MAJOR PAPER

Serial Scans in Healthy Volunteers Following Intravenous Administration of Gadoteridol: Time Course of Contrast Enhancement in Various Cranial Fluid Spaces

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(Received June 4, 2013; Accepted July 17, 2013; published online January 31, 2014)

Purpose: Heavily T₂-weighted, 3-dimensional, fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) imaging has been reported to detect low concentrations of gadolinium-based contrast media (GBCM) in the anterior eye segment (AES), subarachnoid space (SAS), and labyrinthine perilymph as well as in the cerebrospinal fluid (CSF) of the internal auditory canal (IAC) 4 hours after intravenous administration of a single dose (IV-SD-GBCM) in patients with inner ear disorders. To elucidate the time course of contrast enhancement in healthy volunteers, we obtained hT₂W-3D-FLAIR serially after IV-SD-GBCM.

Materials and Methods: We obtained hT₂W-3D-FLAIR before and 0.5, 1.5, 3, 4.5 and 6 hours after IV-SD-GBCM in 6 healthy volunteers and measured signal intensity of the AES, SAS surrounding the optic nerve (SAS-ON), SAS in Meckel's cave (SAS-MC), pontine parenchyma, CSF in the IAC (CSF-IAC), CSF in the ambient cistern (CSF-AC), CSF in the lateral ventricles (CSF-LV), perilymph (PL), and endolymph (EL) in the labyrinth. We then compared averaged values among all time points using analysis of variance (ANOVA).

Results: After IV-SD-GBCM, we observed no change in signal intensity in the pontine parenchyma, CSF-LV, or EL and significant enhancement in all other structures. Maximum enhancement was most frequent at 4.5 hours after IV-SD-GBCM in the SAS-ON and PL, at 1.5 hours in the AES and SAS-MC, and at 3 hours in the CSF-IAC and CSF-AC.

Conclusions: Contrast enhancement can be detected by hT₂W-3D-FLAIR in the AES, SAS-ON, SAS-MC, PL, CSF-IAC, and CSF-AC in healthy volunteers after IV-SD-GBCM. Timing of maximum enhancement differed among locations. These data might serve as basic knowledge for future clinical research.

Keywords: *advanced imaging techniques, anterior eye segment, magnetic resonance imaging, 3D imaging*

Introduction

Low concentrations of gadolinium-based contrast media (GBCM) have been detected using 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) imaging,^{1–3} and further sensitivity to low concentrations is reported using heavily T₂-weighted 3D-FLAIR.^{4–6} We previously described⁶ contrast enhancement of the anterior eye segment (AES), subarachnoid space (SAS) surrounding the optic nerve (ON), cerebrospinal fluid (CSF) in the internal auditory canal

(IAC), and the labyrinthine perilymph (PL) 4 hours after intravenous administration of a single dose of gadolinium-based contrast medium (IV-SD-GBCM) using heavily T₂-weighted (hT₂W) 3D-FLAIR. However, that study was limited because subjects were patients with inner ear symptoms and did not include healthy volunteers, scanning was acquired at only a single time point approximately 4 hours after IV-SD-GBCM, and the precontrast data for reference were obtained in a different patient group. In another study³ in volunteers that evaluated enhancement of only the labyrinthine fluid in serial scans before and at 2, 4, and 6 hours after IV-SD-GBCM using a conventional 3D-FLAIR sequence, we reported maximum enhancement

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of the fluid 4 hours after IV-SD-GBCM.³ However, that study did not separately evaluate the perilymph and endolymph.

Intratympanic⁷ or intravenous⁵ administration of GBCM using 3D-FLAIR and hT₂W-3D-FLAIR sequences has permitted visualization of endolymphatic hydrops in patients with Ménière's disease. Based on the previous study,³ the waiting time after IV-SD-GBCM has been determined to be 4 hours. However, the time course of enhancement of the perilymph versus that of the endolymph has not been investigated separately in healthy volunteers.

The time course of enhancement of the AES, SAS-ON, SAS of Meckel's cave (MC), CSF in the ambient cistern (AC), CSF in the lateral ventricle (LV), CSF in the IAC, perilymph (PL), and endolymph (EL) has not been evaluated using hT₂W-3D-FLAIR in healthy volunteers.

The purpose of this study was to evaluate the time course of enhancement after IV-SD-GBCM of the AES, SAS-ON, SAS-MC, CSF-AC, CSF-IAC, CSF-LV, EL, and PL of the labyrinth on hT₂W-3D-FLAIR in healthy volunteers and report the basic data for future clinical studies.

Materials and Methods

The medical ethics committee of our institution approved this study of healthy volunteers, and we obtained written informed consent from all participants. Subjects were 6 healthy male volunteers (aged 30 to 53 years, median 37 years) with no history of hearing loss, vertigo attack, cranial disease, head trauma, renal disease, or heart disease who took no daily medications.

All magnetic resonance (MR) imaging was performed on a 3-tesla scanner (Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil. All volunteers underwent heavily T₂-weighted MR cisternography (MRC) for anatomical reference of the fluid space and hT₂W-3D-FLAIR with inversion time of 2250 ms according to the clinical protocol of our hospital to evaluate endolymphatic hydrops. Parameters were set as previously reported.^{8,9} Detailed scan parameters for MRC were: variable flip angle 3D-turbo spin-echo (SPACE: sampling perfection with application-optimized contrasts by using different flip angle evolutions): repetition time (TR), 4400 ms; echo time (TE), 544 ms; initial refocusing flip angle of 180° rapidly decreased to a constant 120° for turbo spin-echo refocusing echo train; echo train length, 173 with restore magnetization pulse (fast recovery pulse); matrix size, 322 × 384; 104 axial slices of 1.0-mm thickness; field of view (FOV), 15 × 18 cm; generalized autocalibrating partially parallel acquisition

(GRAPPA) imaging technique; acceleration factor, 2; number of excitations (NEX), 1.8; and scan time, 3 min.

We used similar scan parameters to those of MRC for hT₂W-3D-FLAIR imaging but applied an inversion pulse with inversion time, 2250 ms; TR, 9000 ms; NEX, 2; and scan time, 7 min. The hT₂W-3D-FLAIR did not utilize a restore pulse.

MRC and hT₂W-3D-FLAIR employed identical FOV, matrix size, and slice thickness to facilitate comparisons. We obtained sets of MRC and hT₂W-3D-FLAIR images before and 0.5, 1.5, 3, 4.5 and 6 hours after IV-SD-GBCM. After the pre-contrast scan, subjects received a single-dose (0.2 mL/kg body weight or 0.1 mmol/kg body weight) intravenous administration of gadoteridol (Gd-HP-DO3A: ProHance, Eisai, Tokyo, Japan) and were permitted to exit the magnet room and rest during the interval of the MR scans without restricted behavior.

Image analysis

A neuroradiologist with 24 years' experience in the field of clinical MR imaging quantitatively evaluated images. Signal intensities in the AES, SAS-ON, SAS-MC, pontine parenchyma (PON), CSF-IAC, CSF-AC, CSF-LV, cochlear perilymph (Co-PL), vestibular perilymph (V-PL), and vestibular endolymph (EL) in the labyrinth were measured with reference to MRC images. We compared the averaged values of the 6 volunteers at each time point using one-factor analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. For all statistical analyses, we adopted 5% as the level of statistical significance.

Signal intensities were measured in a circular region of interest (ROI) of one-mm diameter drawn for both the right and left structures in the AES, SAS-ON, SAS-MC, CSF-IAC, CSF-AC, Co-PL, V-PL, EL, and CSF-LV and in a circular ROI of 3-mm diameter in the PON placed in the center of the pons at the slice level of the IAC. The ROI for the EL was placed in the vestibular EL according to the hT₂W-3D-FLAIR obtained 4.5 hours after IV-SD-GBCM and was copied onto the MRC. The position of the ROI for the vestibular EL of the other time points was manually placed on the hT₂W-3D-FLAIR with reference to the MRC obtained at each time point. The ROI for the V-PL was placed anterior to the vestibular EL with reference to the MRC. The signal intensity of the Co-PL was measured by setting the ROI in the anterior part of the scala tympani in the basal turn of the cochlea with reference to the MRC. Other ROIs were placed in the AES at its center anterior to the lens, the SAS-ON just posterior to the globe, the fluid area of the SAS-MC excluding the trigeminal nerve bundles, the CSF-IAC in the triangular space surrounded by the IAC fundus, cochlear

Fig. 1. A 36-year-old male volunteer. Images of magnetic resonance (MR) cisternography and serially acquired heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery (hT₂W-3D-FLAIR) are presented. **(a)** Images at the level of the anterior eye segment (AES) and subarachnoid space around the optic nerve (SAS-ON). Fluid in the right AES (long arrows) shows low signal on hT₂W-3D-FLAIR images prior to and 0.5 hours after intravenous administration of a single dose of gadolinium-based contrast medium (IV-SD-GBCM). Enhancement of the AES is most intense 3 hours after IV-SD-GBCM. The subarachnoid space surrounding the right optic nerve (SAS-ON, short arrows) shows low signal on the hT₂W-3D-FLAIR images prior to and 0.5 hours after IV-SD-GBCM. Enhancement of the SAS-ON is most intense 4.5 hours after IV-SD-GBCM in this subject. **(b)** Images at the level of the cerebrospinal fluid (CSF) of the ambient cistern (CSF-AC). The signal of the CSF-AC (arrows) is enhanced after 1.5 hours. Visually, this enhancement is faint, but a significant increase in signal intensity is observed quantitatively for the CSF-AC.

nerve, and inferior vestibular nerve, and the CSF-LV in the lateral ventricular trigone excluding the choroid plexus.

In the previous study,⁶ we compared signal intensity values using a ratio to those values of the brain parenchyma. On hT₂W-3D-FLAIR, signal intensity of the brain parenchyma is similar to that of background noise. Use of very small values as the denominator in the ratio might increase the error in results. The MR scanner employed in the present study utilizes a fixed receiver gain value for a given receive coil, so we used the actual signal intensity value instead of a ratio against that of the brain parenchyma.

Results

In all volunteers, all regions, including the AES, SAS-ON, SAS-MC, CSF-IAC, CSF-AC, Co-PL, V-PL, EL, PON, and CSF-LV, showed low signal intensity on non-contrast hT₂W-3D-FLAIR images. No significant signal increase was observed in the CSF-LV, PON, or EL at any time point following contrast administration. Significant signal intensity changes after IV-SD-

GBCM were observed in the AES, SAS-ON, SAS-MC, CSF-AC, CSF-IAC, V-PL, and Co-PL. Figures 1 and 2 show examples. However, even in structures that showed enhancement, we observed no significant change 0.5 hours after IV-SD-GBCM but significant difference 1.5 to 6 hours after IV-SD-GBCM. Figure 3 plots the results of the signal intensity measurements at each time point from pre- to post IV-SD-GBCM. Table 1 shows the results of the multiple comparisons.

Table 2 shows the number of sides out of 12 in the 6 volunteers that demonstrated maximum enhancement in each enhanced structure at a given time point after contrast administration. We observed maximum enhancement after IV-SD-GBCM at 4.5 hours for the SAS-ON, V-PL, and Co-PL, 1.5 hours for the AES and SAS-MC, and 3 hours for the CSF-IAC and CSF-AC.

Discussion

In the healthy state, enhancement of the AES, SAS, and CSF is not demonstrated on routine T₁-weighted or FLAIR images, which are usually obtained within 30 min after IV-SD-GBCM.⁶ Even in the normal state,

Fig. 2. A 31-year-old male volunteer. Images of magnetic resonance (MR) cisternography and serially acquired heavily T_2 -weighted 3-dimensional fluid-attenuated inversion recovery (hT_2W -3D-FLAIR) are presented. **(a)** Images at the level of the subarachnoid space of Meckel's cave (SAS-MC). The SAS-MC (arrows) is enhanced bilaterally with peak intensity at 1.5 hours after intravenous administration of a single dose of gadolinium-based contrast medium (IV-SD-GBCM), after which enhancement decreases gradually. **(b)** Images at the level of the cerebrospinal fluid (CSF) in the internal auditory canal (CSF-IAC, arrows). Enhancement of the CSF-IAC is most intense 1.5 hours after IV-SD-GBCM and then decreases gradually. Enhancement of the cochlear perilymph (Co-PL) is most intense 4.5 hours after IV-SD-GBCM.

enhancement of the AES, though visually very weak, has been reported on delayed T_1 -weighted images.¹⁰ Peak enhancement of the AES in normal subjects is reported 74 min after intravenous GBCM administration, a finding that was generally consistent with the results of this present study.

In various pathological states, increased enhancement of the AES,¹¹ SAS, and CSF in the ventricles and cisterns^{1,12,13} is reported. Therefore, there might be potential clinical applications using IV-SD-GBCM and hT_2W -3D-FLAIR. In the present study, we utilized hT_2W -3D-FLAIR, which is very sensitive to low concentrations of GBCM in fluid.⁴ We could observe distinct enhancement of the AES and SAS-ON on hT_2W -3D-FLAIR obtained 1.5 to 6 hours after IV-GBCM in healthy subjects without eye disease. Reducing the delay time to less than 1.5 hours might enable visual differentiation between healthy and pathological conditions, such as glaucoma, optic neuritis, and others. The use of hT_2W -3D-FLAIR images obtained after IV-GBCM with some delay time might lead to various new clinical applications. In patients with meningeal pathologies, prompt enhancement in the CSF-IAC has been reported using 3D-FLAIR.¹⁴ The use of hT_2W -3D-FLAIR might allow detection of fainter meningeal abnormalities.

The rise of the time intensity curve of the CSF-IAC is steeper than that of the cochlear perilymph, and peak enhancement of the CSF-IAC comes sooner. These findings suggest that some part of the GBCM in the cochlear perilymph might come from the CSF-IAC through the porous cochlear modiolus.¹⁵ The flow

direction and concentration gradient of the intravenously injected drug between the Co-PL and CSF-IAC might provide new insight into our understanding of cochlear homeostasis and drug delivery.

The time course of perilymph enhancement is important in setting up the timing protocol for MR scanning to evaluate the size of endolymphatic hydrops. Our present results in healthy volunteers are consistent with those previously reported in patients with inner ear disorders.¹⁶ Timing of peak enhancement of the perilymph seems comparable in healthy subjects and patients with endolymphatic hydrops. This is convenient for evaluating the size of endolymphatic space in patients with various conditions because we cannot examine patients who might have endolymphatic hydrops at so many time points in a clinical setting.

Our study has some limitations. We included a small number of only male volunteers within a limited age range. Age or gender dependency of the enhancement time course might be of interest for future research. The manual placement of ROIs to measure signal intensity might be susceptible to operator bias. However, the objects we measured were quite small in size and had complex shapes, and there were individual anatomical variations. Although the future development of a less operator-dependent measuring method is desired, other recent studies have utilized similar manually placed ROIs.^{6,16} An automatic segmentation method for the region of interest might be difficult with the current spatial resolution and signal-to-noise ratio.

In conclusion, contrast enhancement can be detected by hT_2W -3D-FLAIR 1.5 hours after IV-SD-GBCM in

Fig. 3. Mean signal intensity in the 6 volunteers. The time intensity curves of each location are shown with standard deviation. An asterisk (*) indicates the statistically significant difference against precontrast signal ($P < 0.05$). (a) The time intensity curve of the anterior eye segment (AES) shows a steep rise 1.5 hours after intravenous administration of a single dose of gadolinium-based contrast medium (IV-SD-GBCM) and then decreases gradually. (b) The time intensity curve of the subarachnoid space surrounding the optic nerve (SAS-ON) shows a slower rise and a later peak than the AES. (c) The time intensity curve of the cerebrospinal fluid in Meckel's cave (CSF-MC) shows a similar pattern as that of the AES. (d) The time intensity curve of the CSF in the internal auditory canal (CSF-IAC) reaches a peak 3 hours after IV-SD-GBCM. The peaks of the time intensity curves of the vestibular perilymph (V-PL) (e) and cochlear perilymph (Co-PL) (f) seem to be later than that of the CSF-IAC. There were no significant signal changes in the pontine parenchyma (PON) (g), CSF in the lateral ventricle (CSF-LV) (h), or vestibular endolymph (V-EL) (i). Although the signal increase of the CSF in the ambient cistern (CSF-AC) after IV-SD-GBCM (j) is small, a statistically significant increase was observed quantitatively.

Table 1. Multiple comparisons by Bonferroni correction ($P < 0.05$) of contrast enhancement at various time points after administration of gadolinium-based contrast medium

	AES	SAS-ON	SAS-MC	CSF-AC	CSF-IAC	V-PL	Co-PL
PRE vs 0.5H							
PRE vs 1.5H	S	S	S	S	S	S	S
PRE vs 3H	S	S	S	S	S	S	S
PRE vs 4.5H	S	S	S	S	S	S	S
PRE vs 6H	S	S	S	S	S	S	S
0.5H vs 1.5H	S	S	S	S	S	S	S
0.5H vs 3H	S	S	S	S	S	S	S
0.5H vs 4.5H	S	S	S	S	S	S	S
0.5H vs 6H	S	S		S	S	S	S
1.5H vs 3H		S		S		S	
1.5H vs 4.5H	S	S	S			S	S
1.5H vs 6H	S	S	S			S	S
3H vs 4.5H							
3H vs 6H	S		S	S			
4.5H vs 6H	S						

PRE, prior to contrast injection; H, hour/s; S, significant difference

AES, anterior eye segment; CSF-AC, cerebrospinal fluid in the ambient cistern; CSF-IAC, cerebrospinal fluid in the internal auditory canal; Co-PL, cochlear perilymph; SAS-MC, subarachnoid space in Meckel's cave; SAS-ON: subarachnoid space surrounding the optic nerve; V-PL: vestibular perilymph

Table 2. Number of sides out of 12 in 6 volunteers that demonstrated maximum enhancement at each time point after administration of gadolinium-based contrast medium

	0.5 hour	1.5 hours	3 hours	4.5 hours	6 hours
AES	0	6	4	2	0
SAS-ON	0	0	3	6	3
SAS-MC	0	9	3	0	0
CSF-AC	0	1	7	2	2
CSF-IAC	0	4	7	1	0
V-PL	0	1	1	7	3
Co-PL	0	0	0	8	4

AES, anterior eye segment; Co-PL, cochlear perilymph; CSF-AC, cerebrospinal fluid in the ambient cistern; CSF-IAC, cerebrospinal fluid in the internal auditory canal; SAS-MC, subarachnoid space in Meckel's cave; SAS-ON, subarachnoid space surrounding the optic nerve; V-PL, vestibular perilymph

the AES, SAS-ON, SAS-MC, V-PL, Co-PL, CSF-IAC, and CSF-AC in healthy volunteers. The times of peak enhancement differed among locations. These data might serve as basic knowledge for future clinical research and aid understanding of physiological homeostasis of the AES, SAS, CSF, and labyrinthine lymph fluid.

Acknowledgements

This study was supported by JSPS KAKENHI Grant Numbers 25293263, 24659562, 24591754, and 24791288 to S.N., M.Y., and K.S.

References

1. Hirai T, Ando Y, Yamura M, et al. Transthyretin-related familial amyloid polyneuropathy: evaluation of CSF enhancement on serial T₁-weighted and fluid-attenuated inversion recovery images following intravenous contrast administration. *AJNR Am J Neuroradiol* 2005; 26:2043–2048.
2. Mamourian AC, Hoopes PJ, Lewis LD. Visualization of intravenously administered contrast material in the CSF on fluid-attenuated inversion-recovery MR images: an *in vitro* and animal-model investigation. *AJNR Am J Neuroradiol* 2000; 21:105–111.
3. 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; 16:733–737.
4. Naganawa S, Kawai H, Sone M, Nakashima T. Increased sensitivity to low concentration gadolinium contrast by optimized heavily T₂-weighted 3D-FLAIR to visualize endolymphatic space. *Magn Reson Med* 2010; 9:73–80.
5. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hy-

- drops in Ménière's disease with single-dose intravenous gadolinium-based contrast media using heavily T₂-weighted 3D-FLAIR. *Magn Reson Med Sci* 2010; 9:237–242.
6. Naganawa S, Yamazaki M, Kawai H, Sone M, Nakashima T. Contrast enhancement of the anterior eye segment and subarachnoid space: detection in the normal state by heavily T₂-weighted 3D FLAIR. *Magn Reson Med Sci* 2011; 10:193–199.
 7. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Ménière's disease. *Laryngoscope* 2007; 117:415–420.
 8. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Ménière's disease after intravenous administration of single-dose gadodiamide: utility of subtraction images with different inversion time. *Magn Reson Med Sci* 2012; 11:213–219.
 9. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid after intravenous administration of single-dose gadodiamide. *Magn Reson Med Sci* 2012; 11:145–150.
 10. Bert RJ, Caruthers SD, Jara H, et al. Demonstration of an anterior diffusional pathway for solutes in the normal human eye with high spatial resolution contrast-enhanced dynamic MR imaging. *Invest Ophthalmol Vis Sci* 2006; 47:5153–5162.
 11. de Graaf P, van der Valk P, Moll AC, et al. Contrast-enhancement of the anterior eye segment in patients with retinoblastoma: correlation between clinical, MR imaging, and histopathologic findings. *AJNR Am J Neuroradiol* 2010; 31:237–245.
 12. Henning EC, Latour LL, Warach S. Verification of enhancement of the CSF space, not parenchyma, in acute stroke patients with early blood-brain barrier disruption. *J Cereb Blood Flow Metab* 2008; 28:882–886.
 13. Hickman SJ, Miszkiel KA, Plant GT, Miller DH. The optic nerve sheath on MRI in acute optic neuritis. *Neuroradiology* 2005; 47:51–55.
 14. Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Nakashima T, Maruyama K. Prompt contrast enhancement of cerebrospinal fluid space in the fundus of the internal auditory canal: observations in patients with meningeal diseases on 3D-FLAIR images at 3 Tesla. *Magn Reson Med Sci* 2006; 5:151–155.
 15. Kawai H, Naganawa S, Ishihara S, Sone M, Nakashima T. MR imaging of the cochlear modiolus after intratympanic administration of Gd-DTPA. *Magn Reson Med Sci* 2010; 9:23–29.
 16. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière's disease after single-dose intravenous gadolinium-based contrast medium: timing of optimal enhancement. *Magn Reson Med Sci* 2012; 11: 43–51.
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