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Research Paper

MRI detection of endolymphatic hydrops in Meniere's disease in 8 minutes using MIIRMR and a 20-channel coil after targeted gadolinium delivery

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KEYWORDS
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Abstract *Background:* Endolymphatic hydrops (EH) become visible in vertigo patients, particularly in those with Meniere's disease (MD), in vivo using gadolinium-enhanced MRI. However, the image quality is not satisfying after intravenous injection of gadolinium chelate (GdC), and occasional failure in GdC uptake has been noticed after traditional intratympanic injection. In the present report, targeted delivery of GdC and using a cost-effective MRI system to obtain high quality images of EH in only 8 min will be introduced.
Methods: 39 MD patients were recruited in the study. First, 0.1 ml of 20-fold diluted gadolinium-diethylenetriamine acid (Gd-DTPA) was delivered onto the posterior upper part of the tympanic medial wall using a soft-tipped micro-irrigation catheter through an artificially perforated tympanic membrane. Inner ear MRI was performed 24 h after Gd-DTPA administration using a 3T MR machine and a 20-channel head/neck coil with an 8 min sequence of medium inversion time inversion recovery imaging with magnitude reconstruction (MIIRMR). The parameters were as follows: TR 16000 ms, TE 663 ms, inversion time 2700 ms, flip angle 180°, slices per slab 60.
Results: Efficient inner ear uptake of Gd-DTPA was detected 24 h after delivery and it created excellent contrast in the inner ear of all cases. High quality images demonstrating EH in the vestibule and cochlea were obtained.

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Conclusion: Targeted delivery of minimum Gd-DTPA (0.1 ml, 20-fold dilution) onto the posterior upper portion of the tympanic medial wall and MRI with MIIRMR in a 3T machine and 20-channel head/neck coil are clinically practical to obtain high quality images displaying EH.

Background

The etiology of Meniere's disease (MD) has been associated with endolymphatic hydrops (EH) that became MRI visible in 2000, attributed to the work of Zou et al in an experimental setup.[1,2] Inspired by the translational clinical studies based on transtympanic injection of gadolinium chelate (GdC) and MR machine improvements from 1.5 T to 3.0 T using a three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence,[3,4] a

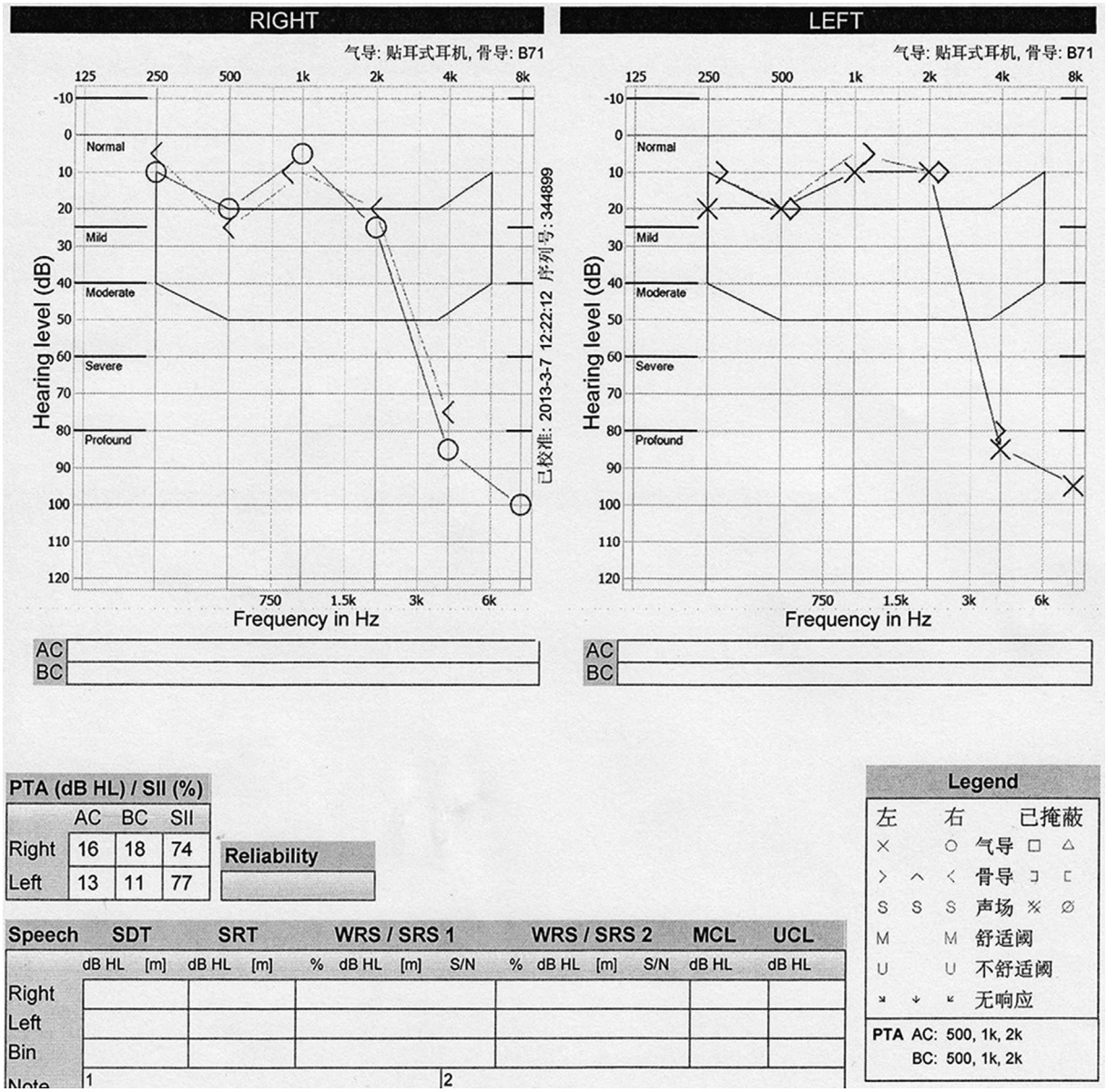

Fig. 1 Audiogram of a probable MD (case A) demonstrating high-frequency hearing loss on both sides. A 40-year-old man complained of episode of vertigo attacks lasted for more than half year that were accompanied by bilateral tinnitus, aural fullness, and fluctuating hearing loss. The longest duration of vertigo attack was 1 d.

new classification concept of hydropic ear disease has recently emerged.[5–8] Intravenous injection of GdC introduced limited entry of contrast agent into the inner ear, and the image quality was not satisfying even though newly improved 3D-real inversion recovery (i3D-real IR) sequences were applied.[9] Such problems have hampered the broad clinical dissemination of the EH examination, which is far from becoming a routine protocol.

Recently, Zou et al[10,11] reported a novel method of delivering minimum GdC onto the posterior upper portion of tympanic medial wall and obtained high quality images of EH in only 8 min using a cost-effective MRI system in combination with a modified heavily T2-weighted 3D-FLAIR (mhT2W-3D-FLAIR) sequence. After that, we further improved the protocol by using a medium inversion time inversion recovery imaging with magnitude reconstruction (MIIRMR) sequence with the parameters extracted from i3D-real IR[9] but with magnitude reconstruction instead of real reconstruction and obtained excellent images of EH by providing stronger gadolinium-enhancement signal and sharper borders. As of now, consistent results have been achieved in 39 MD patients in our hospital, and the details of the protocol will be reported as follows.

Methods

The study population consisted of 39 patients (17 males and 22 femals; age range, 20—81 years; mean age, 55.8 years) who were imaged in our hospital between July 2018 and

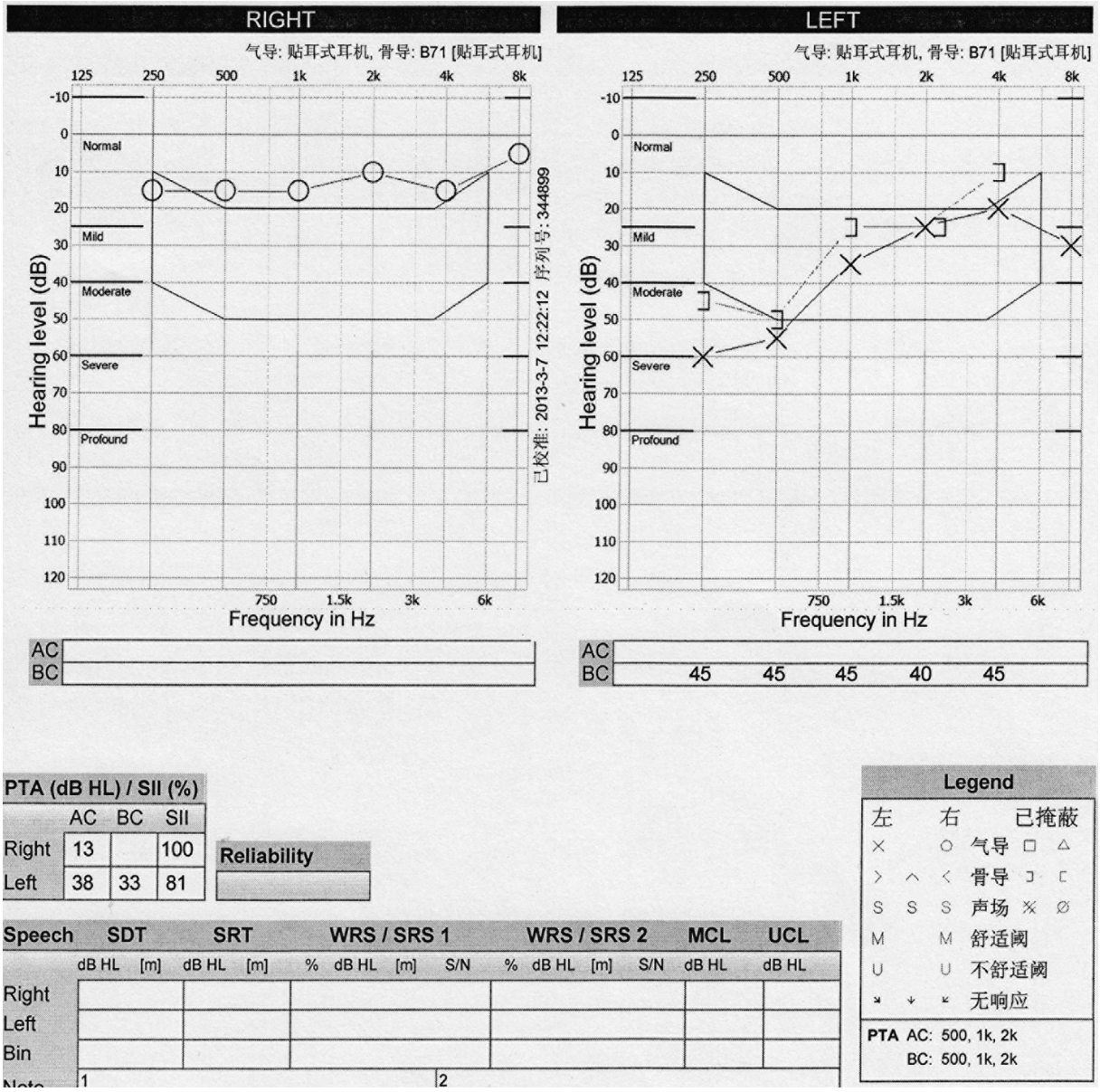

Fig. 2 Audiogram of a definite MD (case B) demonstrating low-frequency hearing loss on the left side. A 47-year-old man complained of episode of vertigo attacks lasted for more than 7 mon that were accompanied by tinnitus, aural fullness, and fluctuating hearing loss in the left ear. The longest duration of vertigo attack was 2 h. The vertigo was also induced by the sound of car horn and tapping.

March 2019.37 cases were diagnosed as definite MD and 2 cases were diagnosed as probable MD according to the diagnostic criteria for MD of the Barany Society in 2015.[12] The protocol was reviewed and approved by the ethical committee of The Sixth People's Hospital affiliated with Shanghai Jiaotong University. Typical audiograms of probable MD (case A) and definite MD (case B, C) are shown in Figs. 1—3. The patients received targeted delivery of dexamethasone (10 mg/ml, 0.1 ml) onto the posterior upper portion of the tympanic medial wall twice a week, which was repeated 4 times, using a soft-tipped micro-irrigation tympanic drug spray catheter (patent no. 201721665246.6) (ZJ-XWCXG-RT-180, Shijiazhuang zouji medical equipment limitedscience & technology Co, Ltd., Shijiazhuang, China) (Certificate Number UCN: 802258101745) through an artificially perforated tympanic membrane using a previously reported procedure.[10,11] The tip of the catheter is a high-performance polyimide tube with inner diameter 122 μm and outer diameter 180 μm (Microlumen, Tampa, Fla., USA) that has been extensively used in cochlear drug delivery in animal studies and medical applications.[13,14] The vertigo and aural fullness were ameliorated in patients after dexamethasone delivery before the MRI studies.

Before the imaging, 0.1 ml of 20-fold diluted gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) was delivered onto the posterior upper part of tympanic medial wall of each ear using the same method as was used for the dexamethasone delivery (Fig. 4).[10,11] After each injection, the patient was instructed to lie on the bed in a lateral position with the injected ear upward and turned approximately 30° backward for 15 min. Inner ear MRI was performed 24 h after Gd-DTPA administration using a 3T MR machine (Skyra, Siemens, Munich, Germany) and a 20-channel Tim 4G head/neck coil (Siemens, Munich, Germany). T2-sampling perfection with application-optimized contrasts by using a flip angle evolution (SPACE) sequence was used to detect potential inner ear fibrosis or vestibular schwannoma.[15] The gadolinium-enhancement signal within the inner ear and possible EH were imaged using either MIIRMR based on SPACE or a mhT2W-3D-FLAIR sequence in the same patient. The parameters for SPACE were as follows: TR 4 400 ms, TE 544 ms, echo

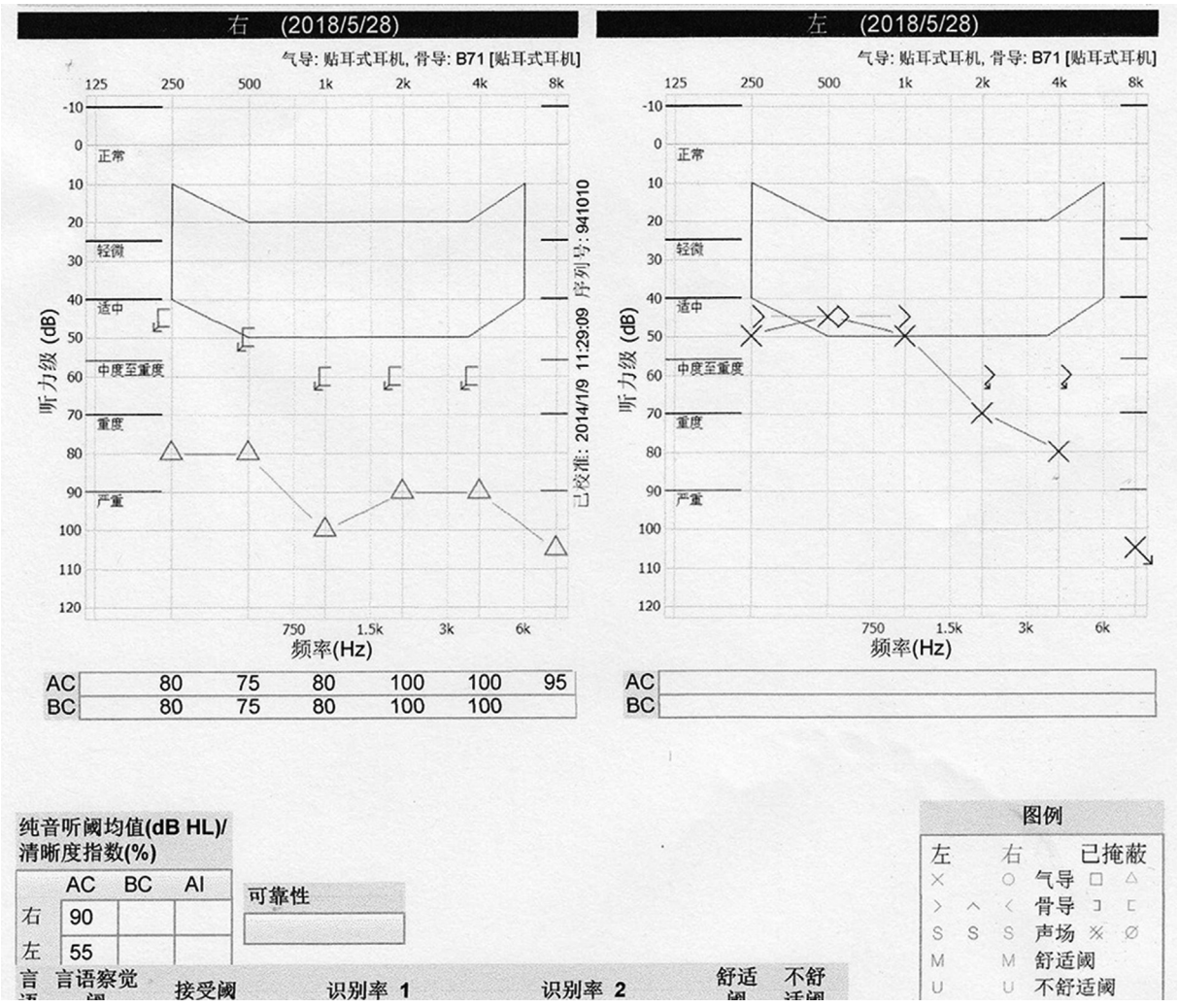

Fig. 3 Audiogram of a definite MD at the late stage (case C). A 61-year-old man complained of episode of vertigo attacks lasted for more than 10 years that were accompanied by bilateral tinnitus, aural fullness, and fluctuating hearing loss. The longest duration of vertigo attack was 12 h.

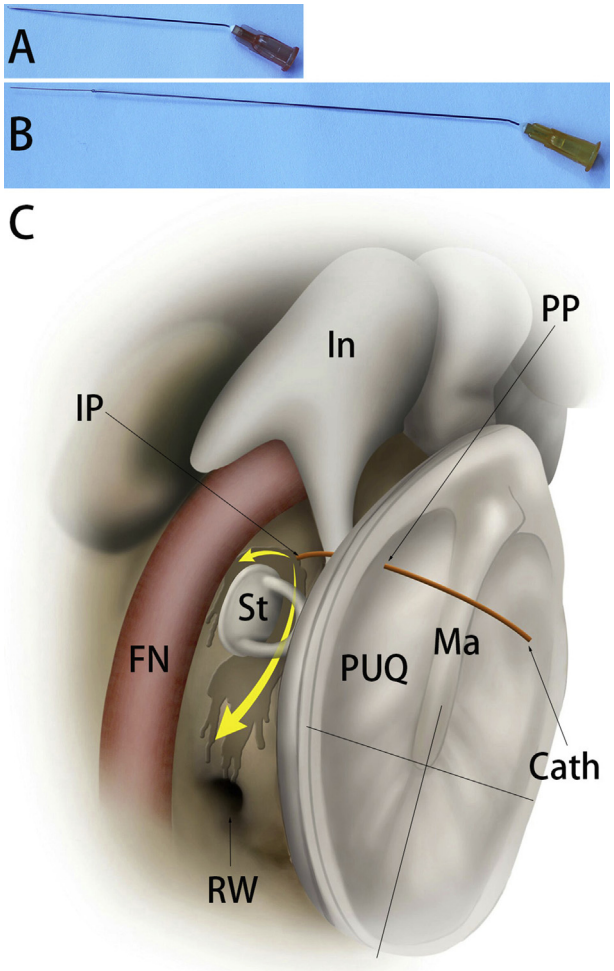

Fig. 4 Illustration of the targeted delivery of Gd-DTPA onto the posterior upper portion of the tympanic medial wall. A tiny penetration was made in the posterior upper quadrant (PUQ) of tympanic membrane adjacent to the pars flaccida with a 25-gauge needle (A). A soft-tipped microirrigation catheter was inserted onto the posterior tympanic medial wall through the penetration (B, C). The tip touched the tympanic medial wall at the injection point (IP) was insured by being able to observe a bent catheter (Cath). Ga-DTPA diffused from the injection point to the oval and round windows (yellow arrows). Fn: facial nerve; In: incus; Ma: malleus; PP: penetration point; RW: round window; St: stapes.

spacing 5.43 ms, allowed delay 30 s, bandwidth 434 Hz/Px, flip angle (FA) 120°, strong fat suppression, FOV 196 mm × 84.4 mm, slice thickness 1.0 mm, averages 1.8, slices per slab of 104, scanning time 3.4 min. The parameters for MIIRMR were as follows: TR 16000 ms, TE 663 ms, echo spacing 5.43 ms, inversion time (TI) 2700 ms, FA 180°, strong fat suppression, FOV read 196 mm × 165.4 mm, matrix 384 × 324, slice thickness 1.0 mm, averages 2, magnitude reconstruction. Slices per slab of either 104 or 60 were selected, which correspond to a scanning time of either 15 min 11 s or 8 min 50 s, respectively. The parameters for hT2W-FLAIR were as follows: TR 9 000 ms, TE 544 ms, TI2 250 ms, echo spacing 5.43 ms, FA120°, strong fat suppression, FOV read 196 mm × 165.4 mm, matrix 384 × 324, slice thickness 1.0 mm, averages 4, magnitude reconstruction, slices per slab 60, scanning time 8 min 35 s.

Results

Efficient inner ear uptake of Gd-DTPA was detected and it created excellent contrast in the inner ear of all cases 24 h after delivery using the present targeted delivery method imaged with both MIIRMR and hT2W-FLAIR sequences. There were no visible differences in the signal to noise ratios in images acquired with 104 or 60 slices per slab (Fig. 5). In the representative case A, mild hydrops was detected in the vestibule on both sides and extreme hydrops was detected in the left cochlea imaged using 60 slices per slab (Fig. 5).

In the representative case B, there was no EH in either the vestibule or the cochlea of the right ear. However, there was significant hydrops in the vestibule and marked hydrops in the cochlea of the diseased left ear, which were defined according to the methods used in previous reports (Fig. 6).[16,17] In the representative case C, the speculated endolymph-perilymph leakage in the cochlea and vestibule (Fig. 7) was supported by our previous study demonstrating that all the cochlear scalae were enhanced by GdC in an animal with histologically proved rupture of the Reissners' membrane.[2] Among the 37 definite MD, there was no EH in 2 cases, unilateral EH in 9 cases, bilateral EH in 26 cases, and the EH sites varied from 1 to 4 (Table 1). There was mild cochlear EH in 2 cases, marked cochlear EH in 9 cases, and extreme cochlear EH in 11 cases (Table 2). There mild vestibular EH in 8 cases and marked vestibular EH in 24 cases (Table 3).

Discussion

In general, the images acquired using the head/neck coil of a 32-channel have higher spatial resolution than that obtained with a coil of fewer channels.[4] However, 32-channel coils are not common in Chinese hospitals due to their high cost. In addition to compromised image quality, the scanning time would also be lengthened using a coil with fewer channels. The imaging time might be reduced by using fewer slices per slab in MIIRMR, which would result in a decreased signal to noise ratio. The drawback of imaging using 60 slices per slab was efficiently compensated for by introducing abundant uptake of GdC into the inner ear using our novel targeted delivery method that guaranteed an extremely high signal to noise ratio with a half-scanning time of 104 slices per slab in a heavily T2-weighted 3D FLAIR sequence.[10,11] Targeted delivery of contrast agent onto the posterior upper portion of the tympanic medial wall has also been proven to introduce highly efficient inner ear uptake of GdC, liposome nanocarrier, and super-paramagnetic maghemite (γ-Fe_2O_3) nanoparticles in rats.[18–20] In addition to round window pathway, a direct oval window entry of GdC into the vestibule was indicated in our early studies in both animals and humans that demonstrated greater uptake of the contrast agent in the scala vestibuli (SV) than the scala tympnai (ST) following intratympanic administration.[3,21] In 2000, we proved oval window entry

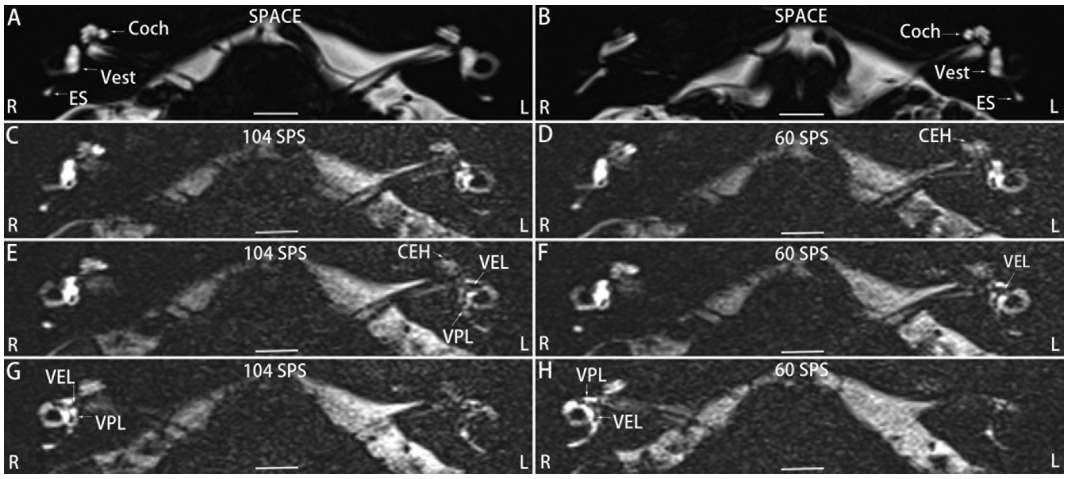

Fig. 5 Comparison between 104 and 60 slices per slab for inner ear MRI using MIIRMR sequence. MRI was performed 24 h after targeted delivery of Gd-DTPA onto the posterior upper portion of the tympanic medial wall in a patient with probable Meniere's disease (case A). There was no fibrosis in the inner ear imaged using SPACE (A, B). There were insignificant differences in the signal to noise ration imaged with 104 slices per slab (SPS) (C, E, G) and 60 SPS (E, F, H). Coch: cochlea; CEH: cochlear endolymphatic hydrops; ES: endolymphatic sac; L: left ear; R: right ear; VEL: vestibular endolymphatic hydrops; Vest: vestibule; VPL: vestibular perilymph. Scale bar = 8 mm.

of GdC into the vestibule by sealing the oval window that blocked the vestibular uptake of the contrast agent following intratympanic delivery, a method that is extensively applied in physiological research to prove the existence and essential role of an ion channel in the biological activity.[22,23] In the same year, we submitted a manuscript (ON-10-521) titled with "Selective vestibular drug delivery through the oval window and the impact of oval window sealing on the immediate distribution of Gd-DOTA in the rat inner ear" to *Otology & Neurotolog*, but was rejected. The novel results were finally published on *Ann Otol Rhinol Laryngol* in 2012.[24] King et al[25] reported direct entry of gadolinium into the vestibulefollowing intratympanic applications in guinea pigsin 2011. However, it is impossible to identify the oval window for accurate quantification as claimed in their work, and their results did not add any new information to our earlier studies.[3,21,25]

With the routine transtympanic injection, the posterior upper quadrant should be avoided of penetration due to the risks of injuring ossicular structures, especially the stapes. However, in the present study, the needle was only applied to make a perforation on the tympanic membrane; the tip of the catheter that was used for drug delivery has been used in intracochlear drug delivery without any risk of making damages to even cochlear structures.[13]

In the current study, high quality images demonstrating details of the inner ear fluids and surrounding tissues were created using MIIRMR sequence that further improved the contrast by increasing the TR and TE and slightly highlighted the background fluids through the TI of 2700 ms[9] and a 20-channel Tim 4G head/neck coil in 8 min. Using the present

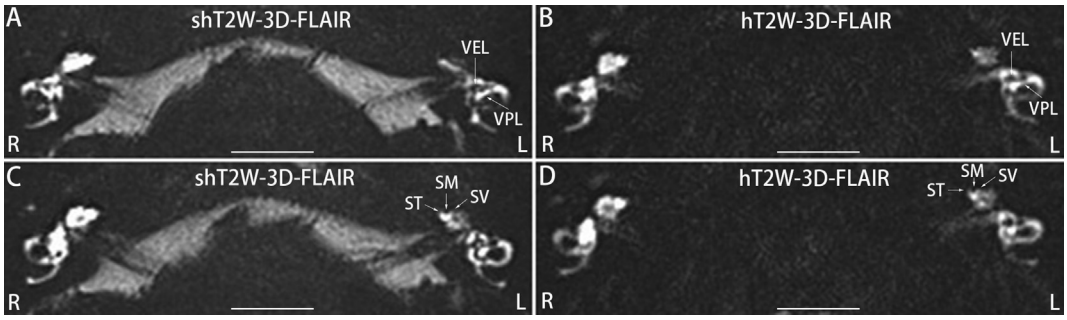

Fig. 6 Comparison of EH detection effect in gadolinium-enhanced MRI between MIIRMR and hT2W-FLAIR sequences with 60 slices per slab in the same patient. MRI was measured 24 h after targeted delivery of Gd-DTPA onto the posterior upper part of tympanic medial wall in a patient with Meniere's disease (case B) on the left side. Significant EH in the vestibule (A) and marked EH in the cochlea (B) of the left ear are apparent. Although the applied Gd-DTPA dose is extremely small, the MR signal intensity that could be achieved was clearly higher compared to intravenous GdC application. The borders between the enhanced perilymphatic compartments and surrounding structures were sharper imaged using MIIRMR sequence (A, C) than did that using hT2W-FLAIR sequence (B, D). VEL: vestibular endolymph; VPL: vestibular perilymph, SM: scala media; ST: scala tympani; SV: scala vestibuli. Scale bar = 16 mm.

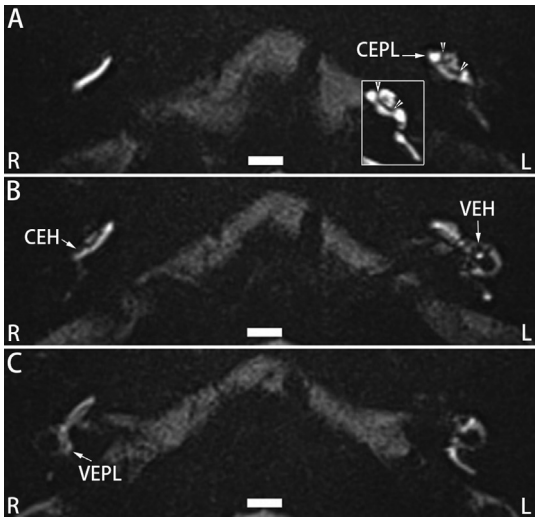

Fig. 7 Speculative endolymph-perilymph leakage and EH detected in a definite MD patient using MIIRMR sequence. Cochlear endolymph-perilymph leakage (CEPL) was suspected in the left ear in which Gd-DTPA appeared in all scalae. The dark area represents the bony separate between the basal and second turns (arrowheads) that was confirmed in SPACE image (window) (A). Marked vestibular EH (the ratio of the area of the endolymphatic space to that of the fluid space in the vestibule = 63.4%) in the left ear and extreme cochlear EH (a straight line appearance of the perilymph) in the right ear were detected (B). A vestibular endolymph-perilymph leakage (VEPL) was supposed in the right ear where the endolymphatic area showed enhancement and Gd-DTPA update was less efficient than that in the left ear (C). L: left ear; R: right ear. Scale bars = 8.0 mm.

method, both the concentration and the volume of GdC delivered to the middle ear were the smallest and the imaging time was the shortest among all those described in previous literature reports.[4,9,26] This has important practical implications, since it is generally advisable to use the smallest possible dosage of GdC, although clinical studies using a 1:8 dilution have not shown any clinically significant ototoxicity.[27–29] The suspected cochlear endolymph-perilymph leakage in the left ear and extreme cochlear EH in the right ear coordinated with the degree of hearing loss indicating that the EH had higher impact on hearing function than did the endolymph-perilymph leakage (Figs. 3 and 7). Since the MRI was performed 24 h after delivery of Gd-DTPA, the suspected leakage might result from inflammation in the labyrinth rather than a rupture of the Reissners' membrane that induced immediate entry of GdC into the endolymph.[2,30]

To conclude, targeted delivery of minimum Gd-DTPA (0.1 ml, 20-fold dilution) onto the posterior portion of the tympanic medial wall and MRI using MIIRMR in a 3T machine is clinically practical to obtain high quality images displaying EH in 8 min and reduced the requirement for MRI hardware.

Table 1 Endolymphatic hydrops in Meniere's disease detected using MIIRMR and a 20-channel coil after targeted gadolinium delivery.

Items	No[b]	percentage
No EH	2	5.4%
Unilateral EH	9	24.3%
Bilateral EH	26	70.3%
1 site EH[a]	6	16.2%
2 sites EH[a]	14	37.8%
3 sites EH[a]	8	21.6%
4 sites EH[a]	5	13.5%

[a] 1 site was counted when either cochlear or vestibular endolymphatic hydrops appear any ear, 4 sites were counted when both cochlear and vestibular endolymphatic hydrops appeared in both ears.
[b] a total of 37 cases with definite Meniere's disease were counted.

Table 2 Cochlear endolymphatic hydrops in Meniere's disease detected using MIIRMR and a 20-channel coil after targeted gadolinium delivery.

Extent of EH	No[b]	percentage
No EH	15	40.5%
Mild EH	2	5.4%
Marked EH	9	24.3%
Extreme EH[a]	11	29.7%
Total	37	100.0%

[a] Three cases had suspected endolymph-perilymph leakage; one had leakage in one cochlea and extreme EH in another cochlea; one had leakage and perilymphatic fibrosis in one cochlea and extreme EH in another cochlea; one had only leakage in one cochlea.
[b] A total of 37 cases with definite Meniere's disease were counted.

Table 3 Vestibular endolymphatic hydrops in Meniere's disease detected using MIIRMR and a 20-channel coil after targeted gadolinium delivery.

Extent of EH	No[b]	percentage
No EH	5	13.5%
Mild EH	8	21.6%
Marked EH[a]	24	64.9%
Total	37	100.0%

[a] Three cases with insufficient uptake of Gd in the vestibule were counted as marked EH; four cases were suspected to have endolymph-perilymph leakage accompanying marked EH in the other ear, among them one had only unilateral leakage without EH in the other ear; one case had the leakage and perilymphatic fibrosis.
[b] A total of 37 cases with definite Meniere's disease were counted.

Declaration of Competing Interest

There were no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, the work.

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