MAJOR PAPER

Signal Alteration of the Cochlear Perilymph on 3 Different Sequences after Intratympanic Gd-DTPA Administration at 3 Tesla: Comparison of 3D-FLAIR, 3D-T₁-weighted Imaging, and 3D-CISS

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Purpose: Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging after intratympanic gadolinium injection is useful for pathophysiologic and morphologic analysis of the inner ear. However, statistical analysis of differences in inner ear signal intensity among 3D-FLAIR and other sequences has not been reported. We evaluated the signal intensity of cochlear fluid on each of 3D-FLAIR, 3D-T₁-weighted imaging (T₁WI), and 3D-constructive interference in the steady state (CISS) to clarify the differences in contrast effect among these 3 sequences using intratympanic gadolinium injection.

Methods: Twenty-one patients underwent 3D-FLAIR, 3D-T₁WI, and 3D-CISS imaging at 3 tesla 24 hours after intratympanic injection of gadolinium. We determined regions of interest of the cochleae (C) and medulla oblongata (M) on each image, evaluated the signal intensity ratio between C and M (CM ratio), and determined the ratio of cochlear signal intensity of the injected side to that of the non-injected side (contrast value).

Results: The CM ratio of the injected side (3.00 ± 1.31 , range, 0.53 to 4.88, on 3D-FLAIR; 0.83 ± 0.30 , range, 0.36 to 1.58 on 3D-T₁WI) was significantly higher than that of the non-injected side (0.52 ± 0.14 , range, 0.30 to 0.76 on 3D-FLAIR; 0.49 ± 0.11 , range, 0.30 to 0.71 on 3D-T₁WI) on 3D-FLAIR and 3D-T₁WI ($P < 0.001$), although no significant difference was observed on 3D-CISS (10.03 ± 2.19 , range, 5.19 to 14.98, on the injected side; 9.52 ± 1.63 range, 7.48 to 13.48, on the non-injected side) ($P = 0.11$). The mean contrast value on 3D-FLAIR (5.93 ± 2.57 , range, 1.22 to 11.05) was significantly higher than that on 3D-T₁WI (1.73 ± 0.60 , range, 0.98 to 3.09) ($P < 0.001$).

Conclusion: The 3D-FLAIR sequence is the most sensitive for observing alteration in inner ear fluid signal after intratympanic gadolinium injection. Our results warrant use of 3D-FLAIR as a sensitive imaging technique to clarify the pathological and morphological mechanisms of disorders of the inner ear.

Keywords: *cochlea, FLAIR, high resolution, intratympanic gadolinium injection, magnetic resonance imaging*

Introduction

Fluid-attenuated inversion recovery (FLAIR) imaging is a sensitive technique for detecting fluid or tissue with high protein content, such as cerebrospinal fluid (CSF) and various cystic intracranial mass lesions.^{1,2} Three-dimensional FLAIR (3D-FLAIR) imaging can minimize the undesired ghosts of CSF³ and enable recognition of subtle compositional

changes in lymph fluid in the inner ear.^{4–6} Increased permeability of the blood-labyrinthine barrier can also be observed on 3D-FLAIR imaging after intravenous gadolinium injection, a technique reported useful for pathophysiologic analysis of the inner ear in many auditory diseases, such as sudden sensorineural hearing loss, cholesteatoma, cochlear otosclerosis, and vestibular schwannoma.^{7–10} Furthermore, 3D-FLAIR imaging of the inner ear after intratympanic gadolinium injection as well as before and after intravenous gadolinium injection has been reported to permit separate visualization of

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perilymph and endolymph fluid and enable preliminary prediction of distribution of drugs, such as gentamicin and steroids, to the inner ear.^{11–16} Those reports, using 3D-FLAIR to investigate the condition of inner ear fluid, indicated that the alteration in signal of the inner ear was easier to recognize on 3D-FLAIR imaging than 3D-T₁-weighted imaging (3D-T₁WI). Therefore, 3D-FLAIR is apparently better suited than 3D-T₁WI to investigate the composition of inner ear fluid, although a statistical analysis of differences in signal intensity in the inner ear between 3D-FLAIR and 3D-T₁WI has not been reported.

We evaluated the signal intensity of cochlear fluid on both 3D-FLAIR and 3D-T₁WI and attempted to clarify the differences in contrast effect between these 2 sequences using intratympanic gadolinium injection. We also determined the alteration in cochlear signal on 3D-constructive interference in the steady state (3D-CISS) because this technique is used to obtain reference images of labyrinthine fluid space anatomy, reflects liquid T₂/T₁ contrast,¹⁷ and is useful for predicting prognosis in patients with vestibular schwannoma.¹⁸

Materials and Methods

Study population

Twenty-one patients (7 men, 14 women; aged 16 to 80 years, mean age 48.0 years), 15 with clinically diagnosed Ménière's disease, two with low-tone sensorineural hearing loss, two with sudden sensorineural hearing loss, one with intracochlear acoustic schwannoma (middle turn), and one with delayed endolymphatic hydrops,^{19,20} received unilateral intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid (Gd-DTPA; Magnevist, Bayer Yakuhin, Ltd., Osaka, Japan). The patient with intracochlear acoustic schwannoma was assessed for tumor extent and detailed evaluation of vertigo. Other patients were evaluated for endolymphatic hydrops and underwent simulated intratympanic injection therapy with gentamicin to control severe vertigo or with steroids to treat sensorineural hearing loss.^{21–24} We obtained written informed consent from all patients and study approval from the Ethics Review Committee of our institution (approval numbers 369, 369–2).

Intratympanic gadolinium injection

Intratympanic injection of gadolinium was performed as reported previously¹¹ in a study that indicated a delay of 24 hours between intratympanic gadolinium injection and MR imaging to be optimal to allow wide gadolinium distribution in the

perilymphatic space of the labyrinth.

Briefly, Gd-DTPA (500 mmol/L) was diluted 8 fold with saline (v/v 1:7) and injected intratympanically using a 23-gauge needle and a 1-mL syringe after the patient was placed in the supine position with head turned approximately 30° away from the sagittal line toward the healthy ear. The diluted Gd-DTPA was injected until a backflow of fluid into the external ear was observed through a microscope, resulting in an injected volume of 0.4 to 0.5 mL per patient. After the injection, the patient remained in the supine position for 60 min with head turned approximately 60° away from the sagittal line toward the healthy ear. Gentamicin or steroids were not injected at the same time as Gd-DTPA.

MR imaging protocol

All scans were performed on a 3-tesla MR imaging scanner (Magnetom Trio; Siemens AG, Erlangen, Germany) using a receive-only, 32-channel phased-array coil. Patients underwent T₁-weighted 3D-volumetric interpolated breath-hold examination (VIBE) and 3D-FLAIR imaging 24 hours after intratympanic injection of diluted Gd-DTPA. In addition, 3D-CISS imaging was performed to obtain reference images of the labyrinthine fluid space anatomy.

Parameters for 3D-VIBE were: repetition time (TR), 7.7 ms; echo time (TE), 3.3 ms; flip angle, 10° with radio frequency spoiling; matrix size, 256 × 256; 96 axial, 0.8-mm-thick sections covering the posterior fossa with field of view (FOV), 160 mm × 160 mm; voxel size, 0.6 mm × 0.6 mm × 0.8 mm; number of excitations (NEX), 2; and total scan time, 3 min 49 s with readout bandwidth, 490 Hz/pixel.

Parameters for 3D-FLAIR were: TR, 9000 ms; effective TE, 458; inversion time (TI), 2500 ms; variable flip-angle echo train with average flip angle, 120°; echo train length, 119; matrix size, 256 × 256; 48 axial, 0.8-mm-thick slices covering the labyrinth with 180- × 150-mm FOV; generalized autocalibrating partially parallel acquisition (GRAPPA); acceleration factor, 2; and voxel size, 0.7 mm × 0.7 mm × 0.8 mm; NEX, 2; scan time, 5 min 26 s; readout bandwidth, 592 Hz/pixel; and echo spacing, 3.7 ms.

Parameters for 3D-CISS were: TR, 6.4 ms; TE, 3.2 ms; flip angle, 50°; matrix size, 256 × 256; 128 axial, 0.4-mm-thick sections; FOV, 140 mm × 140 mm; voxel size, 0.5 mm × 0.5 mm × 0.4 mm; NEX, 1; scan time, 5 min 8 s; and readout bandwidth, 543 Hz/pixel.

MR imaging evaluation and statistical analysis

We analyzed images on a picture archiving and communication system (PACS) workstation (Rapideye Station; Toshiba Medical Systems Corporation, Otawara, Japan) (Fig. 1) with location information corresponding among the different sequences. For each patient, we determined circular 0.6-mm² regions of interest (ROI) of both cochleae and circular 50-mm² ROIs of the medulla oblongata on 3D-CISS images at a workstation. On each cochlea, we set the ROI on the scala tympani of the basal turn because the gadolinium agent injected into the tympanic cavity distributes into the perilymph space of the scala tympani through the round window initially,¹¹ and elevation of the cochlear signal is most easily observed at this position 24 hours after intratympanic gadolinium injection. ROIs were also determined on the 3D-T₁WI and 3D-FLAIR images by referring to the 3D-CISS im-

ages. Because cochlear signal intensity of the non-injected side on the 3D-T₁WI and 3D-FLAIR images was very faint and had ill-defined borders, ROIs were initially determined on 3D-CISS images and then copied onto identical slices of 3D-T₁WI and 3D-FLAIR images. To assure the reliability of the signal intensity measured in the small ROI of the cochlea, we determined the ROIs of both cochleae twice for each patient on different days and averaged the signal intensities of the 2 measurements for analysis. We evaluated the ratio of the signal intensity of each cochlea to that of the medulla oblongata (CM ratio) and the ratio of the cochlear signal intensity of the injected side to that of the non-injected side (contrast value). In calculating the CM ratio, we selected the medulla oblongata for reference to enable statistical comparison of the cochlear signal intensity of the injected and non-injected sides.¹⁰ We determined circular

Fig. 1. Three-dimensional constructive interference in the steady state (3D-CISS; **a, b, c**), 3D-T₁-weighted imaging (3D-T₁WI; **d, e, f**) and 3D-fluid-attenuated inversion recovery (3D-FLAIR; **g, h, i**) images at the level of the bilateral cochlear basal turns (**a, b, d, e, g, h**) and the medulla oblongata (**c, f, i**) of a 68-year-old man with Ménière's disease. Intratympanic gadolinium injection was administered into his left ear 24 hours prior to magnetic resonance (MR) scanning. We determined 0.6-mm² circular regions of interest (ROIs) of both cochleae on 3D-CISS at the scala tympani of each basal turn (**a, b**), then copied the ROIs onto identical slices of 3D-T₁WI (**d, e**) and 3D-FLAIR (**g, h**), which provided the ROIs for 3D-T₁WI and 3D-FLAIR. The 50-mm² circular ROIs of the medulla oblongata were similarly established (**c, f, i**).

ROIs of 50 mm² for both cerebellar hemispheres on cerebellar white matter at the identical slice of the basal turn of the cochlea on each sequence to estimate the uniformity of the magnetic field and evaluated the ratio of the signal intensity of each region of cerebellar white matter to that of the medulla oblongata (WM ratio). One radiologist (M.Y.) with knowledge of prior intratympanic gadolinium injection performed these measurements. Blinded measuring of signal was not feasible in the present study. We used paired *t*-test to compare the differences in CM ratio between the injected and non-injected sides, WM ratio between the right and left, and contrast value between 3D-T₁WI and 3D-FLAIR. $P < 0.05$ represented statistical significance.

Results

No image of any patient showed severe body motion during examination or visible abnormality of the medulla oblongata and mastoid air cells. WM ratios between the right and left sides were not sig-

nificantly different. On 3D-FLAIR, the mean WM ratio for the right side was 1.11 ± 0.13 (range, 0.91 to 1.42), whereas that for the left was 1.10 ± 0.14 (range, 0.84 to 1.40) ($P = 0.39$); on 3D-T₁WI, the mean WM ratio for the right side was 1.15 ± 0.09 (range, 0.99 to 1.41), and that for the left was 1.16 ± 0.10 (range, 0.99 to 1.32) ($P = 0.76$); and on 3D-CISS, the mean WM ratio for the right side was 1.01 ± 0.11 (range, 0.79 to 1.20), and that for left side was 1.04 ± 0.12 (range, 0.72 to 1.26) ($P = 0.96$).

Figure 2 shows the CM ratios for both the gadolinium-injected and non-injected sides on each sequence. On 3D-FLAIR, the mean CM ratio for the gadolinium-injected side was 3.00 ± 1.31 (range, 0.53 to 4.88), and that for the non-injected side was 0.52 ± 0.14 (range, 0.30 to 0.76) ($P < 0.001$); on 3D-T₁WI, the mean CM ratio for the injected side was 0.83 ± 0.30 (range, 0.36 to 1.58), and that for the non-injected side was 0.49 ± 0.11 (range, 0.30 to 0.71) ($P < 0.001$); and on 3D-CISS, the CM ratio between the injected side (mean CM ratio, $10.03 \pm$

Fig. 2. Signal intensity ratios between the cochleae (C) and medulla oblongata (M) (CM ratio) for both the gadolinium-injected (diamond) and non-injected sides (triangle) on 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR), 3D-T₁-weighted imaging (3D-T₁WI), and 3D-constructive interference in the steady state (3D-CISS) ($n = 21$). On 3D-FLAIR, the mean CM ratio for the gadolinium-injected side was 3.00 ± 1.31 (range, 0.53 to 4.88), and that for the non-injected side was 0.52 ± 0.14 (range, 0.30 to 0.76) ($P < 0.001$). On 3D-T₁WI, the mean CM ratio for the injected side was 0.83 ± 0.30 (range, 0.36 to 1.58), and that for the non-injected side was 0.49 ± 0.11 (range, 0.30 to 0.71) ($P < 0.001$). On 3D-CISS, there was no significant difference in CM ratio between the injected side (mean CM ratio, 10.03 ± 2.19 ; range, 5.19 to 14.98) and the non-injected side (mean CM ratio, 9.52 ± 1.63 , range, 7.48 to 13.48) ($P = 0.11$).

Fig. 3. The contrast values on 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR), 3D-T₁-weighted imaging (3D-T₁WI), and 3D-constructive interference in the steady state (3D-CISS) (n = 21). The mean contrast value on 3D-FLAIR was 5.93 ± 2.57 (range, 1.22 to 11.05); on 3D-T₁WI, 1.73 ± 0.60 (range, 0.98 to 3.09) ($P < 0.001$); and on 3D-CISS, 1.06 ± 0.20 (range, 0.63 to 1.37).

2.19; range, 5.19 to 14.98) and non-injected side (mean CM ratio, 9.52 ± 1.63 , range, 7.48 to 13.48) was not significantly different ($P = 0.11$). The mean contrast value on 3D-FLAIR was 5.93 ± 2.57 (range, 1.22–11.05), and that on 3D-T₁WI was 1.73 ± 0.60 (range, 0.98 to 3.09) ($P < 0.001$, Fig. 3). We observed no side effects related to intratympanic gadolinium injection.

Discussion

The CM ratio was significantly higher for the gadolinium-injected side than the non-injected side on both 3D-FLAIR and 3D-T₁WI, and the contrast value was significantly higher on 3D-FLAIR than on 3D-T₁WI. These findings statistically support previous reports of the superiority of 3D-FLAIR over 3D-T₁WI for observing alteration in cochlear signal after intratympanic gadolinium injection.^{11–16}

Contrast effect is reportedly higher on FLAIR than on T₁WI at a concentration below 0.7 mmol/L of extravasated gadolinium into CSF.^{25,26} In the present study, the contrast value was significantly higher on 3D-FLAIR than 3D-T₁WI, so the concentration of extravasated gadolinium into perilymph fluid 24 hours after intratympanic gadolinium injection is likely to fall below 0.7 mmol/L. On the other hand, in past studies of 3D-FLAIR imaging after intravenous gadolinium injection, most alterations in cochlear signal observed on 3D-FLAIR could not be detected on 3D-T₁WI.^{4–10} In those stud-

ies, contrast was determined within approximately 10 min after the administration of gadolinium. Because the concentration of extravasated gadolinium in the inner ear lymph fluid 10 min after intravenous gadolinium injection is most likely lower than that 24 hours after intratympanic injection, detection of signal alterations on 3D-T₁WI shortly after intravenous gadolinium injection would be difficult.

The gadolinium agent injected into the tympanic cavity distributes mainly into the perilymphatic space through the round window and barely enters the endolymphatic space.²⁷ Because 3D-FLAIR shows a higher contrast value than 3D-T₁WI, as demonstrated in the present study, 3D-FLAIR appears to be the more appropriate sequence for inner ear investigation after intratympanic gadolinium injection. From this viewpoint, its use in previous studies to observe the inner ear after intratympanic gadolinium injection is reasonable.^{11–16}

On the other hand, in clinical conditions with a strong T₁- and T₂-shortening effect, such as inner ear hemorrhage, 3D-FLAIR signal can decrease from signal-reducing T₂ effects that obscure signal-enhancing T₁ effects.^{25,26} Under such unforeseen conditions, the low intensity of the perilymph space on 3D-FLAIR after intratympanic gadolinium injection may lead to misconceptions of bad distribution of gadolinium or procedural complications. Thus, at the present time, to eliminate this unexpected condition, 3D-T₁WI cannot be removed

from the protocol for inner ear MR imaging after intratympanic gadolinium injection.

Because 3D-CISS reflects liquid T_2/T_1 contrast,¹⁷ a signal decrease in cochlear lymph fluid can occur after intratympanic gadolinium injection. However, our results indicate no significant difference in CM ratio between the injected and non-injected sides on 3D-CISS, suggesting that 3D-FLAIR might be more sensitive than 3D-CISS in detecting small amounts of gadolinium in fluid. Furthermore, because the signal alteration in 3D-CISS is represented as a decrease in signal intensity, it is difficult to completely avoid the influence of magnetic susceptibility artifacts.²⁸ Therefore, 3D-FLAIR is more suitable for observing alteration in inner ear fluid signal, although obtaining 3D-CISS images for morphological assessment of the inner ear after intratympanic gadolinium injection is still meaningful.

In the present study, we observed no side effects relating to intratympanic gadolinium injection. In animal study of intratympanic gadolinium injection, gadolinium diluted 8 fold with saline, the concentration of gadolinium used clinically, showed no remarkable effects on the stria vascularis.²⁹ In addition, intravenously administered gadolinium has been reported to infiltrate the inner ear perilymph³⁰ with no remarkable side effects in the inner ear related to such injection reported on clinical application. Therefore, clinical use of gadolinium agents for the inner ear seems safe, but future study requires continued vigilance regarding the small possibility of side effects.

Our study was limited because the measurement of signal intensity was semiquantitative, without use of external phantoms for reference; cochlear ROIs were small; and measurements were performed with knowledge of prior intratympanic gadolinium injection. However, measuring the signal in a blinded manner was not feasible in the present study, and we believe these limitations should not seriously affect the study results because we set ROIs accurately by referring to 0.4-mm-thick, high resolution 3D-CISS.

Conclusion

Our results suggest that the 3D-FLAIR sequence is most appropriate for observing alterations in inner ear fluid signal after intratympanic gadolinium injection and warrant use of 3D-FLAIR as a sensitive imaging technique to clarify the pathological and morphological mechanisms of inner ear disorders.

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