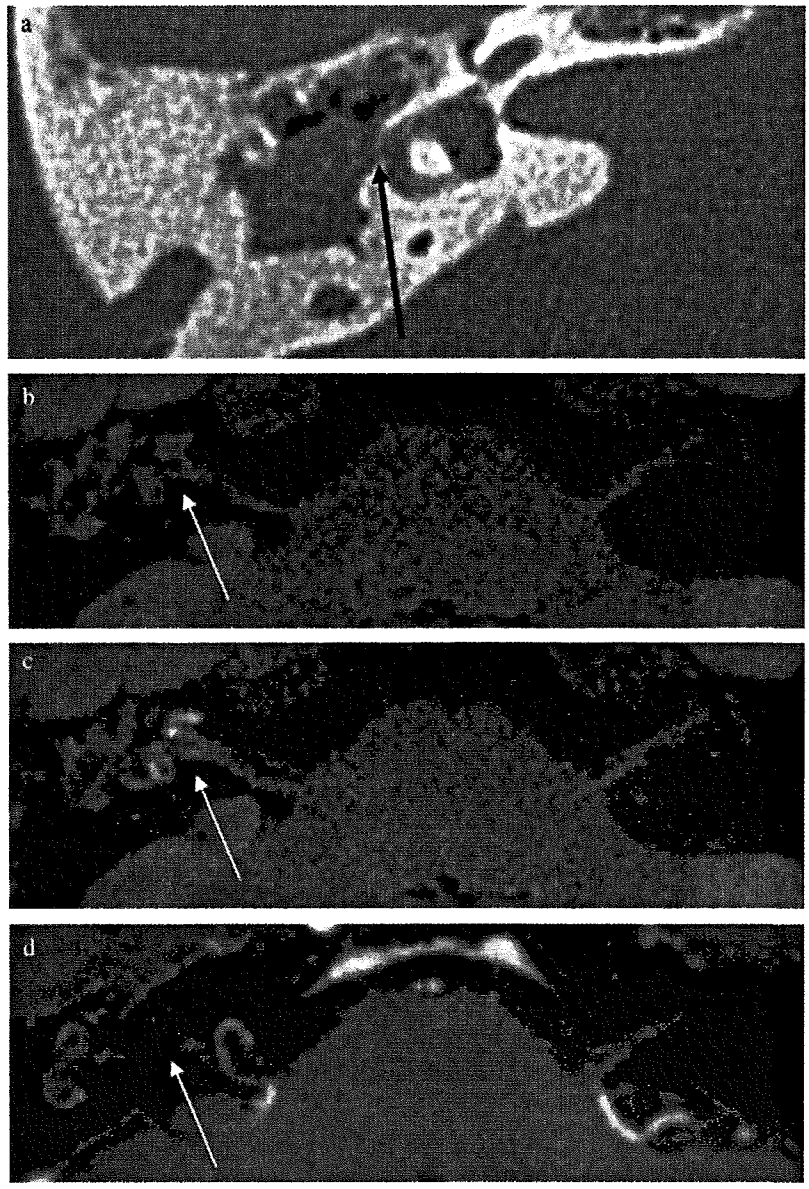

Figure 3. A 58-year-old man with right middle ear cholesteatoma invading the wall of lateral semicircular canal. (a) The CT image shows the erosion of the wall of the lateral semicircular canal by cholesteatoma invasion (arrow). (b) The precontrast 3D-FLAIR image shows the slightly increased signal of the labyrinthine fluid in the right side (arrow) but not in the left side. (c) The post-contrast 3D-FLAIR image reveals marked enhancement in the right labyrinthine fluid (arrow) but not in the left side. (d) The post-contrast 3D T1-weighted image fails to reveal contrast enhancement of the right labyrinthine fluid. These findings show that the increased permeability of the blood–labyrinthine barrier can be visualized by contrast-enhanced 3D-FLAIR images but not by contrast-enhanced T1-weighted images.

cochlear perilymph space but not the scala media (endolymphatic space). Perilymph enhancement of the cochlea began from the basal turn and spread gradually to the apical turn. The round window communicates with the scala tympani, but the scala vestibuli was also enhanced. Gd-DTPA in the perilymph fluid disappeared after several days and no change in the auditory brainstem response (ABR) was seen.

Studies in patients

A study of patients began about 2 years ago [20], and more than 60 patients have been included so far. No severe side effect of Gd-DTPA has been noted. Medical ethics committee approval was acquired and written informed consent was obtained from patients before the study began. In the first few cases, we scanned the patient two to three times at

various time points after the intratympanic injection of Gd-DTPA to determine the optimal scan timing. Vestibular enhancement was observed first followed by advance of the enhancement to the basal cochlear turn and semicircular canals, and finally, the apical turn of the cochlea fills with contrast medium. We concluded that 24 h is the optimal interval between Gd administration and MR examination when evaluating the whole labyrinthine system.

Clinical indications

MRI after intratympanic injection of Gd-DTPA is indicated for patients scheduled for intratympanic drug administration as treatment of sensorineural hearing loss or vertigo. Steroid is used to treat sudden deafness, and gentamicin is used to treat severe vertigo that cannot be controlled by conventional therapy. Drug distribution in the labyrinth is important for maximizing the effects while preventing side effects in the cochlea.

Procedure

The details of the procedure have been reported previously [20]. Eightfold diluted Gd-DTPA-BMA is injected thorough the tympanic membrane using a 23 G needle. The amount of diluted Gd is 0.4–0.6 ml. The patients were asked to avoid swallowing for as long as possible. Patients should remain in a supine position for 1 h with their face turned toward the contralateral side.

MRI protocol

A 3-Tesla scanner and multi-channel coil are preferable for MRI. We started with an eight-channel head coil, then switched to a 12-channel coil, and we now use a 32-channel array head coil to obtain a high signal-to-noise ratio. The detailed pulse-sequence protocol has been reported previously [21]. MR cisternography using a 3D-CISS sequence is obtained for anatomic reference, and 3D-FLAIR is then obtained to detect perilymph enhancement while suppressing the signal from the endolymph. Finally, we obtain 3D-real IR images to visualize the endolymph, perilymph, and bone separately on a single image [22] (Figure 4). The parameters for 3D-CISS were as follows: TR of 6.4 ms, TE of 3.2 ms, flip angle of 50°, matrix size of 256 × 256, and 48 axial 0.8 mm thick slices with a 14 cm-square field of view. The number of excitations was 1, and the scan time was 3 min 42 s.

The parameters for 3D-FLAIR were as follows: TR of 9000 ms, TE of 128 ms, TI of 2500 ms, flip angle of 180° (constant) for the turbo-spin-echo refocusing echo train, echo-train length of 23, matrix size of 384 × 384, and 12 axial 2 mm thick slices covering the labyrinth with a 16 cm-square field of view, acquired using the GRAPPA parallel imaging technique with an acceleration factor of 2. The

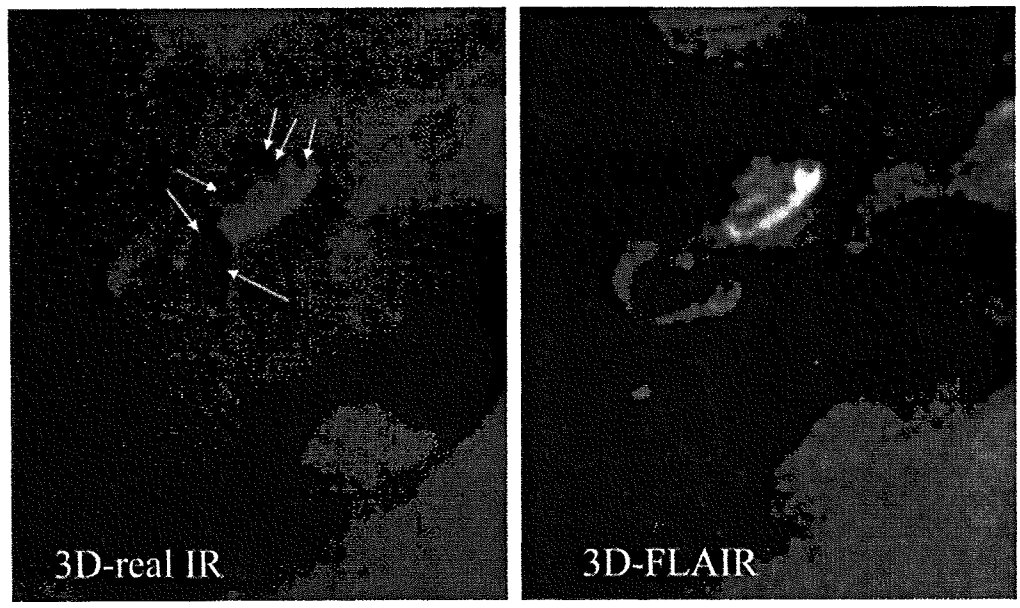

Figure 4. A 38-year-old man with right endolymphatic hydrops 1 day after intratympanic injection of Gd-DTPA. The 3D-real IR image reveals the enlargement of the endolymphatic space (black signal areas indicated by white arrows) in both the cochlea and vestibule. On the 3D-FLAIR image, the separation of the endolymphatic space and bone is unclear.

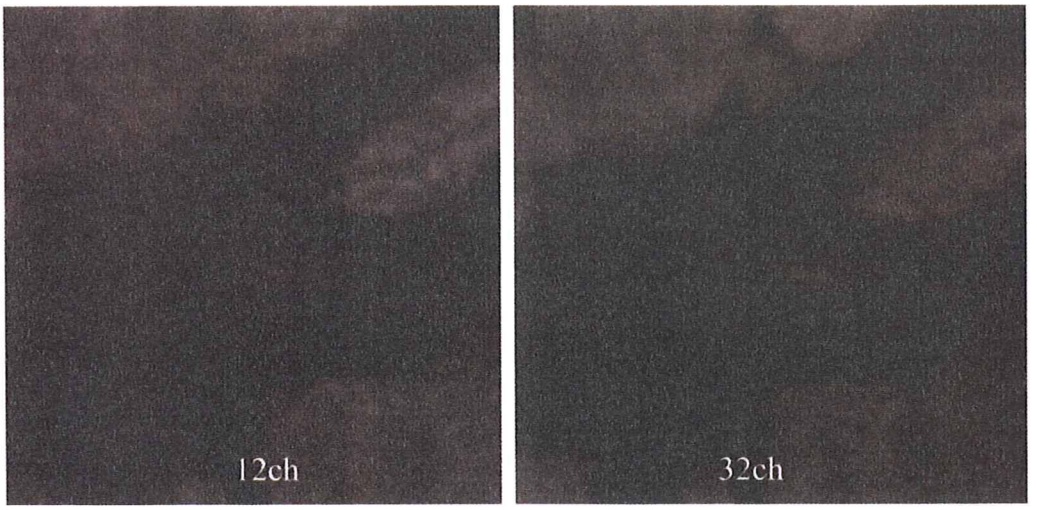

Figure 5. Thin section 3D-FLAIR images of a normal inner ear using a 12-channel coil and 32-channel coil. Scan parameters were identical for both images. The voxel size was 0.7 ×0.7 ×0.8 mm, and the scan time was 5.5 min. The image produced by the 12-channel coil is noisier than that produced by the 32-channel coil.

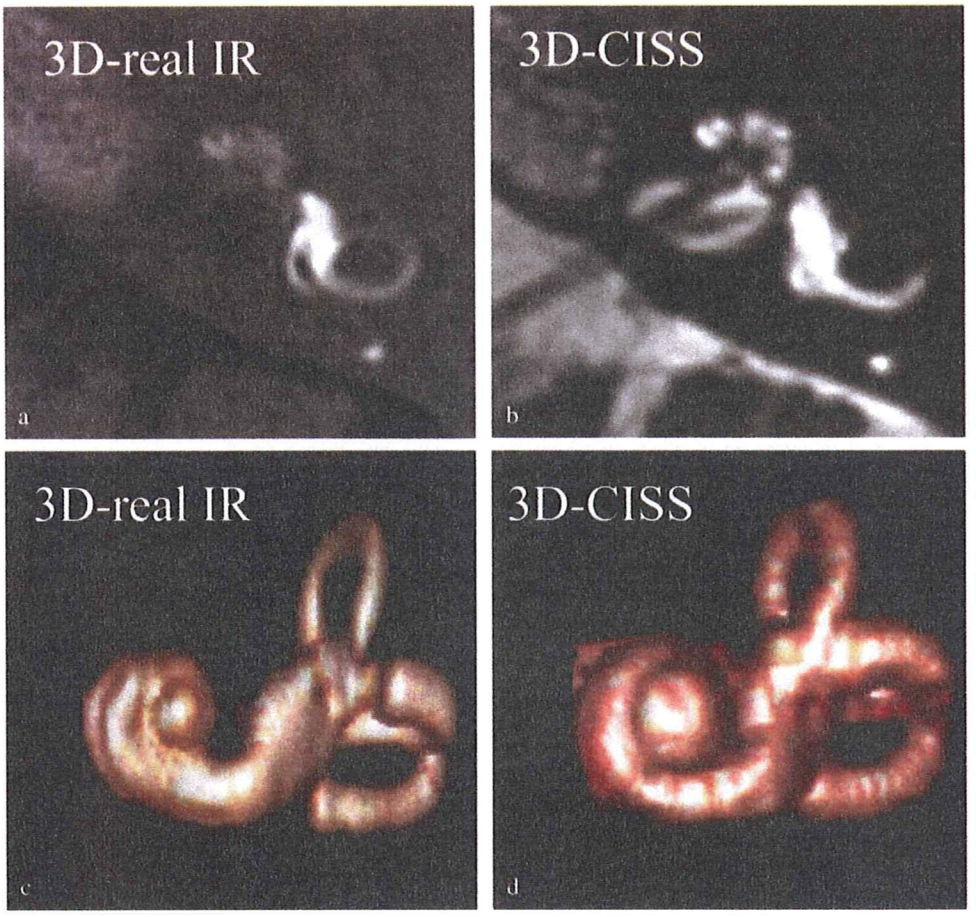

Figure 6. A 59-year-old man with Ménière's disease. High spatial resolution 3D-real IR image (a, 0.8 mm thick) and 3D-CISS image (b, 0.4 mm thick), and their volume-rendering images (c, d) were obtained using a 32-channel coil. Increasing the signal-to-noise ratio reduces the slice thickness of 3D-real IR from 2 mm to 0.8 mm. This higher spatial resolution allowed the volume-rendering image. By comparing the perilymphatic volume-rendered image (c) and total lymphatic volume-rendered image (d), we can appreciate the degree of endolymphatic hydrops three-dimensionally.

number of excitations was 1, and the scan time was 15 min. The parameters for 3D-real IR are almost the same as 3D-FLAIR except for the TI of 1700 ms and real reconstruction mode for 3D-real IR.

Future prospects

Intratympanic injection of Gd-DTPA shows excellent separation of endolymph and perilymph. However, intratympanic administration of Gd-DTPA is off-label use, and we are planning to achieve separate visualization of endolymph and perilymph by intravenous administration of Gd-DTPA. To do so, we must develop a more sensitive method to detect very low concentrations of Gd-DTPA. A 32-channel coil is one key factor because the signal-to-noise ratio of a 32-channel coil in the vicinity of the inner ear is 50% higher than that of a conventional 12-channel coil used in the phantom experiment. Images obtained with a 32-channel coil show less noise than those obtained with a 12-channel coil with identical scan parameters (Figure 5). This also means that the same quality images can be obtained by a 32-channel coil in less than half the scan time needed for the 12-channel coil. Using a 32-channel coil, we have reduced the slice thickness of 3D-real IR images from 2 mm to 0.8 mm while maintaining the signal-to-noise ratio obtained with the 12-channel coil. This increased spatial resolution might allow the 3D-volume rendering of the perilymphatic space (Figure 6).

Even with a 32-channel coil, the signal-to-noise ratio is still insufficient to clearly demonstrate the endolymph and perilymph spaces with intravenous Gd-DTPA, and a breakthrough in the delivery of the pulse sequence is needed. Another issue to be solved is the volume quantification of endolymph and perilymph. To monitor the effect of therapy with MRI, it is essential to quantify the volume of each compartment of the lymph space. A much higher spatial resolution is needed to achieve reliable measurements.

Conclusions

Developments of new MR technologies and new drug delivery have opened the door to better MRI of the inner ear. Through the close collaboration of radiologists and otologists, we will apply these advanced techniques to discover the new frontier of inner ear pathologies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Individual Differences in the Permeability of the Round Window: Evaluating the Movement of Intratympanic Gadolinium Into the Inner Ear

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Objective: Many recent studies have reported on intratympanic gentamicin therapy for the treatment of intractable Ménière's disease. Intratympanic administration of steroids has also been used to treat sudden sensorineural hearing loss. These intratympanic drug therapies are based on the assumption that the drug administered intratympanically enters the inner ear through the round window membrane. We used magnetic resonance imaging (MRI) to evaluate whether and how intratympanically administered gadolinium (Gd) enters the inner ear.

Methods: GD hydrate was injected intratympanically through the tympanic membrane using a 23-G needle into 61 ears of 55 patients with inner ear diseases. The injected Gd was diluted 8-fold in saline for injection into 58 ears and 16-fold for 3 ears. Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging was performed using a 3-Tesla MRI unit 1 day after the intratympanic injection.

Results: In 53 of 61 ears, the Gd-containing inner ear was detected well as a high signal on 3D-FLAIR imaging. However, Gd was not visible in 2 ears with Ménière's disease and in 1 ear with profound deafness. The concentration of Gd in the perilymph was lower in 4 ears with Ménière's disease and 1 ear with delayed endolymphatic hydrops than after intratympanic administration of the 16-fold Gd dilution.

Conclusion: Round window permeability was absent in 5% of ears, and 13% of ears had poor round window permeability. These results should be considered when planning intratympanic drug administration therapy to treat inner ear diseases.

Key Words: Fluid-attenuated inversion recovery (FLAIR)—Gadolinium—Intratympanic therapy—Magnetic resonance imaging—Permeability—Round window membrane.

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Endolymphatic sac surgery or intratympanic gentamicin therapy is now used widely to treat intractable Ménière's disease (1,2). Intratympanic steroid therapy has also been used recently to treat sudden sensory hearing loss. Several studies have shown good results after the injection of steroids through the tympanic membrane to treat sudden sensorineural hearing loss (3,4). In PubMed, the number of papers on intratympanic gentamicin therapy and intratympanic steroid therapy has been increasing. These intratympanic therapies are based on the assumption that the intratympanically administered drug passes into the inner ear through the round window membrane.

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Silverstein et al. (5) reported that the round window membrane is impermeable or its permeability is inhibited markedly in about 20% of cases. They observed the round window itself but did not measure the actual permeability of the round window membrane.

We have reported on the size of the endolymphatic space obtained by imaging after intratympanic gadolinium (Gd) injection (6). This method is based on the permeability of the round window membrane and the assumption that intratympanically administered Gd moves into the inner ear through the round window membrane. In the present study, we evaluated the round window permeability after intratympanic Gd administration.

MATERIALS AND METOHDS

Patients

Fifty-five patients aged 23 to 78 years (mean age, 48.2 years; 27 men and 28 women) with clinically suspected endolymphatic hydrops or inner ear abnormalities underwent intratympanic