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MAJOR PAPER

# Contrast Enhancement of the Normal Infundibular Recess Using Heavily T2-weighted 3D FLAIR

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**Purpose:** The purpose of the present study was to evaluate contrast enhancement of the infundibular recess in the normal state using heavily T2-weighted 3D fluid-attenuated inversion recovery (FLAIR) (HT2-FLAIR).

**Methods:** Twenty-six patients were retrospectively recruited. We subjectively assessed overall contrast enhancement of the infundibular recess between postcontrast, 4-hour (4-h) delayed postcontrast, and precontrast HT2-FLAIR images. We also objectively conducted chronological and spatial comparisons by measuring the signal intensity (SI) ratio (SIR). Chronological comparisons were performed by comparing SI of the infundibular recess/SI of the midbrain ($SIR_{IR\text{-}MB}$). Spatial comparisons were conducted by comparing SI on postcontrast HT2-FLAIR/SI on precontrast HT2-FLAIR ($SIR_{Post\text{-}Pre}$) of the infundibular recess with that of other cerebrospinal fluid (CSF) spaces, including the superior part of the third ventricle, lateral ventricles, fourth ventricle, and interpeduncular cistern.

**Results:** In the subjective analysis, all cases showed contrast enhancement of the infundibular recess on both postcontrast and 4-h delayed postcontrast HT2-FLAIR, and showed weaker contrast enhancement of the infundibular recess on 4-h delayed postcontrast HT2-FLAIR than on postcontrast HT2-FLAIR. In the objective analysis, $SIR_{IR\text{-}MB}$ was the highest on postcontrast images, followed by 4-h delayed postcontrast images. $SIR_{Post\text{-}Pre}$ was significantly higher in the infundibular recess than in the other CSF spaces.

**Conclusion:** The present results demonstrated that the infundibular recess was enhanced on HT2-FLAIR after an intravenous gadolinium injection. The infundibular recess may be a potential source of the leakage of intravenously administered gadolinium into the CSF.

**Keywords:** *infundibular recess, three-dimensional fluid-attenuated inversion recovery, magnetic resonance imaging, contrast enhancement, gadolinium deposition*

## Introduction

The infundibular recess is a cerebrospinal fluid (CSF)-filled space of the third ventricle floor that extends into the pituitary stalk. This space is surrounded by the median eminence, one of the circumventricular organs (CVOs) characterized by permeable fenestrated capillaries lacking a blood-brain barrier (BBB). Therefore, substances move freely between the blood and CVOs. Fluorescence endoscopy visualized the median eminence after the intravenous administration of fluorescein sodium.[1,2]

Previous studies indicated that the median eminence was enhanced after the intravenous administration of gadolinium on T1-weighted (T1W) or fluid-attenuated inversion recovery (FLAIR) imaging.[3–5] FLAIR is an MRI sequence with inversion recovery that suppresses the signal from water. FLAIR provides greater sensitivity for detecting subtle T1 shortening induced by contrast material than T1W imaging and has been applied to various intracranial lesions.[6] Heavily T2-weighted (T2W) 3D FLAIR (HT2-FLAIR) is a variant of the 3D turbo spin echo (TSE) FLAIR sequence with variable flip-angle refocusing pulses.[7] This sequence provides greater sensitivity to low concentrations of contrast material in a fluid than conventional 3D FLAIR and has been applied to

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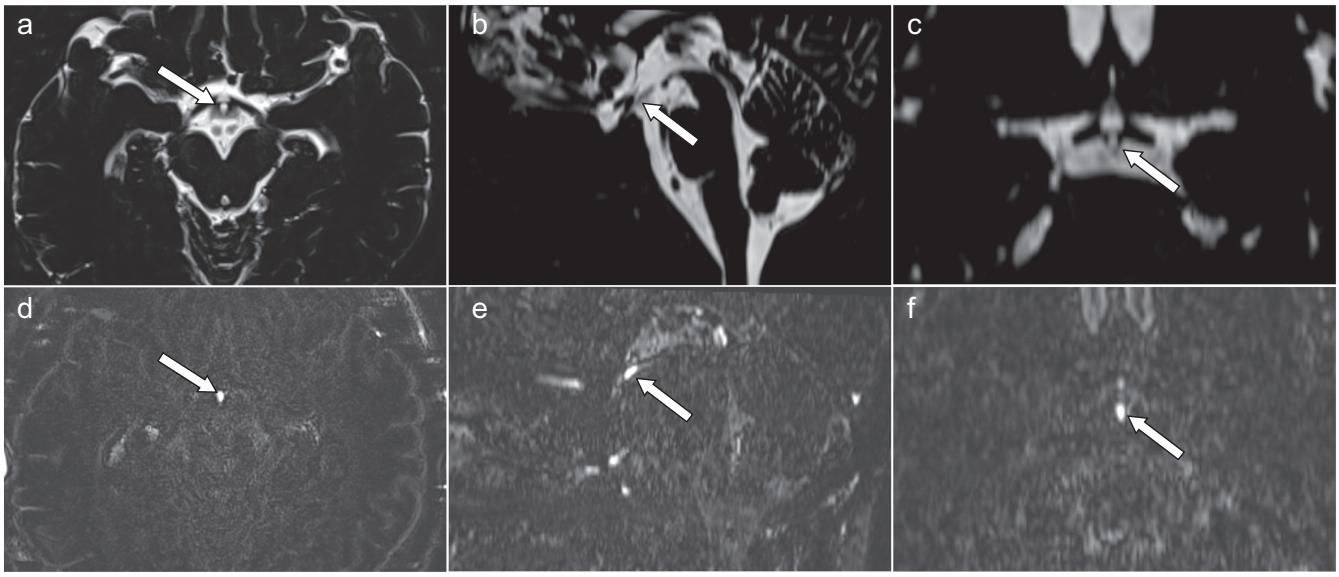


**Fig. 1** Contrast enhancement of the infundibular recess. The infundibular recess is hyperintense on axial (**a**, arrow), midsagittal reformatted (**b**, arrow), and coronal reformatted (**c**, arrow) MRC. The infundibular recess shows contrast enhancement on axial (**d**, arrow), midsagittal reformatted (**e**, arrow), and coronal reformatted (**f**, arrow) postcontrast HT2-FLAIR. HT2-FLAIR, heavily T2-weighted 3D fluid-attenuated inversion recovery; MRC, MR cisternography.

the inner ear and brain.[6] A previous study demonstrated that the anterior eye segment and various areas of the cranial subarachnoid space were enhanced on HT2-FLAIR in patients without eye disease or subarachnoid space disease.[8]

However, to the best of our knowledge, the enhancement of the normal infundibular recess on contrast-enhanced MRI has not yet been demonstrated. In our clinical practice, we noted that the infundibular recess was enhanced on HT2-FLAIR. Although a few studies speculated that a relationship exists between the infundibular recess and endocrine system,[9,10] its function remains unclear. Kanda et al. demonstrated gadolinium deposition in the brain after its intravenous administration.[11] Although the exact mechanisms have not yet been elucidated in detail, several hypotheses have been proposed, one of which is the glymphatic system. The glymphatic system is a functional waste clearance pathway for the central nervous system.[12] This system drives CSF into the interstitial space of the brain along the perivascular space surrounding arteries and out along the perivascular space around the veins. Therefore, an evaluation of contrast enhancement of the infundibular recess may provide novel insights into the transport of gadolinium into CSF and its deposition in the brain. The purpose of the present study was to evaluate contrast enhancement of the infundibular recess in the normal state using HT2-FLAIR.

## Materials and Methods

### *Patients*

This retrospective study was approved by the Institutional Review Board of our institution. We obtained written informed consent for the procedures and opt-out consent for the use of retrospective clinical data from all patients/from parents or legal guardian of patient less than 18 years. We reviewed the imaging records of 27 consecutive patients with suspected endolymphatic hydrops between March 2017 and July 2020. Patients were enrolled according to the following inclusion criteria: 1) MR cisternography (MRC) was available, 2) HT2-FLAIR images with and without gadolinium-based contrast material were available. Patients were excluded if image quality was insufficient to interpret the images, the infundibular recess was not included in the FOV, or the infundibular recess and surrounding tissues (median eminence and pituitary stalk) showed clinical and/or radiological abnormalities.

### *MRI*

MRI was performed on all patients using the 3 Tesla MR imaging unit (MAGNETOM Skyra, Siemens, Erlangen, Germany) with a 32-channel head coil. Twenty-seven patients underwent axial HT2-FLAIR and axial heavily T2W MRC of the inner ear (Fig. 1), according to a protocol proposed by Naganawa et al. for the evaluation of endolymphatic hydrops.[13] MRC was performed for an anatomical reference of total lymph fluid. We fused an MRC image and each HT2-FLAIR image into one blended image to accurately localize contrast enhancing areas.

HT2-FLAIR was conducted using the following parameters: TR 9000 ms, TE 542 ms, inversion time 2250 ms, a frequency-selective fat suppression prepulse, variable flip-angle echo train with an average flip angle of 120° followed by a 90° restore pulse, echo train length 519, matrix size 384 × 384, FOV 166 × 196 mm, axial slices 104, 0.5 × 0.5 mm in-plane resolution at a slice thickness of 1.0 mm, bandwidth

434 Hz/pixel, an acceleration factor 2 using the generalized autocalibrating partially parallel acquisitions (GRAPPA) parallel imaging technique, number of excitations 2, and acquisition time 7.17 min. Postcontrast HT2-FLAIR images were obtained approximately 0.5 to 5 min after an intravenous injection of gadolinium-HP-DO3A (Gadoteridol) at a single dose of 0.2 mL/kg (0.1 mmol/kg).

MRC was acquired with the following parameters: TR 4400 ms, TE 542 ms, a frequency-selective fat suppression prepulse, variable flip-angle echo train with an average flip angle of 120° followed by a 90° restore pulse, echo train length 519, matrix size 384 × 384, FOV 166 × 196 mm, axial slices 104, 0.5 × 0.5 mm in-plane resolution at a slice thickness of 1.0 mm, bandwidth 434 Hz/pixel, an acceleration factor 2 using the GRAPPA parallel imaging technique, number of excitations 1.8, and acquisition time 3.15 min.

### *Imaging analysis*

#### Subjective analysis

We visually assessed overall contrast enhancement of the infundibular recess. The presence of contrast enhancement was defined as a higher signal intensity (SI) on postcontrast or 4-hour (4-h) delayed postcontrast HT2-FLAIR than on precontrast HT2-FLAIR. We also compared SI between postcontrast and 4-h delayed postcontrast HT2-FLAIR. Overall contrast enhancement of the median eminence was evaluated using the same approach and was compared with that of the infundibular recess. All images were independently reviewed in a random order by two board-certified radiologists (I.O and E.K) who were blinded to clinical information and sequence parameters. Discrepancies between the two radiologists were resolved by consensus.

#### Objective analysis

An objective analysis was conducted by measuring the signal intensity ratio (SIR) in predefined ROIs followed by chronological and spatial comparisons on the workstation (Synapse VINCENT version 5.2; Fujifilm, Tokyo, Japan). SIR was calculated as follows: $SIR_{IR\text{-}MB}$ = SI of the infundibular recess ($SI_{IR}$)/SI of the midbrain ($SI_{MB}$) and $SIR_{Post\text{-}Pre}$ = SI on postcontrast HT2-FLAIR ($SI_{Post}$)/SI on precontrast HT2-FLAIR ($SI_{Pre}$). $SI_{IR}$ was the mean SI of the infundibular recess. $SI_{MB}$ was the mean SI of the midbrain. $SI_{Post}$ was the mean SI of the infundibular recess or other CSF spaces on postcontrast HT2-FLAIR. $SI_{Pre}$ was the mean SI of the infundibular recess or other CSF spaces on precontrast HT2-FLAIR.

Chronological comparisons were performed by comparing $SIR_{IR\text{-}MB}$ between each time point. We decided to manually place a freehand ROI on the infundibular recess and an ovoid ROI on the midbrain at the level of the median eminence on MRC, and then copied the ROI to each image on HT2-FLAIR. The size of the ROI on the infundibular recess ranged between 2.6 and 8.6 $mm^2$ (mean 4.9 $mm^2$), while that on the midbrain was 20 $mm^2$. After measuring $SI_{IR}$ and $SI_{MB}$, we calculated $SIR_{IR\text{-}MB}$ to compare between each time point.

Spatial comparisons were conducted by comparing $SIR_{Post\text{-}Pre}$ of the infundibular recess with that of other CSF spaces, including the superior part of the third ventricle (ovoid ROI size 3 $mm^2$), lateral ventricles (ovoid ROI size 1.5 $mm^2$ on each side), fourth ventricle (ovoid ROI size 3 $mm^2$), and prepontine cistern (ovoid ROI size 3 $mm^2$). Each ROI was placed in the same manner as described above. SI of the lateral ventricles was calculated as the mean of the right and left sides. Measurements of the CNR were performed by a single observer (I.O).

### *Statistical analysis*

Chronological comparisons of $SIR_{IR\text{-}MB}$ were performed using the Friedman test followed by the Holm correction for multiple comparisons. We compared $SIR_{Post\text{-}Pre}$ of the infundibular recess with that of other CSF spaces using the Kruskal-Wallis test followed by the Steel test for multiple comparisons to a control. Two-tailed *P* values less than 0.05 were considered to be significant. All statistical calculations were conducted with JMP 14.0.0 software (SAS Institute, Cary, NC, USA) and the statistical computing language R (Version 3.4.3; The R Foundation, https://www.r-project.org).

## Results

### *Patients*

Twenty-seven patients underwent MRC and HT2-FLAIR with and without gadolinium-based contrast material. Twenty-six out of the 27 patients with available images satisfied the inclusion criteria. One patient was excluded because the infundibular recess and surrounding tissues were compressed due to bilateral chronic subdural hematomas. The patient cohort included 11 males and 15 females, with an average age of 53 years (range from 17 to 80 years).

### *Subjective analysis*

All cases showed contrast enhancement of the infundibular recess on both postcontrast and 4-h delayed postcontrast HT2-FLAIR (Fig. 2). All patients showed weaker contrast enhancement of the infundibular recess on 4-h delayed postcontrast HT2-FLAIR than on postcontrast HT2-FLAIR. Among 26 patients, 14 showed contrast enhancement of the median eminence on postcontrast HT2-FLAIR (Fig. 3), whereas the remaining 12 did not on postcontrast or 4-h delayed postcontrast HT2-FLAIR. Furthermore, contrast enhancement of the median eminence decreased on 4-h delayed postcontrast HT2-FLAIR in all 14 patients (weaker enhancement; n = 8, no enhancement; n = 6). Contrast enhancement of the median eminence was weaker than that of the infundibular recess on both postcontrast (n = 14) and 4-h delayed postcontrast (n = 8) HT2-FLAIR.

### *Objective analysis*

Figure 4 shows chronological changes in $SIR_{IR\text{-}MB}$. $SIR_{IR\text{-}MB}$ was significantly higher on postcontrast HT2-FLAIR

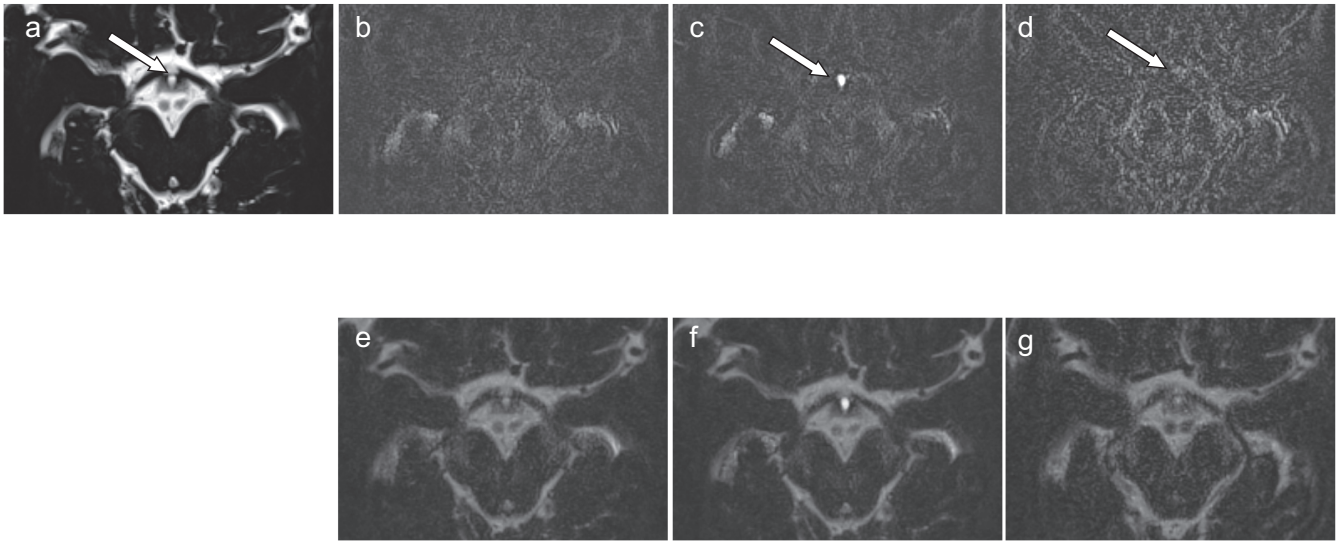


**Fig. 2** Chronological changes in contrast enhancement in the infundibular recess. The infundibular recess shows hyperintensity on MRC (**a**, arrow). On HT2-FLAIR, in comparisons with a precontrast image (**b**), a postcontrast image (**c**, arrow) shows stronger enhancement of the infundibular recess. A 4-h delayed postcontrast image (**d**, arrow) demonstrates decreased contrast enhancement of the infundibular recess. We fused an MRC image and each HT2-FLAIR image into one blended image (**e**, **f**, and **g**), on which contrast enhancement on postcontrast HT2-FLAIR (**f**) corresponds to the hyperintensity of the infundibular recess on MRC. 4-h, 4-hour; HT2-FLAIR, heavily T2-weighted 3D fluid-attenuated inversion recovery; MRC, MR cisternography.

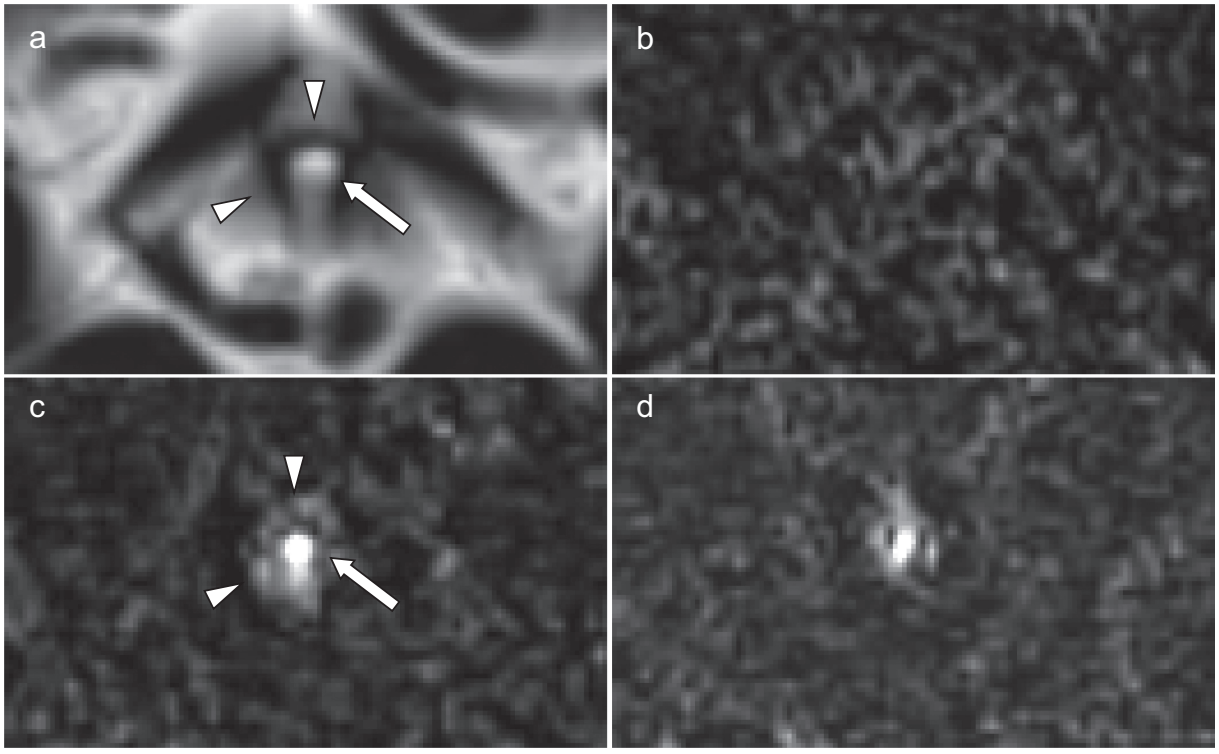


**Fig. 3** Contrast enhancement of the median eminence. The infundibular recess (**a**, arrow) is surrounded by the median eminence (**a**, arrowheads) on MRC. On HT2-FLAIR, in comparisons with a precontrast image (**b**), a postcontrast image (**c**, arrow) shows stronger contrast enhancement of the infundibular recess. The median eminence shows weaker contrast enhancement than the infundibular recess (**c**, arrowheads). A 4-h delayed postcontrast image (**d**) shows decreases in contrast enhancement of the infundibular recess and median eminence. 4-h, 4-hour; HT2-FLAIR, heavily T2-weighted 3D fluid-attenuated inversion recovery; MRC, MR cisternography.

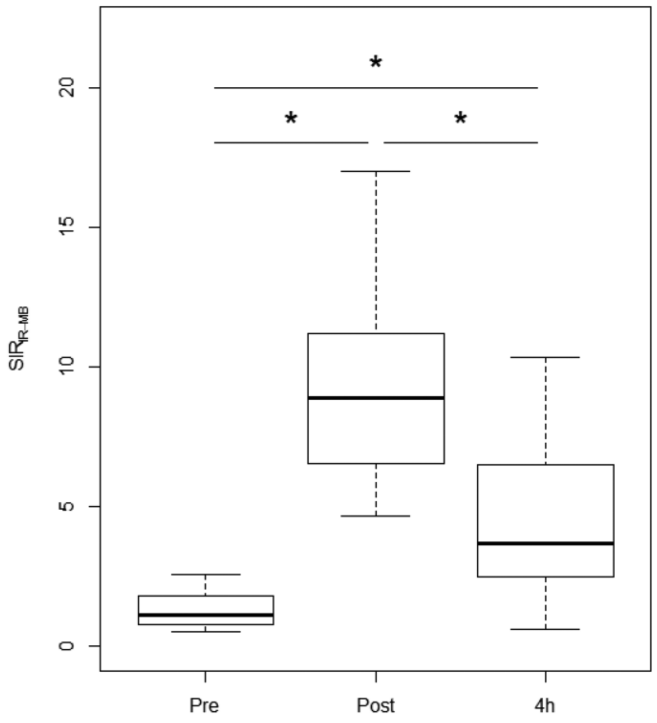


**Fig. 4** Chronological comparison of $SIR_{IR\text{-}MB}$. $SIR_{IR\text{-}MB}$ is significantly higher on postcontrast and 4-h delayed postcontrast HT2-FLAIR than on postcontrast HT2-FLAIR. $SIR_{IR\text{-}MB}$ is lower on 4-h delayed postcontrast HT2-FLAIR than on postcontrast HT2-FLAIR. Asterisks indicate a significant difference. $SIR_{IR\text{-}MB}$ is defined as the ratio of the mean SI of the infundibular recess to the mean SI of the midbrain. 4-h, 4-hour; HT2-FLAIR, heavily T2-weighted 3D fluid-attenuated inversion recovery; SI, signal intensity; $SIR_{IR\text{-}MB}$, SI of the infundibular recess/SI of the midbrain.

(9.23 $\pm$ 3.43) than that on precontrast (1.30 $\pm$ 0.63; $P < 0.0001$) and 4-h delayed postcontrast (4.55 $\pm$ 2.72; $P < 0.0001$) HT2-FLAIR. $SIR_{IR\text{-}MB}$ was significantly higher on 4-h delayed postcontrast HT2-FLAIR than on precontrast HT2-FLAIR ($P < 0.0001$). Figure 5 shows spatial comparisons of $SIR_{Post\text{-}Pre}$. The infundibular recess showed significantly higher $SIR_{Post\text{-}Pre}$ (7.46 $\pm$ 2.41) than the other CSF spaces (the superior part of the third ventricle 1.04 $\pm$ 0.56; $P < 0.0001$, the lateral ventricles 1.16 $\pm$ 0.80; $P < 0.0001$, the fourth ventricle 0.96 $\pm$ 0.30; $P < 0.0001$, and the prepontine cistern 1.24 $\pm$ 0.61; $P < 0.0001$).

## Discussion

The present results demonstrated that the normal infundibular recess was enhanced on HT2-FLAIR. Enhancement of the infundibular recess was stronger on postcontrast HT2-FLAIR than on 4-h delayed postcontrast HT2-FLAIR. Furthermore, the infundibular recess was more strongly enhanced than other CSF spaces.

Currently, it remains unclear why the infundibular recess showed contrast enhancement. One possible explanation is the leakage of contrast material into CSF from the median eminence. The median eminence is a CVO that is located at the interface between the ventral hypothalamus and infundibular recess. CVOs are midline structures located around the third and fourth ventricles. Although the functions and morphologies of CVOs vary, they have several common features: 1) a fenestrated capillary lacking BBB and surrounded by large perivascular spaces, 2) specialized neuroglial cells (tanycytes and pituicytes), and 3) an interface between the brain, blood, and CSF. These organs play a critical role as a transducer of information between the brain, blood, and CSF.

There are seven major CVOs that include the median eminence, neurohypophysis, pineal gland, subcommissural organ, organum vasculosum laminae terminalis (OVLT), subfornical organ, and area postrema. CVOs may be classified as secretory (the median eminence, neurohypophysis, pineal gland, and subcommissural organ) and sensory (OVLT, the subfornical organ, and area postrema). Secretory CVOs allow the discharge of substances into the blood or ventricles, while sensory CVOs receive a wide range of chemical signals from the blood and then pass information to other brain regions.

The median eminence is characterized by permeable fenestrated capillaries lacking BBB. As a result, substances move freely between the blood and extracellular space within the median eminence. A series of tracers (Trypan blue, Evans blue, ferritin, and horseradish peroxidase) administered intravenously escape from the portal capillaries into the perivascular space and readily reach the intercellular space within the median eminence.[14] The vascular permeability of CVOs is size-selective; low-molecular-weight substances are more permeable than high-molecular-weight substances.[15] Secretory CVOs may be more permeable than sensory CVOs.[16] The median eminence contains specialized ependymal cells called tanycytes, which line the floor of the third ventricle and form a bridge between the portal capillary

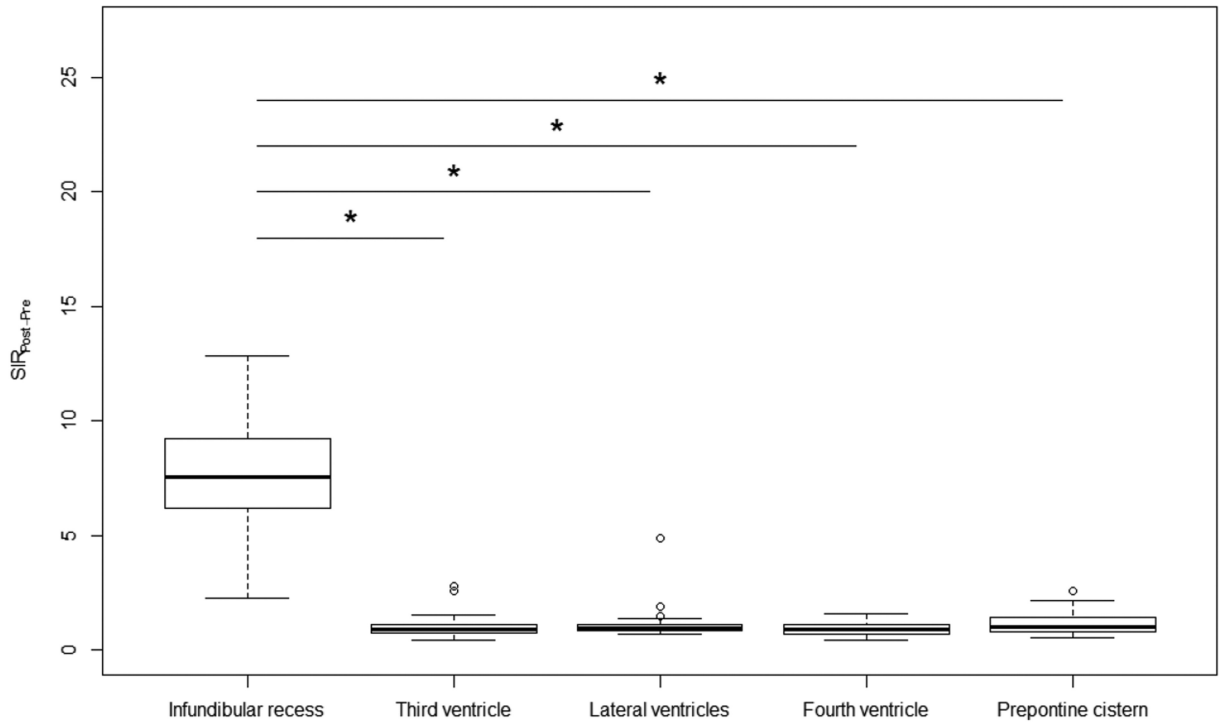


**Fig. 5** Spatial comparison of $SIR_{Post\text{-}Pre}$. $SIR_{Post\text{-}Pre}$ is significantly higher in the infundibular recess than in other CSF spaces. $SIR_{Post\text{-}Pre}$ is defined as the ratio of $SI_{Post}$ to $SI_{Pre}$. $SI_{Post}$ represents the mean SI of the infundibular recess or other CSF spaces on postcontrast HT2-FLAIR. $SI_{Pre}$ is the mean SI of the infundibular recess or other CSF spaces on precontrast HT2-FLAIR. Asterisks indicate a significant difference. CSF, cerebrospinal fluid; HT2-FLAIR, heavily T2-weighted 3D fluid-attenuated inversion recovery; SI, signal intensity; $SIR_{Post\text{-}Pre}$, SI on postcontrast HT2-FLAIR/SI on precontrast HT2-FLAIR.

system and the third ventricle. The dorsal wall of the median eminence bordering the floor of the infundibular recess is lined by β2 tanycytes. Tight junctions between β2 tanycytes at the ventricular pole restrict the passage of substances between CSF and the extracellular space within the median eminence.

However, previous studies reported the transport of substances from the median eminence to CSF in the third ventricle.[9,17,18] Caraty et al. demonstrated that gonadotropin-releasing hormone (GnRH) was not uniformly distributed throughout the third ventricle and was more concentrated in the infundibular recess.[9] They hypothesized that the median eminence may be a major, if not the only, source of GnRH entering CSF. Other studies revealed that peptide hormones, including leptin and ghrelin, were transported after their peripheral administration from the blood to the CSF via tanycytes in the median eminence.[17,18] Therefore, tight junctions between β2 tanycytes may be leaky. Since the infundibular recess is devoid of multiciliated ependymal cells, CSF flow may be reduced at this level,[14] which may contribute to the accumulation of gadolinium within the infundibular recess.

Gadolinium deposition in the brain after its intravenous administration was initially reported by Kanda et al. in 2014.[11] The risk of gadolinium accumulation has been extensively debated. Although the exact mechanisms by which gadolinium is deposited in the brain remain unknown, several hypotheses have been proposed. Recent studies indicated that the glymphatic system may be one of the transport pathways of gadolinium into the brain parenchyma.[19–24] Iliff et al. used contrast-enhanced MRI and revealed that gadolinium-based contrast agents administered intrathecally passed through the paravascular pathways to enter the live rat brain.[19] In humans, contrast-enhanced MR studies also demonstrated that gadolinium entered the brain parenchyma after its intrathecal administration.[20,21] Previous studies reported that intravenously administered gadolinium was distributed into perivascular spaces[22] as well as CSF spaces around various tissues, including the peripheral part of the cranial nerves[8], OVLT[23], and the cortical veins[24]. The perivascular space, comprising the glymphatic system, plays the role of a transport conduit of CSF and solutes in the brain. The constellation of these MRI findings suggests the involvement of the glymphatic system in the transportation and deposition of gadolinium in the brain. Large perivascular spaces surrounding the median eminence might act as conduits for the transport of gadolinium.

The present results revealed the weaker enhancement of the median eminence than that of the infundibular recess on HT2-FLAIR in some cases. Contrast-enhanced MRI studies showed that CVOs, including the median eminence, were enhanced using T1W imaging or FLAIR.[3–5] Azuma et al. reported that among CVOs on postcontrast 3D T2-FLAIR, marked enhancement of the median eminence was most frequently observed;[5] they did not describe contrast

enhancement of the infundibular recess. Although the imaging parameters employed for 3D FLAIR in the present study were not equivalent or comparable to those in Azuma's study, contrast enhancement of the median eminence and infundibular recess may not be differentiated on 3D T2-FLAIR, possibly because of lower in-plane resolution (0.9 × 0.9 mm) than with HT2-FLAIR (0.5 × 0.5 mm).

The present study demonstrated that the infundibular recess was enhanced relatively early (0.5 to 5 min) after the intravenous administration of gadolinium. On the other hand, in an MRI study on the heads of healthy male volunteers, the signal intensities of various CSF spaces (such as the subarachnoid space surrounding the optic nerve and Meckel's cave) did not significantly differ between precontrast and 0.5-h postcontrast HT2-FLAIR.[25] However, this finding does not necessarily suggest that intravenous gadolinium does not rapidly move into CSF spaces. Since that study only had a small sample size (n = 6), a larger sample size may yield a significant difference. Furthermore, Naganawa et al. reported that not only the OVLT but also the surrounding CSF spaces were enhanced on HT2-FLAIR 0.5 h after the administration of gadolinium.[23] Therefore, contrast leakage from the OVLT was readily visualized after contrast agent administration.

Although the mechanisms underlying the early enhancement of the infundibular recess remain unknown, gadolinium leakage from the median eminence into the infundibular recess has been proposed. The present study showed that strong enhancement may occur at an early time point, nearly equivalent to that of the OVLT and the surrounding CSF spaces.[23] Since the median eminence lacks a BBB, similar to the OVLT, intravenous gadolinium may rapidly move to the median eminence and then to the infundibular recess.

Another reason may be associated with CSF flow in the infundibular recess. As described earlier, since the infundibular recess is devoid of multiciliated ependymal cells, CSF flow may be reduced at this level,[14] which may contribute to the accumulation of gadolinium. In addition, CSF flow may influence the sensitivity of 3D FLAIR to gadolinium; 3D FLAIR was sensitive to not only low concentrations of gadolinium but also to slow flow.[5] If the infundibular recess contains slow-flowing CSF, HT2-FLAIR may improve the detection of gadolinium in the CSF. Therefore, early and prolonged enhancement of the infundibular recess may be associated with its CSF flow.

There were several limitations that need to be addressed. The present study was a retrospective evaluation of a limited number of patients. Furthermore, data were acquired at a few time points. In future studies, more time points need to be examined. Moreover, we assessed patients with cochleovestibular symptoms and did not include completely healthy subjects. However, we consider the results obtained to reflect the normal state of the infundibular recess because patients did not have neurological symptoms or MRI findings associated with the infundibular recess and surrounding tissues.

## Conclusion

In conclusion, the present study demonstrated that the infundibular recess was enhanced on HT2-FLAIR after the intravenous gadolinium injection. Contrast enhancement of the infundibular recess was stronger than that of other CSF spaces and decreased 4 h after the administration of gadolinium. The infundibular recess is a potential source of the leakage of intravenously administered gadolinium into the CSF.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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