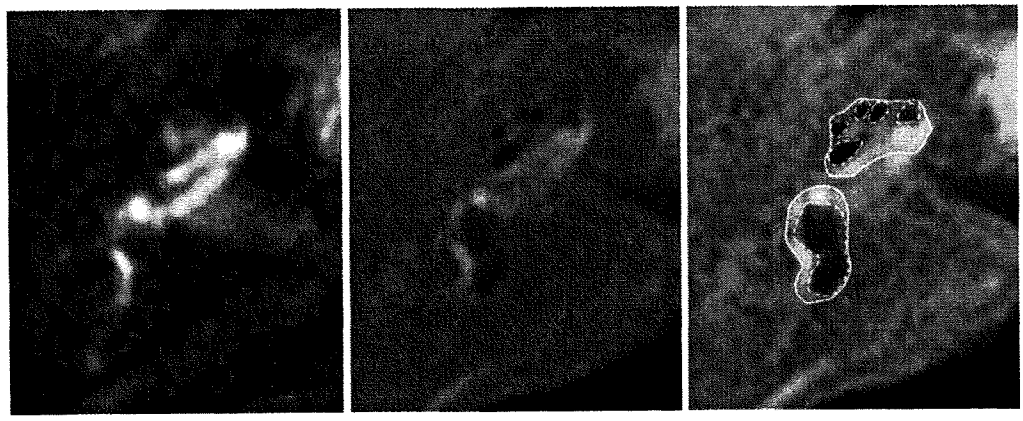

Figure 3. MRI in a 60-year-old woman with right Ménière's disease. 3D-FLAIR MRI (left side), 3D-real IR MRI (center), line drawing of the endolymphatic hydrops (right side). In the vestibule, the area ratio of endolymphatic space (dotted circle) to total fluid space (solid line) is 58.6% (significant 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).

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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.

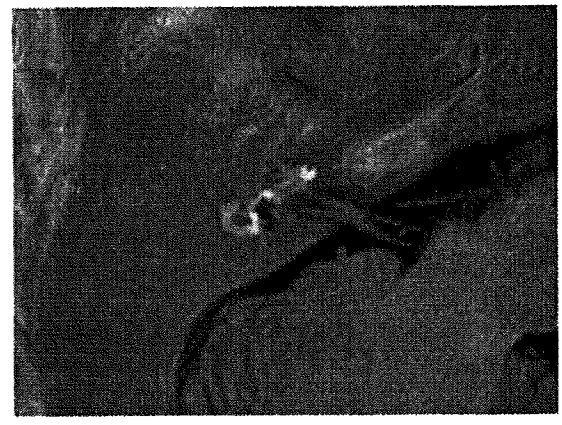

Figure 5. 3D-real IR MRI in a 42-year-old man who had 'probable' Ménière's disease. He had frequent nonrotatory vertigo lasting 7 years but had experienced only one definitive episode of rotatory vertigo. This 3D-real IR MRI reveals endolymphatic hydrops in the vestibule and cochlea.

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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.

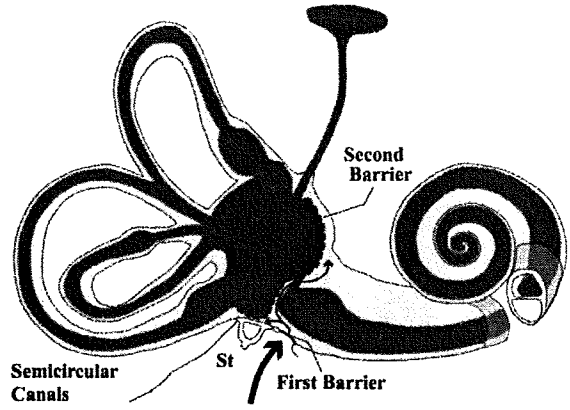

Figure 6. A schematic view of Gd movement from the tympanic cavity toward the semicircular canals. The round window membrane is the first barrier. Extremely large endolymphatic hydrops becomes the second barrier (shown in dotted line). St, stapes.

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

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

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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;117:415–20.

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

[3] 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;113:181–5.

[4] Helling K, Schonfeld U, Clarke AH. Treatment of Meniere's disease by low-dosage intratympanic gentamicin application: effect on otolith function. Laryngoscope 2007;117:2244–50.

[5] Steenerson RL, Hardin RB, Cronin GW. Gentamicin injections for Meniere disease: comparison of subjective and objective end points. Ear Nose Throat J 2008;87:452–6.

[6] Postema RJ, Kingma CM, Wit HP, Albers FW, Van Der Laan BF. Intratympanic gentamicin therapy for control of vertigo in unilateral Menire's disease: a prospective, double-blind, randomized, placebo-controlled trial. Acta Otolaryngol 2008;128:876–80.

[7] Ho HG, Lin HC, Shu MT, Yang CC, Tsai HT. Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. Laryngoscope 2004;114: 1184–9.

[8] Vrabec JT. Effectiveness of intratympanic dexamethasone injection in sudden deafness patients as salvage treatment. Laryngoscope 2005;115:378; author reply 378–9.

[9] Xenellis J, Papadimitriou N, Nikolopoulos T, Maragoudakis P, Segas J, Tzagaroulakis A, et al. Intratympanic steroid treatment in idiopathic sudden sensorineural hearing loss: a control study. Otolaryngol Head Neck Surg 2006;134: 940–5.

[10] Fitzgerald DC, McGuire JF. Intratympanic steroids for idiopathic sudden sensorineural hearing loss. Ann Otol Rhinol Laryngol 2007;116:253–6.

[11] Silverstein H, Rowan PT, Olds MJ, Rosenberg SI. Inner ear perfusion and the role of round window patency. Am J Otol 1997;18:586–9.

[12] Silverstein H, Arruda J, Rosenberg SI, Deems D, Hester TO. Direct round window membrane application of gentamicin in the treatment of Meniere's disease. Otolaryngol Head Neck Surg 1999;120:649–55.

[13] Kakigi A, Nishimura M, Takeda T, Okada T, Murata Y, Ogawa Y. Effects of gadolinium injected into the middle ear on the stria vascularis. Acta Otolaryngol 2008;128:841–5.

[14] 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;18:920–4.

[15] Tanigawa T, Tanaka H, Banna S, Inafuku S. In reference to visualization of endolymphatic hydrops with Meniere's disease. Laryngoscope 2008;118:946; author reply 946–7.

[16] Goycoolea MV. Clinical aspects of round window membrane permeability under normal and pathological conditions. Acta Otolaryngol 2001;121:437–47.

[17] 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: 145–52.

[18] Kimitsuki T, Nakagawa T, Hisashi K, Komune S, Komiyama S. Gadolinium blocks mechano-electric transducer current in chick cochlear hair cells. Hear Res 1996;101: 75–80.

[19] 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 (in press).

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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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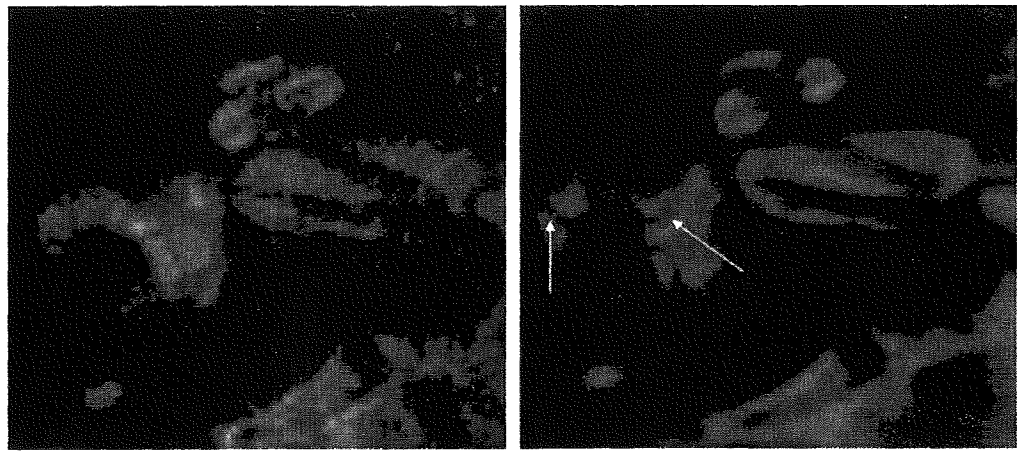

Figure 1. Images of a normal subject. High spatial resolution T2-weighted image at 3 Tesla. Spatial resolution is 0.3 × 0.3 × 0.5 mm. The left image was obtained with a 3D-turbo spin-echo sequence and the right image was obtained with 3D-CISS. On 3D-CISS, band-like artifacts (arrows) are prominent because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

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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

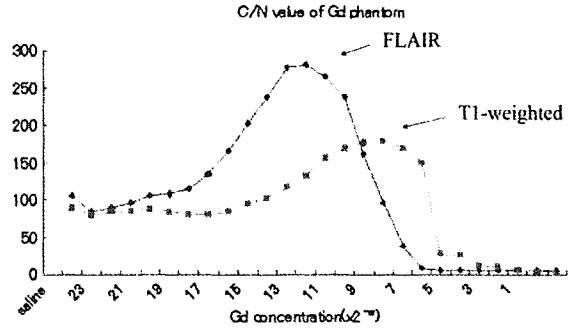

Figure 2. Sensitivity to low concentration of Gd-DTPA solution evaluated in a phantom study. The contrast-to-noise ratio by FLAIR and T1-weighted image are plotted against various diluted Gd-DTPA solution phantoms. FLAIR shows higher sensitivity to lower concentrations of Gd-DTPA solution than the T1-weighted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

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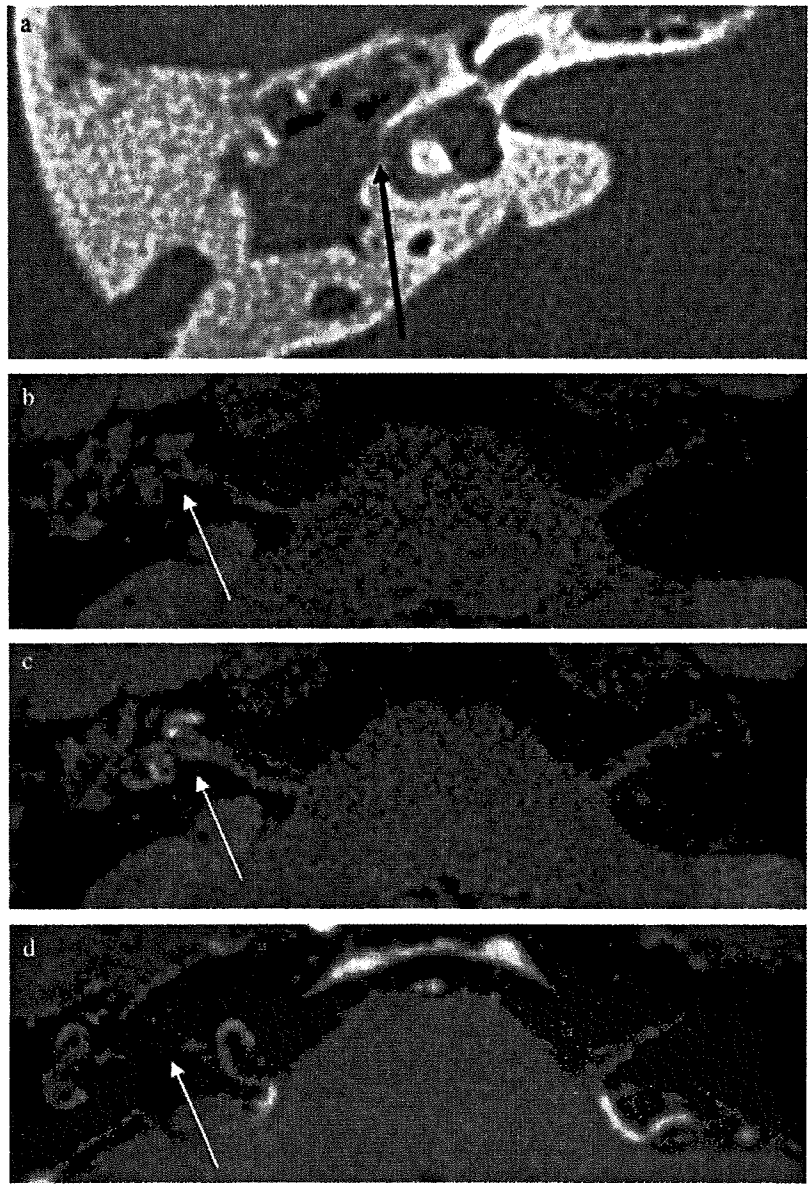

Figure 3. A 58-year-old man with right middle ear cholesteatoma invading the wall of lateral semicircular canal. (a) The CT image shows the erosion of the wall of the lateral semicircular canal by cholesteatoma invasion (arrow). (b) The precontrast 3D-FLAIR image shows the slightly increased signal of 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

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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

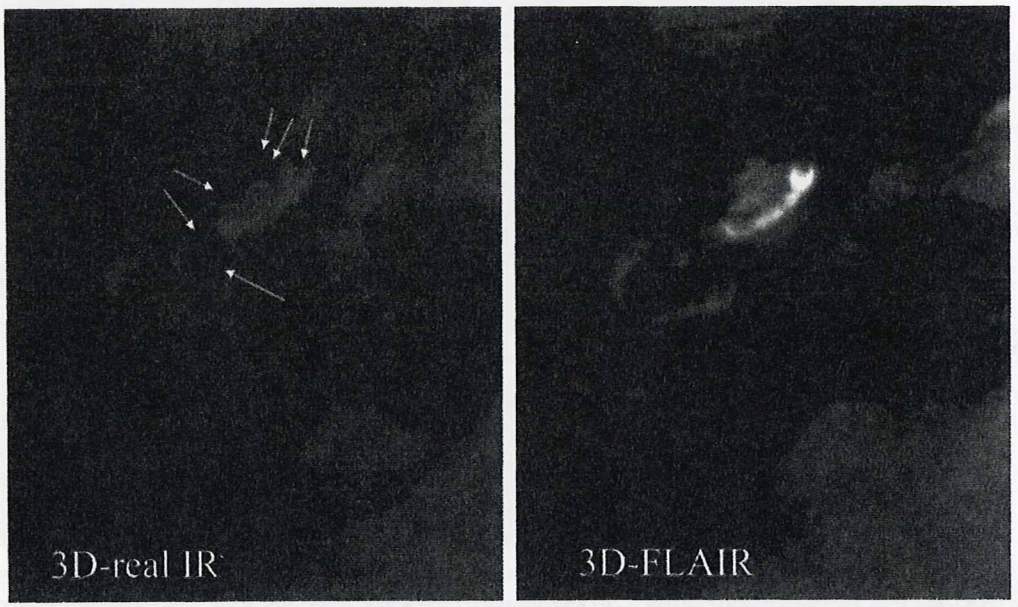

Figure 4. A 38-year-old man with right endolymphatic hydrops 1 day after intratympanic injection of Gd-DTPA. The 3D-real IR image reveals the enlargement of the endolymphatic space (black signal areas indicated by white arrows) in both the cochlea and vestibule. On the 3D-FLAIR image, the separation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

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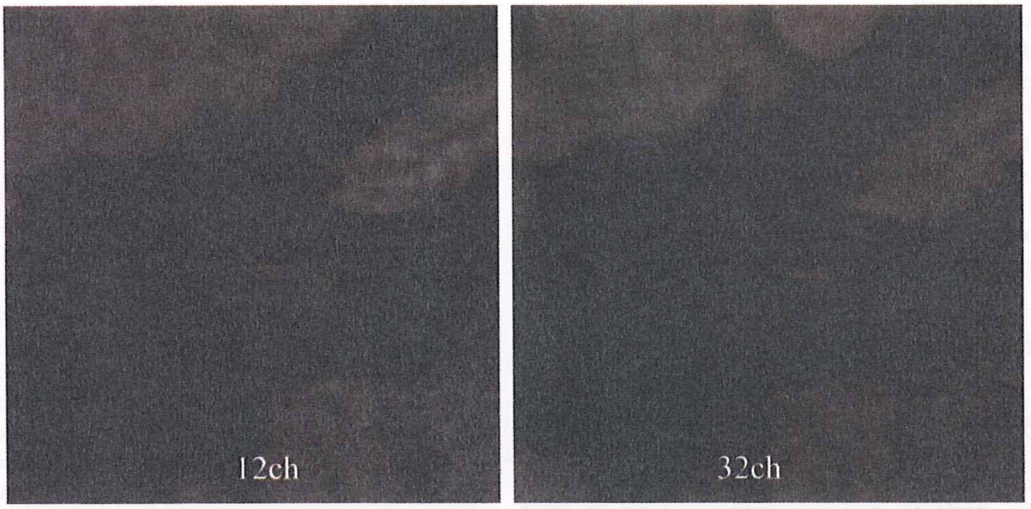

Figure 5. Thin section 3D-FLAIR images of a normal inner ear using a 12-channel coil and 32-channel coil. Scan parameters were identical for both images. The voxel size was 0.7 × 0.7 × 0.8 mm, and the scan time was 5.5 min. The image produced by the 12-channel coil is noisier than that produced by the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

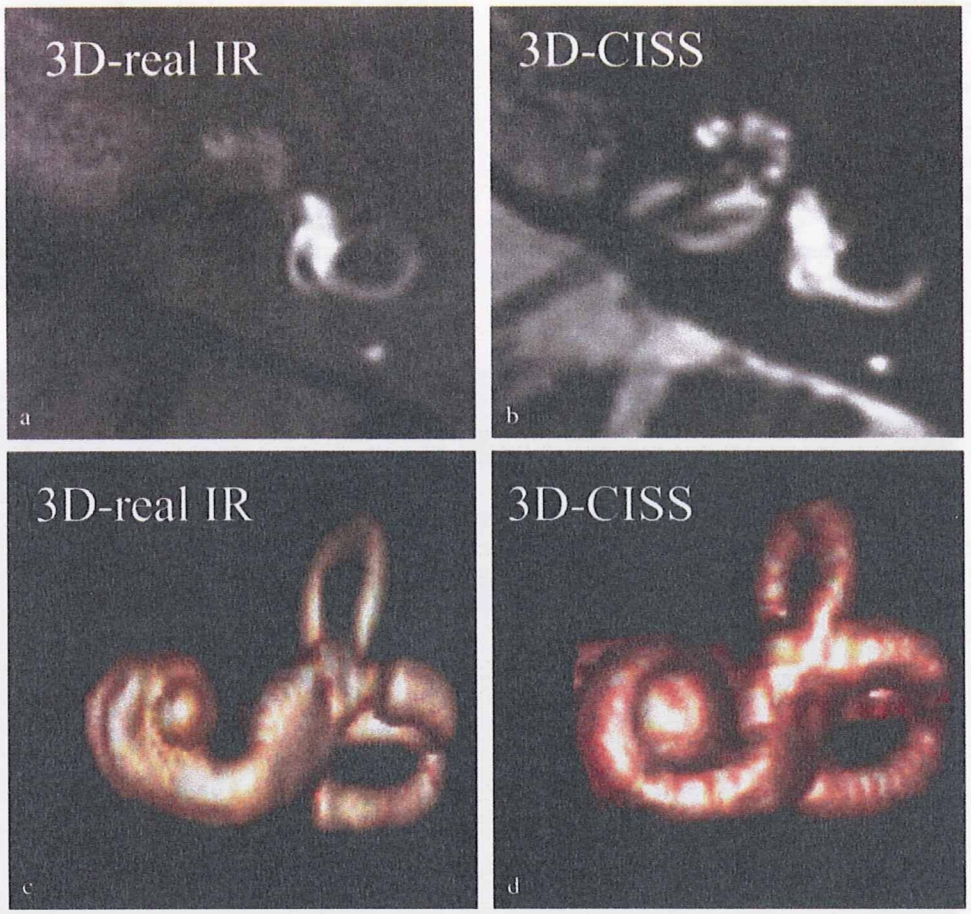

Figure 6. A 59-year-old man with Ménière's disease. High spatial resolution 3D-real IR image (a, 0.8 mm thick) and 3D-CISS image (b, 0.4 mm thick), and their volume-rendering images (c, d) were obtained using a 32-channel coil. Increasing the signal-to-noise ratio reduces the slice thickness of 3D-real 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.

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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.

References

[1] Daniels DL, Millen SJ, Meyer GA, Pojunas KW, Kilgore DP, Shaffer KA, et al. MR detection of tumor in the internal auditory canal. AJR Am J Roentgenol 1987;148:1219–22.

[2] Jackler RK, Shapiro MS, Dillon WP, Pitts L, Lanser MJ. Gadolinium-DTPA enhanced magnetic resonance imaging in acoustic neuroma diagnosis and management. Otolaryngol Head Neck Surg 1990;102:670–7.

[3] Naganawa S, Ito T, Fukatsu H, Ishigaki T, Nakashima T, Ichinose N, et al. MR imaging of the inner ear: comparison of a three-dimensional fast spin-echo sequence with use of a dedicated quadrature-surface coil with a gadolinium-enhanced spoiled gradient-recalled sequence. Radiology 1998;208:679–85.

[4] Naganawa S, Itoh T, Fukatsu H, Ishigaki T, Nakashima T, Kassai Y, et al. Three-dimensional fast spin-echo MR of the inner ear: ultra-long echo train length and half-Fourier technique. AJNR Am J Neuroradiol 1998;19:739–41.

[5] Iwayama E, Naganawa S, Ito T, Fukatsu H, Ikeda M, Ishigaki T, et al. High-resolution MR cisternography of the cerebellopontine angle: 2D versus 3D fast spin-echo sequences. AJNR Am J Neuroradiol 1999;20:889–95.

[6] Casselman JW, Kuhweide R, Deimling M, Ampe W, Dehaene I, Meeus L. Constructive interference in steady state-3DFT MR imaging of the inner ear and cerebellopontine angle. AJNR Am J Neuroradiol 1993;14:47–57.

[7] Naganawa S, Koshikawa T, Fukatsu H, Ishigaki T, Fukuta T. MR cisternography of the cerebellopontine angle: comparison of three-dimensional fast asymmetrical spin-echo and three-dimensional constructive interference in the steady-state sequences. AJNR Am J Neuroradiol 2001;22: 1179–85.

[8] Nakamura T, Naganawa S, Koshikawa T, Fukatsu H, Sakurai Y, Aoki I, et al. High-spatial-resolution MR cisternography of the cerebellopontine angle in 90 seconds with a zero-fill interpolated fast recovery 3D fast asymmetric spin-echo sequence. AJNR Am J Neuroradiol 2002;23:1407–12.

[9] 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;16:733–7.

[10] 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;3:177–87.

[11] Sugiura M, Naganawa S, Teranishi M, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings in patients with sudden sensorineural hearing loss. Laryngoscope 2006;116:1451–4.

[12] Yoshida T, Sugiura M, Naganawa S, Teranishi M, Nakata S, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging findings and prognosis in sudden sensorineural hearing loss. Laryngoscope 2008; 118:1433–7.

[13] Sugiura M, Naganawa S, Teranishi M, Sato E, Kojima S, Nakashima T. Inner ear hemorrhage in systemic lupus erythematosus. Laryngoscope 2006;116:826–8.

[14] Otake H, Sugiura M, Naganawa S, Nakashima T. 3D-FLAIR magnetic resonance imaging in the evaluation of mumps deafness. Int J Pediatr Otorhinolaryngol 2006;70: 2115–7.

[15] Sone M, Mizuno T, Sugiura M, Naganawa S, Nakashima T. Three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging investigation of inner ear disturbances in cases of middle ear cholesteatoma with labyrinthine fistula. Otol Neurotol 2007;28:1029–33.

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[16] Sugiura M, Naganawa S, Nakata S, Kojima S, Nakashima T. 3D-FLAIR MRI findings in a patient with Ramsay Hunt syndrome. Acta Otolaryngol 2007;127:547–9.

[17] 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: 501–5.

[18] Duan M, Bjelke B, Fridberger A, Counter SA, Klason T, Skjonsberg A, et al. Imaging of the guinea pig cochlea following round window gadolinium application. Neuroreport 2004;15:1927–30.

[19] 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: 145–52.

[20] 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: 415–20.

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

[22] 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;18:920–4.

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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

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administration of Gd-diethylenetriamine pentaacetic acid–*bis* (methylamide; Gd-DPTA–BMA; Omniscan, Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan). There pathologies included Ménière's disease (34 patients), delayed endolymphatic hydrops (8 patients), sudden deafness (5 patients), acute low-tone sensorineural hearing loss (2 patient), fluctuating hearing loss without vertigo (2 patient), bilateral hearing loss without vertigo (1 patient), profound hearing loss with vertigo (1 patient), large vestibular aqueduct syndrome (1 patient), and acoustic tumor (1 patient). In 6 patients (3 with delayed endolymphatic hydrops, 2 with Ménière's disease, and 1 with bilateral profound deafness with vertigo), intratympanic injection was performed in both ears. Thus, 61 ears were included in this study. The diagnosis of each disease was made according to the criteria described in the literature (7–9).

The study protocol was approved by the Ethics Review Committee of Nagoya University School of Medicine (approval nos. 369, 369–2, 369–3, and 369–4). All patients gave their informed consent to participate in this study. The patient's written informed consent was attached to the electronic medical record after he or she gave permission in accordance with the suggestion of the Ethics Review Committee.

Intratympanic Gd Injection

The detailed methods for intratympanic Gd injection have been reported previously (6). Based on the results from this previous study, the scan delay after intratympanic Gd injection was determined as 24 hours to allow the Gd to be distributed widely in the perilymphatic space of the labyrinth.

Gd-DPTA BMA was diluted 8-fold with saline (v/v 1:7) in 58 ears or 16-fold with saline (v/v 1:15) in 3 ears. Because Kakigi et al. (10) reported adverse effects on the stria vascularis when nondiluted Gd was injected into the tympanic cavity of guinea pigs, we tried to use Gd diluted 16-fold to avoid toxicity more securely and compared the results to those obtained with Gd diluted 8-fold.

The patient was placed in the supine position with his or her head turned about 30 degrees away from the sagittal line toward the other ear. The diluted Gd-DPTA BMA was injected intratympanically through the tympanic membrane using a 23-G needle and a 1-ml syringe. In many patients, small gauze soaked by 4% lidocaine was put for 10 minutes before the injection, but in some patients, the injection was done without anesthesia. The amount of diluted Gd injected was 0.4 to 0.5 ml. After the injection, the patient remained in the supine position for 60 minutes with the head turned about 60 degrees away from the sagittal line toward the other ear.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed with a 3-Tesla unit in 54 patients (Trio, Siemens, Erlangen, Germany) and a 1.5-Tesla unit in 1 patient because of mechanical problem on the 3-Tesla unit using a receive-only 12-channel phased-array coli. T1-Weighted 3-dimensional fast low-angle shot (3D-FLASH) and conventional 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging were performed as described previously (11). T2-weighted 3-dimensional constructive interference in the steady-state (3D-CISS) imaging was performed to obtain reference images of labyrinthine fluid-space anatomy.

In 1 patient who underwent the intratympanic Gd injection first, the Gd was not observed in apical turn of cochlea 7 hours later when we undertook twice MRI 1 and 7 hours after the intratympanic Gd injection. MRI performed 1 day after the intratympanic injection of Gd showed that the border of the perilymph and endolymph was clearly visible, and that the Gd was observed almost entirely inside the inner ear. Then we concluded that MRI undertaken 1 day after the intratympanic Gd injection would provide maximum information (12).

RESULTS

Enhancement by 16-fold dilution of Gd intratympanically was fainter than by 8-fold dilution of Gd, although endolymphatic space could be evaluated with the 16-fold dilution of Gd. So, we used eightfold dilution of Gd in the other patients. In 53 ears, the Gd-containing perilymphatic space of the inner ear appeared clearly in the MRI as a high signal on 3D-FLAIR. However, in 2 ears with Ménière's disease and 1 ear with profound deafness with vertigo, movement of Gd into the inner ear was not visible. Figure 1 shows an example of MRI of the inner ear in which the Gd appeared in the perilymphatic space clearly. Figure 2 shows that the movement of Gd into the inner ear was not visible. Of the 3 ears that did not show evidence of movement of Gd into the inner ear, 2 ears had calcification of the tympanic membrane in association with a previous history of otitis media, but 1 ear had no abnormal findings of the tympanic membrane and no history of otitis media. To rule out the possibility of an incorrect method of injection, we repeated the intratympanic injection of Gd into the same ear and MRI, and found the same result (i.e., no evidence of Gd movement into the inner ear).

In 5 ears (4 with Ménière's disease and 1 with delayed endolymphatic hydrops), movement of Gd into the inner ear was observed more faintly than usual (Fig. 3). These 5 ears received the 8-fold dilution of Gd intratympanically, and the Gd density in the inner ear was less than that in the 3 ears treated with the 16-fold dilution of Gd. One of the 5 ears had calcification of the tympanic

FIG. 1. Axial magnetic resonance image. The right inner ear of a 33-year-old man with Ménière's disease. Three-dimensional fluid-attenuated invention recovery magnetic resonance image taken 1 day after intratympanic injection of Gd shows that the Gd is in the basal and second turns of the cochlea, vestibule, and semicircular canals. The *long arrow* indicates the horizontal semicircular canal, and the *short arrow* indicates the posterior semicircular canal.

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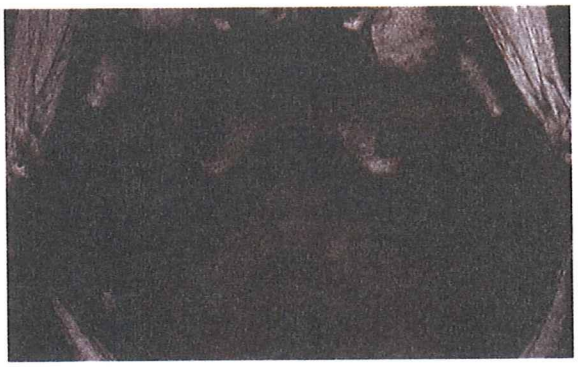

FIG. 2. Axial magnetic resonance image of the right inner ear of a 39-year-old woman with Ménière's disease. Three-dimensional fluid-attenuated invention recovery magnetic resonance image taken 1 day after intratympanic injection of Gd. The high signals of the cochlea are not visible. We injected Gd intratympanically into the same ear again, but the MRI showed no movement of Gd into the inner ear.

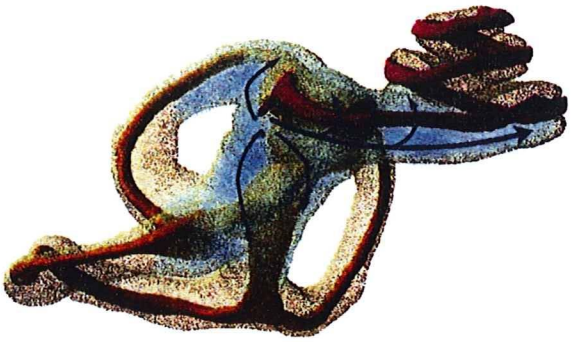

FIG. 4. Schema of Gd distribution inside the perilymph 2 hours after intratympanic Gd injection from an example of the inner ear in which the Gd appeared in the perilymphatic space clearly. The Gd distribution in the perilymph is shown in *light blue*, and the direction of Gd movement is shown in *dark blue*. Two hours after the intratympanic injection, Gd appears in the scala vestibule through the lateral route of the cochlea (*curved arrows*) and not through the helicotrema.

membrane, and 1 ear had slight inflammation in mastoid cells caused by otitis media, which had been diagnosed with computerized tomography (CT); however, 3 of the 5 ears showed no abnormal finding of the tympanic membrane.

DISCUSSION

Figure 4 shows the Gd distribution in the perilymph after 2 hours from the intratympanic injection. The intratympanically administered Gd entered the scala tympani of the cochlea through the round window membrane and moved quickly into the perilymph of the vestibule. On MRIs taken 2 hours after the injection, the Gd was observed in the vestibule, parts of the lateral semicircular canals close to the vestibule, and the scala tympani of the basal turn of the cochlea (6). One day after the intratympanic injection, the Gd had infiltrated a wider area in the semicircular canals and the cochlea, and was observed almost entirely inside the perilymph of the inner ear. Gd appeared in the scala vestibule of the basal turn by way of the lateral wall of the cochlea and not by way of the helicotrema (Fig. 4). These results show that before Gd moves inside the inner ear, it enters through the round window membrane.

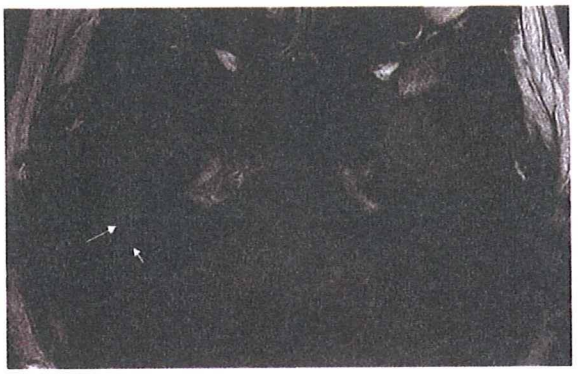

FIG. 3. Axial magnetic resonance image. Right inner ear of a 38-year-old woman with Ménière's disease. Three-dimensional fluid-attenuated invention recovery magnetic resonance image taken 1 day after intratympanic injection of Gd. The *long arrow* indicates the horizontal semicircular canal, and the *short arrow* indicates the posterior semicircular canal. The bright signals of the semicircular canal and the high signals of the cochlea are fainter than usual.

In our experience, Gd did not reach the apical turn of the cochlea when 7 hours passed after the intratympanic injection. Zou et al. (13) reported that Gd was observed in all locations of the inner ear when 12 hours passed after intratympanic Gd injection. Twelve hours of waiting time may be sufficient, but we waited for 24 hours to keep daily works.

We found that the passage of the drug through the round window membrane is poor in 13% of ears even if no active otitis media was present at the time of the intratympanic injection. When considering intratympanic gentamicin therapy in patients with Ménière's disease or intratympanic steroid therapy in patients with sudden sensorineural hearing loss, the clinician should also consider using intratympanically administered Gd to evaluate the permeability of the round window membrane. The results of the intratympanically administered Gd should contribute valuable information for choosing the appropriate treatment.

For 5% of ears that round window permeability was absent by imaging after intratympanic Gd injection, intratympanic drug therapy is not appropriate for the treatment of inner ear diseases. In these patients, we need to choose the treatment excepting intratympanic drug therapy. For 8% of ears that movement of Gd into the inner ear was observed more faintly than usual, we tell the results to patients and talk about treatment plan.

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Because Gd entered the inner ear partially, it is possible to choose intratympanic drug therapy. However, the effect may not be sufficient.

Because 87% of patients are likely to have patent and permeable round window membranes, intratympanic drug therapy can be done without the inner ear imaging. Intratympanic Gd injection may be reserved for those not responding to the treatment. When there is no permeability of the round window, intratympanic drug therapy should be abandoned. When the permeability of the round window is not sufficient, treatment plan should be talked with the patients.

The molecular weight of Gd-DPTA BMA is 645.7. Gentamicin is given as one of 3 drugs—gentamicin C1, gentamicin C2, and gentamicin C1a—whose molecular weights are 477.6, 449.5, and 463.6, respectively. Previous researchers have used dexamethasone (392.5) or methylprednisolone (374.5) as intratympanically administrated steroids (14,15). It is thought that the lower the molecular weight, the greater the permeability of the round window membrane (16). However, the Gd movement demonstrated by MRI may be an indicator of movement of intratympanically applied steroids or gentamicin.

CONCLUSION

In patients who are unresponsive to intratympanic gentamicin therapy for the treatment of intractable Ménière's disease, it is probable that the permeability of the round window is impaired. Inner ear MRI after intratympanic Gd administration can be used to assess the permeability of the round window membrane in addition to its use in the evaluation of the endolymphatic space size.

REFERENCES

1. Durland WF Jr, Pyle GM, Connor NP. Endolymphatic sac decompression as a treatment for Ménière's disease. *Laryngoscope* 2005; 115:1454–7.
2. Cohen-Kerem R, Kisilevsky V, Einarson TR, et al. Intratympanic gentamicin for Ménière's disease: a meta-analysis. *Laryngoscope* 2004;114:2085–91.
3. Slattery WH, Fisher LM, Iqbal Z, et al. Intratympanic steroid injection for treatment of idiopathic sudden hearing loss. *Otolaryngol Head Neck Surg* 2005;133:251–9.
4. Allens MJ, der Gaag MA, Stokroos RJ. Intratympanic steroid therapy for inner ear diseases, a review of the literature. *Eur Arch Otorhionolaryngol* 2006;263:792–7.
5. Silverstein H, Rowan PT, Olds MJ, et al. Inner ear perfusion and the role of round window patency. *Am J Otol* 1997;18:586–9.
6. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope* 2007;1173:415–20.
7. Committee on Hearing and Equilibrium. Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg* 1995; 113:181–5.
8. Nomura Y. Diagnosis criteria for sudden deafness, mumps deafness and perilymphatic fistula. *Acta Otolaryngol Suppl* 1988; 456:7–8.
9. Abe T, Tsuiki T, Murai M, et al. Review of the evaluation criteria for low tone sudden deafness [in Japanese]. *Nippon Jibiinkoka Gakkai Kaiho* 1992;95:7–14.
10. Kakigi A, Nishimura M, Takeda T, et al. Effect of gadolinium injection into the middle ear on the stria vascularis. *Acta Otolaryngol* 2008;128:841–5.
11. Naganawa S, Satake H, Kawamura M, et al. 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;5:920–4.
12. Naganawa S, Sugiura M, Kawamura M, et al. Imaging of endolymphatic and perilymphatic fluid at 3T after intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. *AJNR Am J Neuroradiol* 2008;29:724–6.
13. Ahn JH, Yoo MH, Yoon TH, et al. Can intratympanic dexamethasone added to systematic steroids improve hearing outcome in patient with sudden deafness? *Laryngoscope* 2008;118:279–82.
14. Zou J, Pyykkö I, Bjelke B, et al. Communication between the perilymphatic scalae and spiral ligament visualized by in vivo MRI. *Audiol Neurotol* 2005;10:145–52.
15. Fitzgerald DC, McGuire JF. Intratympanic steroids for idiopathic sudden hearing loss. *Ann Otol Rhinol Laryngol* 2007; 116:253–6.
16. Juhn SK, HAmaguchi Y, Goycoolea M. Review of round window membrane permeability. *Acta Otolaryngol Suppl* 1989;457:43–8.

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ORIGINAL ARTICLE

Cochlear blood flow during occlusion and reperfusion of the anterior inferior cerebellar artery – effect of topical application of dexamethasone to the round window

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Abstract

Conclusion. Topical application of dexamethasone may support autoregulation of cochlear blood flow (CBF), although it had no direct effect on CBF. *Objectives.* Although intratympanic steroid therapy for patients with inner ear disorders is common, the mechanism by which steroids exert their effect is unclear. We investigated the response of CBF to topical application of dexamethasone onto the round window. *Materials and methods.* Two concentrations of dexamethasone (3.3 mg/ml and 33 mg/ml dexamethasone in 0.5 μl saline) were applied to the round windows of rats, and CBF responses were measured using a laser Doppler flowmeter. The effects on CBF of a 2 h occlusion of the anterior inferior cerebellar artery (AICA) and subsequent release of the clamp with or without previous dexamethasone application were investigated. *Results.* No significant change in CBF was observed after topical application of dexamethasone, and it did not affect the decrease in CBF caused by AICA occlusion. However, recovery of CBF after release of the AICA clamp was better in animals treated with dexamethasone than in those that did not receive dexamethasone.

Keywords: *Cochlear blood flow, occlusion, reperfusion, anterior inferior cerebellar artery, dexamethasone*

Introduction

The concentration of steroids in the fluid of the inner ear is significantly greater after local administration of steroids to the round window than after systemic steroid administration [1,2]. Many reports have recently been published on intratympanic steroid therapy for the treatment of sudden deafness. Most of these reports indicate that intratympanic steroid therapy is useful for this purpose [3,4]. Intratympanic steroid therapy has also been used to treat Meniere's disease [5]. Some patients with Meniere's disease benefit from intratympanic steroid therapy, but there is controversy about its efficacy.

Although glucocorticoids are often administered to patients with sudden sensorineural hearing loss, the mechanism by which steroids exert their effects is unclear. Fukushima et al. [6] reported that intratympanic injection of steroids up-regulated aquaporin 1 mRNA in the rat cochlea in a dose-dependent manner. Their results suggest that steroids may affect water homeostasis in the rat inner ear via aquaporin 1. An anti-inflammatory effect of intratympanic steroids on experimentally induced inner ear inflammation has also been described [7].

The effect of local application of steroids to the round window on cochlear blood flow (CBF) has also been investigated. Shirwany et al. [8] observed an initial increase in CBF, which persisted for at least 1 h after intratympanic dexamethasone administration to guinea pigs. Sone et al. [7] investigated the effect of prostaglandin E1 application to the round window on CBF in rats with inner ear inflammation induced by lipopolysaccharide treatment. The elevation in CBF caused by topical application of prostaglandin E1 was greater when dexamethasone was applied intratympanically in advance than when animals received saline instead of dexamethasone. Therefore, CBF may be affected by topical administration of steroids. However, there are no reports of

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the effect of intratympanic steroid treatment on cochlear ischemia.

Many studies have been conducted on the effect of steroids on cerebral blood flow when cerebral edema is present [9,10]. The effect of steroids on focal cerebral ischemia after permanent and temporary occlusion of the middle cerebral artery has also been investigated using rats [11]. In the aforementioned study, high-dose methylprednisolone treatment decreased the volume of the infarct after temporary, but not permanent, focal ischemia. This suggests that high doses of methylprednisolone may be clinically useful if reperfusion can be established. Because there are no reports on the effect of steroids on CBF reperfusion, we investigated the effect of dexamethasone administration to the round window on CBF under normal, ischemic, and reperfusion conditions using laser Doppler (LD) flowmetry.

Materials and methods

Surgical approach

Twenty-five female Sprague Dawley rats (200–280 g, 7–10 weeks old) with normal Preyer's reflexes were used. Experimental protocols were approved by the Nagoya University Committee on the Use and Care of Animals (Permit No. 17082). The rats were anesthetized (i.m.) with 100 mg/kg ketamine and 5 mg/kg xylazine and anesthesia was maintained by supplementary half-doses of ketamine every 60 min. Tracheostomies were performed; all animals breathed spontaneously throughout the experiments. Blood pressure and heart rate were measured using a catheter inserted into the left femoral artery that was connected to a pressure transducer (AS1202, NEC, Tokyo, Japan). Rectal temperature was maintained at $38 \pm 1°C$ using a servoregulated heating blanket.

CBF measurement

The right tympanic bulla was opened using a diamond bur and a ventral–lateral approach. After the middle ear mucosal tissue over the bony wall of the cochlea was gently removed using a cotton pledget, a 1.0 mm diameter LD probe was positioned on the basal turn of the cochlea and connected to an LD flowmeter (ALF21, Advance, Tokyo, Japan) to measure CBF. Petroleum gel was applied to the probe tip to enhance contact between the laser light and the cochlea and to minimize accumulation of blood or fluid underneath the probe. LD and blood pressure data were recorded by a computer every 100 ms.

Administration of dexamethasone

Dexamethasone, a powerful glucocorticoid steroid, was dissolved in saline at concentrations of 3.3 mg/ml or 33 mg/ml. At first, dexamethasone in 0.5 µl saline was administered to the round window and CBF response was observed in five rats at each concentration. Administration of dexamethasone was done after the baseline CBF was confirmed. In 15 rats, the effects on CBF of a 2 h occlusion of the anterior inferior cerebellar artery (AICA) and subsequent release of the clamp with previous dexamethasone or saline application to the round window were investigated. Five rats in group A received saline, five rats in group B received 3.3 mg/ml dexamethasone, and five rats in group C received 33 mg/ml dexamethasone. Among 10 animals in groups A and B, the order of the experiment was random. After that, the experiment in group C rats was performed.

AICA clamping

With the animal's head firmly fixed in a head-holder, the esophagus was transected and muscular attachments to the skull base were excised. A hole was made in the bone at the base of the skull using a diamond burr, and the dura was opened to expose the basilar artery and the AICA. At 30 min after the topical administration to the round window, the right AICA was occluded using the method described previously [12]. A metal rod with a 0.6 mm diameter spherical tip was positioned using a micromanipulator (C1002, Urawa, Tokyo, Japan). Great care was taken not to tear the pia when the metal rod was positioned. The AICA was occluded for 120 min.

Data analysis

Baseline LD output was designated as 100% output. Zero output of the LD flowmeter was designated as 0% output. Data were analyzed using Student's *t* test or analysis of variance (ANOVA) with STATA version 8.0 software. Differences among means were considered statistically significant if the null-hypothesis probability was <0.05. Distributions are expressed as the mean $\pm$ standard deviation (SD).

Results

Topical application of dexamethasone to the round window did not change blood flow volume as estimated from LD flowmeter data. Figure 1 shows blood flow responses to dexamethasone. No significant change in LD output was observed after

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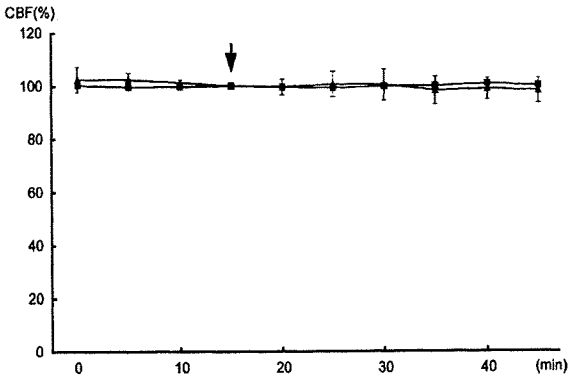

Figure 1. Effect of administration of 0.5 µl dexamethasone to the round window on CBF. The administration was done at the point indicated by the arrow. Squares, 3.3 mg/ml dexamethasone; triangles, 33 mg/ml dexamethasone.

application of either concentration of dexamethasone.

LD output decreased abruptly after AICA clamping, and the low LD output was maintained during the 2 h occlusion of the AICA. When the AICA was occluded after saline administration to the round window (group A; Figure 2), LD values were 50.2 ± 2.7% immediately after occlusion and 47.4 ± 3.0% at 2 h after commencement of the occlusion. After the AICA clamp was released, the LD value increased to 90.9 ± 6.2%. LD values after release of the AICA clamp did not exceed 100% in any of the animals in group A. After the initial elevation upon release of the AICA clamp, the LD value tended to decrease gradually (Figure 2).

For those animals in which the AICA was manipulated after topical administration of 3.3 mg/ml dexamethasone (group B), LD values were 56.4 ± 4.6% immediately after occlusion and 52.5 ± 6.0% at 2 h after commencement of the occlusion. After the AICA clamp was released, the LD value increased to 105.8 ± 8.8% (Figure 3). In four of five animals, the LD value exceeded 100% after release of the clamp. The tendency observed in group A of a decrease in the LD value after the initial abrupt increase consequent to the release of the AICA clamp was not observed in group B.

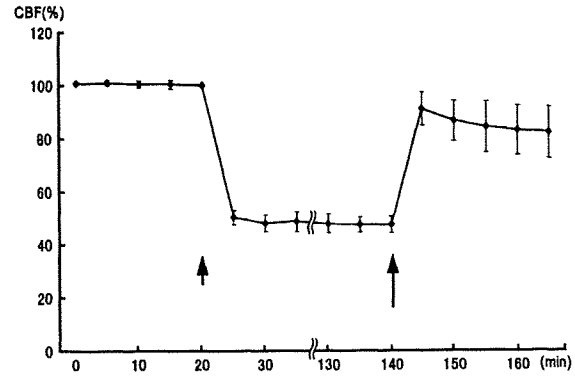

Figure 2. Effect of occlusion and release of AICA on CBF after administration of 0.5 µl saline to the round window. Short arrow indicates beginning of the occlusion, and long arrow indicates the release.

For those animals in which AICA was manipulated after topical administration of 33 mg/ml dexamethasone (group C), LD values were 54.0 ± 8.6% immediately after the occlusion and 52.8 ± 11.7% at 2 h after commencement of the occlusion. After the AICA clamp was released, the LD value increased to 105.0 ± 7.1% (Figure 4). In four of five animals, the LD value exceeded 100% after release of the clamp. The decrease in LD value observed in group A after the abrupt increase caused by the release of the AICA clamp was not observed in group C.

No significant changes in blood pressure were observed after dexamethasone application, AICA clamping or release of the AICA clamp. At the end of the experiment shown in Figures 2–4, mean blood pressure calculated by adding one-third of the pulse pressure to the diastolic pressure was 71.5–49.7 mmHg. The blood pressure did not differ significantly among the three groups.

Among the three groups, blood flow volumes estimated from LD values were compared for each sampling interval after commencement of AICA occlusion. The volumes differed significantly immediately after release of the AICA clamp and for the final measurement (Figures 2–4; $p < 0.05$, ANOVA). There were significant differences between the means of groups A and B for four of the five intervals after release of the AICA clamp and between groups A and C for the first measurement after release of the AICA clamp ($p < 0.05$, t test). However, there were no differences between groups B and C.

Discussion

Tissue hypoxia is intimately associated with inflammatory disease and may constitute a signal for the resolution of inflammatory processes [13–15]. Glucocorticoid signaling, which is mediated through the glucocorticoid receptor, is a clinically important endogenous anti-inflammatory pathway. Microarray analysis has shown that the glucocorticoid receptor is up-regulated by hypoxia [16]. Glucocorticoid receptors are present in the spiral ligament, stria vascularis, organ of Corti, spiral ganglion, and vestibular sensory epithelium of the inner ear. Intratympanically administered dexamethasone rapidly enters the inner ear, where it is converted to its

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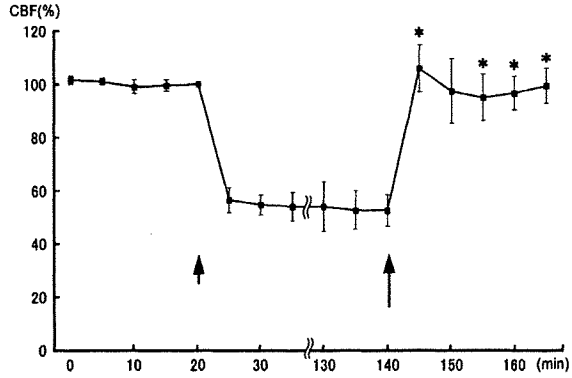

Figure 3. Effect of occlusion and release of AICA on CBF after administration of 0.5 μl dexamethasone (3.3 mg/ml) to the round window. Short arrow indicates beginning of the occlusion, and long arrow indicates the release. Asterisks indicate where there was a significant difference compared with control animals shown in Figure 2.

active form. The distribution of dexamethasone corresponds to that of the glucocorticoid receptor in all tissues of the inner ear except the marginal cells of the stria vascularis [17].

There are few studies on the effects of intratympanic steroid treatment on CBF. Shirwany et al. [8] reported that transtympanic administration of dexamethasone to guinea pigs elevated CBF within 30 s to 29.26%. However, we did not observe any increase in CBF after administration of dexamethasone onto the round windows of rats. Further study is needed to elucidate the response of CBF to topical administration of steroids such as dexamethasone and methylprednisolone, which are now in common use.

After the occlusion of AICA began without leakage of cerebrospinal fluid due to damage to the pia, LD output was stable during the AICA occlusion. During the occlusion, no significant change in the blood flow was observed in each rat, although there were individual differences between animals. The LD probe detects signals from both the cochlea and the bone surrounding the cochlea. The blood supply to the bone originates from the middle ear blood system and differs from the blood supply to the inner ear, which originates from the AICA [18]. LD output during AICA occlusion originates mainly from blood flow in the bone surrounding the cochlea because there is no CBF during AICA occlusion in rats [12]. However, in guinea pigs, CBF tended to recover during AICA occlusion [19]. Therefore, CBF during AICA occlusion differs between rats and guinea pigs.

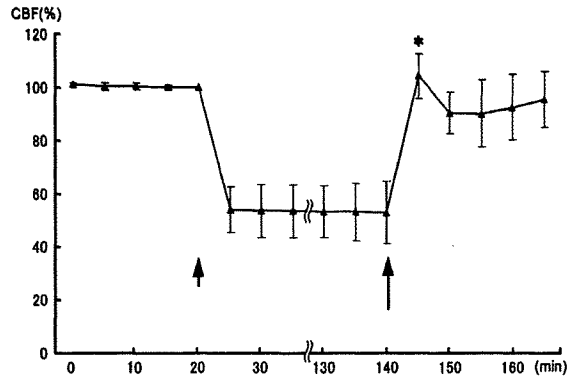

Figure 4. Effect of occlusion and release of AICA on CBF after administration of 0.5 μl dexamethasone (33 mg/ml) to the round window. Short arrow indicates beginning of the occlusion, and long arrow indicates the release. Asterisk indicates where there was a significant difference compared with control animals shown in Figure 2.

After release of the AICA clamp, the autoregulatory rebound phenomenon in which blood flow exceeds 100% of baseline is significant when the occlusion time is relatively short. However, if occlusion is sustained, the rebound phenomenon is minimal or absent. Impaired autoregulation of blood flow may be caused by damage to blood vessels associated with edema. We occluded the AICA for 2 h and found that autoregulation was present when dexamethasone had previously been applied to the round window. The applied dexamethasone may reduce the edema of the inner ear and support autoregulation of CBF. However, additional experiments done with 33 mg/ml dexamethasone did not elevate the autoregulation compared to that done with 3.3 mg/ml. A dexamethasone concentration of 3.3 mg/ml, which is commonly used under clinical conditions, may be sufficient to support autoregulation of CBF after occlusion of the feeder artery.

A protective effect of systemic glucocorticoid administration against ischemia–reperfusion injury of the outer hair cells has been reported for guinea pigs [20]. Attenuation of ischemia-induced damage or reperfusion injury by pretreatment with glucocorticoids has been reported for various organs [16] including the brain. However, glucocorticoids sometimes aggravate ischemia-induced damage [9]. Whether glucocorticoids exert beneficial or adverse effects in ischemia-related injury of the brain may depend on local conditions.

Our study indicates that intratympanic dexamethasone treatment helps maintain autoregulation of CBF after occlusion of the feeder artery. Hearing was not evaluated in this study because intratympanic dexamethasone application affects the middle ear system. However, intratympanic steroid therapy is now widely used for treatment of inner ear diseases. Further histological and functional studies, including hearing tests, on the effects of topical administration of glucocorticoids are warranted.

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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.

References

[1] Yang J, Wu H, Zhang P, Hou DM, Chen J, Zhang SG. The pharmacokinetic profiles of dexamethasone and methylprednisolone concentration in perilymph and plasma following systemic and local administration. Acta Otolaryngol 2007;Oct 4:1–9 [Epub ahead of print].

[2] Bird PA, Begg EJ, Zhang M, Keast AT, Murray DP, Balkany TJ. Intratympanic versus intravenous delivery of methylprednisolone to cochlear perilymph. Otol Neurotol 2007;28: 1124–30.

[3] Kilic R, Safak MA, Oguz H, Kargin S, Demirci M, Samim E, et al. Intratympanic methylprednisolone for sudden sensorineural hearing loss. Otol Neurotol 2007;28:312–6.

[4] Ahn JH, Han MW, Kim JH, Chung JW, Yoon TH. Therapeutic effectiveness over time of intratympanic dexamethasone as salvage treatment of sudden deafness. Acta Otolaryngol 2007;Aug 22:1–4 [Epub ahead of print].

[5] Dodson KM, Woodson E, Sismanis A. Intratympanic steroid perfusion for the treatment of Meniere's disease: a retrospective study. Ear Nose Throat J 2004;83:394–8.

[6] Fukushima M, Kitahara T, Uno Y, Fuse Y, Doi K, Kubo T. Effects of intratympanic injection of steroids on changes in rat inner ear aquaporin expression. Acta Otolaryngol 2002; 122:600–6.

[7] Sone M, Hayashi H, Yamamoto H, Tominaga M, Nakashima T. A comparative study of intratympanic steroid and NO synthase inhibitor for treatment of cochlear lateral wall damage due to acute otitis media. Eur J Pharmacol 2003; 482:313–8.

[8] Shirwany NA, Seidman MD, Tang W. Effect of transtympanic injection of steroids on cochlear blood flow, auditory sensitivity, and histology in the guinea pig. Am J Otol 1998; 19:230–5.

[9] Heinonen K, Fedinec A, Leffler CW. Dexamethasone pretreatment attenuates cerebral vasodilative responses to hypercapnia and augments vasoconstrictive responses to hyperventilation in newborn pigs. Pediatr Res 2003;53: 260–5.

[10] Akdemir G, Ergungor MF, Sezer M, Albayrak L, Daglioglu E, Kilinc K. Therapeutic efficacy of intraventricular cyclosporine A and methylprednisolone on a global cerebral ischemia model in rats. Neurol Res 2005;27:827–34.

[11] Slivka AP, Murphy EJ. High-dose methylprednisolone treatment in experimental focal cerebral ischemia. Exp Neurol 2001;167:166–72.

[12] Nakashima T, Suzuki T, Iwagaki T, Hibi T. Effects of anterior inferior cerebellar artery occlusion on cochlear blood flow – a comparison between laser-Doppler and microsphere methods. Hear Res 2001;162:85–90.

[13] Cummins EP, Comerford KM, Scholz C, Bruning U, Taylor CT. Hypoxic regulation of NF-kappaB signaling. Methods Enzymol 2007;435:479–92.

[14] Ruas JL, Lendahl U, Poellinger L. Modulation of vascular gene expression by hypoxia. Curr Opin Lipidol 2007;18: 508–14.

[15] Frede S, Berchner-Pfannschmidt U, Fandrey J. Regulation of hypoxia-inducible factors during inflammation. Methods Enzymol 2007;435:405–19.

[16] Leonard MO, Godson C, Brady HR, Taylor CT. Potentiation of glucocorticoid activity in hypoxia through induction of the glucocorticoid receptor. J Immunol 2005;174:2250–7.

[17] Hargunani CA, Kempton JB, DeGagne JM, Trune DR. Intratympanic injection of dexamethasone: time course of inner ear distribution and conversion to its active form. Otol Neurotol 2006;27:564–9.

[18] Nakashima T, Naganawa S, Sone M, Tominaga M, Hayashi H, Yamamoto H, et al. Disorders of cochlear blood flow. Brain Res Brain Res Rev 2003;43:17–28.

[19] Ren T, Nuttall AL, Miller JM. Contribution of the anterior inferior cerebellar artery to cochlear blood flow in guinea pig: a model-based analysis. Hear Res 1993;71:91–7.

[20] Tabuchi K, Oikawa K, Murashita H, Hoshino T, Tsuji S, Hara A. Protective effects of glucocorticoids on ischemia-reperfusion injury of outer hair cells. Laryngoscope 2006; 116:627–9.

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ORIGINAL ARTICLE

Imaging analysis in cases with inflammation-induced sensorineural hearing loss

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Abstract

Conclusion. 3D-FLAIR imaging is sensitive to inflammatory inner ear disturbances and may be a useful method in investigating the severity of inner ear disturbance in cases of inflammation-induced SNHL. *Objective.* To evaluate the usefulness of the three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) sequence in investigating different etiology of inner ear disturbances in cases with inflammation-induced acute sensorineural hearing loss (SNHL). *Patients and methods.* Five cases with inflammation-induced acute SNHL by different conditions are included in this study: acute meningitis, acute otitis media, and Wegener granulomatosis. Imaging analysis was performed using a three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) magnetic resonance imaging (MRI) sequence, and correlation between clinical symptoms and FLAIR abnormalities was evaluated. *Results.* In the affected ears in all cases, 3D-FLAIR revealed high pre-contrast signal and increased signal in the cochlea after the administration of gadolinium. Enhancement was still observed in the inner ear after several months with continuing nystagmus in those cases induced by meningitis and severe otitis media. In a case with Wegener granulomatosis, increased signal in the post-contrast images was stronger on the side of the cochlea with the worse hearing level.

Keywords: *Inflammation, etiology, sensorineural hearing loss, inner ear disturbance, 3D-FLAIR*

Introduction

Inflammatory conditions that occur outside the inner ear, such as otitis media or meningitis, can induce inner ear disturbances with symptoms of sensorineural hearing loss (SNHL). Animal studies have investigated the mechanisms of inflammation-induced inner ear disturbances [1–5]; however, etiological investigations in clinical cases are limited.

Previous reports describe the usefulness of gadolinium enhancements in magnetic resonance imaging (MRI) for detecting inflammatory lesions of the inner ear [6–9]; this enhancement has been considered the result of breakdown of the blood–labyrinth barrier (BLB) [6,8,9]. The BLB maintains the composition of the inner ear fluid; its function is to protect the inner ear from toxic substances by selectively limiting the entry of substances into the inner ear [10]. The fluid-attenuated inversion recovery (FLAIR) MRI sequence has been recently applied to the inner ear [11–13]. FLAIR enables the demonstration of hemorrhage and high protein concentration in lesions; these conditions are difficult to detect using T1- and T2-weighted MRI [14]. FLAIR assessment can also be used to evaluate cerebrospinal fluid (CSF) changes in pathologic conditions that cause a breakdown in the blood–brain barrier [15].

In the present paper, we apply 3D-FLAIR MRI at three tesla to cases with inflammation-induced acute SNHL caused by different conditions, and evaluate the results with the aim of demonstrating its advantage in investigating etiologies in these inner ear disturbances.

Materials and methods

Patients

Five cases with inflammation-induced acute SNHL and by different conditions were included in this

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