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Contrast Enhancement of the Anterior Eye Segment and Subarachnoid Space: Detection in the Normal State by Heavily T₂-weighted 3D FLAIR

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Purpose: Fluid-attenuated inversion recovery (FLAIR) has been reported more sensitive than T₁-weighted images in detecting low concentration gadolinium-based contrast media (GBCM) in fluid, and heavily T₂-weighted (hT₂W) 3-dimensional (3D) FLAIR has recently been reported even more sensitive than conventional 3D FLAIR. We investigated whether high signal of the anterior eye segment (AES) and subarachnoid space (SAS) in various locations as well as cerebrospinal fluid (CSF) in cisterns and ventricles can be detected on hT₂W 3D FLAIR images obtained 4 hours after intravenous administration of GBCM in subjects without eye and SAS diseases.

Methods: Ten patients suspected of having Ménière's disease underwent hT₂W 3D FLAIR 4 hours after intravenous administration of single-dose GBCM to evaluate endolymphatic hydrops. We evaluated signal intensity of AES, SAS surrounding the optic nerve, SAS in Meckel's cave, CSF in the internal auditory canal, CSF in the prepontine cistern, CSF in the lateral and fourth ventricles, and lymph fluid in the cochlea by comparison with non-contrast images obtained in a separate group of 5 patients. The signal intensity of each structure was normalized by that of the pontine parenchyma.

Results: We observed no signal difference in images of the pontine parenchyma obtained before and after enhancement. Significant signal difference was seen in all structures except the lateral and fourth ventricles.

Conclusion: Four hours after intravenous injection, GBCM can be detected by hT₂W 3D FLAIR in various fluid-containing spaces, such as the AES and various SAS and CSF spaces.

Keywords: *anterior eye segment, contrast enhancement, fluid-attenuated inversion recovery, magnetic resonance*

Introduction

Contrast enhancement of the anterior eye segment (AES) in healthy condition after intravenous (IV) administration of gadolinium-based contrast medium (GBCM) has been described using serially obtained T₁-weighted images and measurement of signal intensity. However, enhancement of the AES is visually very subtle even on delayed T₁-weighted images.¹ In an animal experiment using very high dose IV GBCM, enhancement of the AES on T₁-weighted images has been reported earlier in a model of chronic glaucoma than in controls.² En-

hancement of the subarachnoid space (SAS) and cerebrospinal fluid (CSF) in normal condition is also very subtle on T₁-weighted images.³ Prompt contrast enhancement of the CSF in the fundus of the internal auditory canal has been observed on 3D FLAIR in patients with meningeal pathologies.³

Enhancement of labyrinthine fluid in healthy subjects is reported using 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) obtained 4 hours after IV administration of GBCM but could not be observed on T₁-weighted images.⁴ In patients with Ménière's disease, either intratympanic⁵ or IV⁶ administration of GBCM using a 3D FLAIR sequence permitted visualization of the endolymphatic hydrops. Although 3D FLAIR is far more sensitive than T₁-weighted images to faint enhance-

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ment of the perilymph by low concentration gadolinium,⁷ in some patients, GBCM concentration is too low to be detected even by 3D FLAIR.⁸ Recently, heavily T₂-weighted (hT₂W) 3D FLAIR has been developed to improve sensitivity to slight fluid enhancement of extremely low concentration GBCM.⁸

We obtain hT₂W 3D FLAIR images 4 hours after IV administration of single-dose GBCM (IV GBCM) to detect enhancement of the perilymph fluid and thereby evaluate endolymphatic hydrops in patients with suspected Ménière's disease.^{8,9} The imaging slab volume also includes the eyes and ventricles. On these hT₂W 3D FLAIR images of a patient with Ménière's disease without disease of the eyes or SAS, we noticed areas of apparent high intensity in the AES, SAS surrounding the optic nerve and in Meckel's cave, CSF in cisterns and the internal auditory canal, and lymph fluid in the labyrinth.

We investigated whether we could detect enhancement of the AES, SAS in various locations, and CSF in cisterns and ventricles in subjects without disease of the eyes or SAS on hT₂W 3D FLAIR images obtained 4 hours after IV administration of GBCM.

Materials and Methods

To confirm contrast enhancement by IV GBCM, we needed to compare images obtained before and after IV administration of GBCM, but pre-contrast images were not included in the protocol because its main purpose was the visualization of endolymphatic hydrops on post-contrast images 4 hours after IV GBCM. All scans were performed on a 3-tesla magnetic resonance (MR) unit (Trio, a TIM system, Siemens AG Medical Solutions, Erlangen, Germany) using a 32-channel array head coil. Details of the hT₂W 3D FLAIR sequence have been detailed.⁸ In brief, this sequence utilizes the sampling perfection with application optimized contrasts using different flip-angle evolution (SPACE) technique with constant low flip-angle refocusing pulses in later echoes to obtain heavily T₂-weighted imaging of a 3D volume without significant blurring. This technique is highly sensitive to low concentrations of GBCM in fluid and enabled visualization of endolymphatic hydrops in patients with Ménière's disease after single-dose IV GBCM injection.⁹

To evaluate the endolymphatic space in 10 patients with suspected Ménière's disease (6 men, 4 women; aged 37 to 74 years, average, 60 years), we obtained hT₂W 3D FLAIR images 4 hours after

GBCM injection. These patients received single-dose (0.2 mL/kg body weight or 0.1 mmol/kg body weight) IV administration of gadodiamide (Gd-DTPA-BMA) (Omniscan™, Daiichi-Sankyo, Tokyo, Japan) and were not then restricted in their behavior before MR examination. As an anatomical reference, we also obtained heavily T₂-weighted MR cisternography. We did not obtain pre-contrast-enhanced images for these patients because our main purpose was to visualize endolymphatic hydrops on post-contrast images obtained 4 hours after IV GBCM rather than recognize effects of contrast enhancement in the AES and SAS.

As a baseline reference, we included 5 consecutive patients (2 men, 3 women; aged 37 to 77 years, average, 62 years) who underwent MR screening of the cerebellopontine (CP) angle without contrast enhancement to assess vertigo or unilateral sudden hearing loss. Two patients had vertigo with suspected Ménière's disease, and 3 patients had unilateral sudden hearing loss. Our routine CP-angle screening protocol includes both hT₂W 3D FLAIR and heavily T₂-weighted MR cisternography. The hT₂W 3D FLAIR was included to detect subtle compositional alterations of lymph fluid in the labyrinth. No patient had any abnormal finding on the routine CP-angle screening MR images.

No patient had history of eye disease, meningitis, or head surgery. All patients who received contrast administration had an estimated glomerular filtration rate (eGFR) value exceeding 60 mL/min/1.73 m², which we calculated using an equation recently reported by the Japanese Society of Nephrology for estimating GFR (eGFR) in Japanese patients based on serum creatinine level (Cr): $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times Cr^{-1.094} \times \text{Age}^{-0.287}$ (if female, $\times 0.739$).

Our institutional medical ethics committee approved this study, and written informed consent was waived because of the study's retrospective nature.

MR imaging protocol for patients

For anatomical reference of the total fluid space of the labyrinth and cistern, we obtained heavily T₂-weighted MR cisternography using fast-recovery 3D turbo-spin-echo (TSE)^{10,11} or constructive interference in the steady state (CISS).

We then obtained hT₂W 3D FLAIR using parameters: repetition time (TR), 9000 ms; echo time (TE), 540 ms; inversion time (TI), 2350 ms; fat-suppression by frequency-selective pre-pulse; initial re-focusing flip angle (FA), 180°, rapidly decreased to constant FA, 120°, for the TSE refocusing echo train in the SPACE sequence; echo

train length, 107; matrix size, 214×256 ; and 112 axial, 0.8-mm-thick slices covering the labyrinth with a 15×18 -cm field of view (FOV); GRAPPA parallel imaging technique; acceleration factor, 2;¹² number of excitations (NEX), 2; and scan time, 5.7 min.

Image analysis of patient data

We evaluated images both quantitatively and qualitatively as described below. Two neuroradiologists with 22 and 12 years' experience in inner-ear MR imaging performed qualitative analysis.

Qualitative analysis

Following a training session in which 2 neuro-radiologists reviewed the non-contrast-enhanced images of 5 patients, each neuroradiologist independently reviewed images and evaluated differences in signal intensity between non-contrast-enhanced images and enhanced images with regard to the AES, SAS surrounding the optic nerve (SON), SAS in Meckel's cave, CSF in the fundus of the internal auditory canal, lymph fluid in the cochlea, CSF in the lateral ventricle, CSF in the prepontine cistern, CSF in the fourth ventricle, and the pontine parenchyma. They graded difference in signal intensity of each structure as positive or negative. The 2 reviewers resolved any discrepancies by consensus after discussion.

Quantitative analysis

We measured the signal of the AES, SAS space surrounding the optic nerve, SAS in Meckel's cave, lymph fluid in the cochlea, CSF in the fundus of the internal auditory canal, and CSF in the lateral ventricle by drawing a circular region of interest (ROI) of one-mm diameter for both the right and left structures. We also measured the signal of CSF in the prepontine cistern, fourth ventricle, and pontine parenchyma using ROIs of 2 mm for CSF and 5 mm for the pontine parenchyma. We calculated the signal intensity ratio (SIR) to normalize the signal of each structure, defining SIR as the signal of a given structure divided by the signal of the pontine parenchyma. The feasibility of using SIR is reported.¹³ We compared average SIR values of pre- and post-contrast images using Mann-Whitney's U test.

Results

Qualitative analysis

In all cases, the pontine parenchyma, lateral ventricle, fourth ventricle, prepontine cistern, cochlea, internal auditory canal, AES, SON, and Meckel's cave showed low signal intensity resembling that of

cerebellar white matter and the vitreous body on non-contrast hT_2W 3D FLAIR images (Fig. 1). On post-contrast-enhanced images, visually apparent signal difference was positive in the bilateral AES, SON, Meckel's cave, internal auditory canal, and cochlea in all patients (Fig. 2). Signal difference was faintly positive in the prepontine cistern in all patients but one. Visual signal difference was negative in the pontine parenchyma, fourth ventricle and lateral ventricle in all patients. The 2 radiologists agreed regarding the presence of signal difference without discussion.

Quantitative analysis

The average SIRs of the AES, SON, Meckel's cave, internal auditory canal, cochlea, and prepontine cistern were significantly higher after contrast enhancement ($P < 0.01$). No significant change in SIR was observed in the lateral or fourth ventricle or pontine parenchyma. Table shows the average SIR results.

Discussion

Enhancement of the anterior eye segment,¹⁴ subarachnoid space, and cerebrospinal fluid in ventricles and cisterns has been reported in various pathological states.¹⁵⁻¹⁷ In the normal state, enhancement of the AES, SAS and CSF was not demonstrated on routine T_1 -weighted images and FLAIR images, which are usually obtained no more than 30 min after IV GBCM. On delayed T_1 -weighted images, even in the normal state, AES enhancement has been reported, although it was visually very weak.¹ Peak enhancement in the AES of healthy subjects occurred 74 min after IV GBCM. Following IV GBCM, the signal intensity first rises rapidly in the ciliary body, then the angle of AES, and finally, the center of the AES.¹ This supports the existence of a diffusional pathway of the blood-aqueous barrier from the ciliary body stroma into the AES via the root of the iris.¹ The blood-aqueous barrier has been investigated in healthy subjects using fluorescein.¹⁸ Investigation of the blood-aqueous barrier using fluorescein in healthy subjects demonstrated approximately 7 times higher permeation in the anterior chamber than the peripheral body compartment.¹⁸ Therefore, detection of high signal in the AES after IV GBCM is reasonable, when a sensitive pulse sequence, such as hT_2W 3D FLAIR, is applied.

The use of IV GBCM and hT_2W 3D FLAIR has potential clinical applications. In the present study, we could detect the visually distinct high signal of the AES and SAS of the optic nerve sheath on

Fig. 1. A 75-year-old woman with vertigo. Non-contrast-enhanced cerebellopontine angle magnetic resonance (MR) imaging was performed for screening. **(a)** Heavily T₂-weighted (hT₂W) 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) image at mid-eye level. No high signal is seen in the anterior eye segment (AES, arrows) or in subarachnoid space surrounding the optic nerve (SON, short arrows). **(b)** An hT₂W 3D FLAIR image at the level of Meckel's cave. No high signal is seen in Meckel's cave (arrows) or the preoptine cistern (short arrows). **(c)** An hT₂W 3D FLAIR image at the level of the internal auditory canal (left side is enlarged). No high signal is seen in the internal auditory canal (short arrow) or cochlea (arrow). **(d)** Corresponding magnetic resonance (MR) cisternographic image of c scanned with a constructive interference in the steady state (CISS) sequence.

hT₂W 3D FLAIR obtained 4 hours after IV GBCM in subjects without eye disease. Shortening the delay time from 4 hours might permit visualization of the difference between healthy and pathological conditions, such as glaucoma, optic neuritis, and others.

We also observed higher signal in the lateral side of the internal auditory canal than in the medial side near the preoptine cistern on these images (Fig. 2). Previous microanatomical study revealed no such compartment in the lateral side of internal auditory canal.¹⁹ We observed high signal as well in Meckel's cave on post-contrast-enhanced images. It can be speculated that GBCM might have emerged from the internal auditory canal and Meckel's cave into the preoptine cistern. GBCM might leak from the peripheral part of a cranial nerve, such as the op-

tic, trigeminal, facial, or vestibulocochlear nerve. Use of hT₂W 3D FLAIR and IV GBCM with some delay might aid evaluation of various cranial nerve conditions.

Our study has some limitations. We evaluated the signal of CSF in the preoptine cistern and fourth ventricle and may have underestimated its contrast enhancement. Three-dimensional acquisition with wide slab for hT₂W 3D FLAIR is thought to have far less in-flow effect than 2-dimensional thin-slice acquisition.²⁰ However, the SPACE sequence we employed for hT₂W 3D FLAIR tends to suppress the signal of flowing spins.²¹ The SPACE sequence utilizing low variable flip angle pulses in the echo train has increased sensitivity to the intravoxel dephasing of flowing spins as a result of increased magnetization in the stimulated echo path-

Fig. 2. A 61-year-old-woman with suspected right-side Meniere's disease. Images were obtained 4 hours after single-dose intravenous administration of gadolinium-based contrast medium. (a) Heavily T₂-weighted (hT₂W) 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) image at mid-eye level. High signal is seen in the anterior eye segment (AES, arrows) and subarachnoid space surrounding the optic nerve (SON, short arrows). (b) An hT₂W 3D FLAIR image at the level of Meckel's cave. High signal is seen in Meckel's cave (arrows) and slightly high signal in the prepontine cistern (short arrows). (c) An hT₂W 3D FLAIR image at the level of the internal auditory canal (left side is enlarged). High signal is seen in the lateral part of the internal auditory canal (short arrow) and in the cochlea (arrow). (d) Corresponding magnetic resonance (MR) cisternographic image of c scanned with a 3D turbo-spin-echo sequence.

Table. Mean signal intensity ratio (SIR) against the pontine parenchyma

	noncontrast (n = 5)	SD	post-contrast (n = 10)	SD	P value
AES (left + right)	0.8	0.4	12.4	4.3	<0.01
ONS (left + right)	0.9	0.3	17.8	6.5	<0.01
cochlea (left + right)	1.7	0.6	12.4	3.4	<0.01
internal auditory canal (left + right)	0.9	0.3	14.2	4.3	<0.01
Meckel's cave (left + right)	0.9	0.3	11.9	5.4	<0.01
prepontine cistern	1	0.3	3.4	1	<0.01
lateral ventricle (left + right)	0.9	0.3	0.9	0.2	n.s.
fourth ventricle	1	0.3	1.9	1.7	n.s.

AES, anterior eye segment; ONS, optic nerve sheath subarachnoid space; SD, standard deviation; n.s., not significant

way.²²

Neither did we directly compare pre- and post-contrast-enhanced images in the same subjects. For baseline reference, we used 2 patients with vertigo and 3 patients with sudden hearing loss, and the 2 patients with vertigo also had suspected Ménière's disease. Therefore, it is quite possible that pre-contrast hT₂W 3D FLAIR findings of our patients with Ménière's disease who received IV GBCM are similar to those of the baseline reference cases. In addition, standard deviation values of the SIR of each structure on pre-contrast images were as small as 0.3–0.6.

Furthermore, we obtained post-contrast scans only at 4 hours after IV GBCM. Additional pre- and post-contrast-enhanced studies in healthy volunteers using more scan time points are needed to increase the significance of our results.

Conclusions

GBCM enhances AES and various SAS and CSF spaces on hT₂W 3D FLAIR 4 hours after IV administration in patients with suspected Ménière's disease. Knowledge obtained in the present study warrants further prospective investigation of the permeability of AES and various SAS and CSF spaces in healthy subjects and thereafter in patients with otolaryngologic or cranial nerve pathologies.

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