

MAJOR PAPER

Relationship between Time-dependent Signal Changes in Parasagittal Perivenous Cysts and Leakage of Gadolinium-based Contrast Agents into the Subarachnoid Space

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Purpose: To investigate the association between signal changes over time in perivenous cystic structures near the superior sagittal sinus and leakage of a gadolinium-based contrast agent (GBCA) into the subarachnoid space in patients with suspected endolymphatic hydrops.

Methods: Fifty-one cystic structures in 27 cases were evaluated. The signal intensity of the cystic structures was measured on 3D real inversion recovery (3D-real IR) images obtained at pre-, and at 10 min, 4 hrs and 24 hrs post-intravenous administration (IV) of GBCA. Signal enhancement of the cystic structures from the pre-contrast images at each time point was compared in subjects with leakage (positive) versus those without leakage (negative) using an ANOVA. Fisher's exact probability test was used to compare the maximum contrast-enhanced time point between positive and negative groups. We used 5% as a threshold to determine statistical significance.

Results: In leakage positive subjects, mean signal enhancement of the cysts was significantly greater at 4 and 24 hrs compared to 10 min. However, although there was a trend of an increase from 4 to 24 hrs, the difference was not significant. In the leakage negative group, mean signal enhancement of the cysts was significantly higher at 4 hrs compared to 10 min and 24 hrs. There was no significant difference between 10 min and 24 hrs. In the positive group, the maximum signal increase was found in 10/38 and 28/38 cysts at 4 and 24 hrs after IV-GBCA, respectively. In the leakage negative group, the maximum signal increase was found in 10/13 and 3/13 cysts at 4 and 24 hrs, respectively ($P = 0.0019$).

Conclusion: There was an association between signal changes over time after IV-GBCA in perivenous cystic structures and leakage of GBCA. Further research to clarify the impact of cystic structures on the function of the waste clearance system of the brain is warranted.

Keywords: gadolinium, glymphatic system, magnetic resonance imaging, parasagittal dura

Introduction

Several minutes after intravenous administration (IV) of a gadolinium-based contrast agent (GBCA), the subpial space

around the cortical veins is enhanced in human patients.^{1,2} In addition, it has been shown that the GBCA often leaks into the surrounding subarachnoid space by 4 hrs after intravenous administration.^{3–5} It has also been reported that leakage of the GBCA into the subarachnoid space around the cortical veins on 3D real inversion recovery (3D-real IR) images obtained at 4 hrs post-administration is observed frequently in subjects over 37 years of age, but significantly less often in individuals younger than 37 years.^{3,4} A potential connection between the subpial space around the cortical veins and the presumed meningeal lymphatic vessels on both sides of the superior sagittal sinus^{6–8} has been reported using MR imaging.¹ Lymphatic vessels were thought to be absent in the brain, but meningeal lymphatic vessels have been discovered in recent years. Because of their importance as a downstream part of the brain's waste clearance system,

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and as a transit route for immune cells, these meningeal vessels have been the focus of much research.⁶

Both the glymphatic system and the intramural periarterial drainage (iPAD) pathway have been proposed as mechanisms for brain waste clearance, and both pathways eventually drain to the lymphatics.^{9–13} Meningeal lymphatics exist along the superior sagittal sinus. It was also reported recently that the number and size of the cystic structures near the superior sagittal sinus were associated with the leakage of GBCA into the subarachnoid space around the cortical veins.¹⁴ It is unclear if these cystic structures are reservoirs with continuity into the subpial space around the cortical veins, or if the cystic structures compress the subpial space around the cortical veins, or alternatively, if the cystic structures are incidental and not specifically related to the subpial space around the cortical veins.

To help distinguish these possibilities, it may be useful to examine the signal changes over time post-IV-GBCA in each cystic lesion. However, to date there are no reports of these findings. If the MR signal intensity of the cystic structures prior to contrast injection could predict the leakage of GBCA into the subarachnoid space, it might be used as the imaging biomarker of blood–cerebrospinal fluid (CSF) barrier permeability. If the MR signal intensity of the lesions at 10 min post-IV-GBCA could predict the leakage of GBCA into subarachnoid space, we could collect patient data without waiting for 4 hrs post-IV-GBCA. Shortening the wait time would be beneficial to research of the glymphatic system in clinical settings.

The purpose of this study was to investigate the association between signal changes over time in perivenous cystic structures near the superior sagittal sinus with leakage of GBCA into the subarachnoid space in patients with suspected endolymphatic hydrops by MR imaging at pre-, and 10 min, 4 hrs, and 24 hrs post-IV-GBCA.

Materials and Methods

Patients

The subjects were 32 patients suspected of endolymphatic hydrops (17 women and 15 men, age: 23–80, median age: 49.5). All patients underwent evaluation for the degree of endolymphatic hydrops, and the permeability of the blood-labyrinthine barrier and the blood–CSF barrier with IV-GBCA and MR imaging. In all cases, the estimated glomerular filtration rate was 50 mL/min/1.73 m² or greater. There were no cases with brain tumors or large cerebral infarctions. The ethical committee of our institution approved this study. Written informed consent was obtained from all patients.

MR Imaging

The MR images were obtained pre-administration, and at 10 min, 4 hrs, and 24 hrs after a single dose (0.1 mmol/kg) of IV-GBCA (gadobutrol; Bayer Pharma, Osaka, Japan). A 3T MRI scanner (MAGNETOM Skyra; Siemens, Erlangen, Germany) with a 32-channel head coil was used.

The detailed parameters for the 3D-real IR imaging were similar to the previous study.¹⁴ We obtained 256 axial slices with 1 mm thickness covering the entire brain. The scan time for the 3D-real IR imaging was 10 min per volume. Briefly, a repetition time of 15130 msec, echo time of 549 msec, inversion time of 2700 msec, pixel size of 0.5 mm × 0.5 mm, with 1 mm thickness, phase sensitive reconstruction (real reconstruction), and scan time of 10 min were applied. A fixed receiver gain was used. The slice position for the 3D-real IR imaging was co-registered between the time points using a scanner-equipped automatic alignment function.

Image Evaluation

The presence of GBCA leakage around the cortical veins was determined in a manner similar to the previous report on the 3D-real IR images obtained at 4 hrs after the IV-GBCA.^{4,14} Briefly, a high signal intensity in the subarachnoid space around the cortical veins with a signal intensity value of 30 or greater, with a length of at least 10 mm, and a width of at least 2 mm on the 3D-real IR images was regarded as a positive finding. Therefore, the thin pial high signal intensity on the brain surface, the pial-sheath around the cortical veins, and the presumed meningeal lymphatics along both sides of the superior sagittal sinus were excluded. The 3D-real IR images were displayed on a PACS viewer (RapideyeCore; Canon Medical Systems, Tokyo, Japan) under very narrowed window conditions (Window width of 2, Window level of 30), as well as regular window conditions (Window width of 80, Window level of 10), which showed the anatomy of the brain, the subarachnoid spaces and the cortical veins. The window level and width parameters were identical to those in a previous study.⁴ An experienced neuroradiologist (T.T.) reviewed all 256 axial, 1 mm thick slices for each patient to determine if GBCA leakage around the cortical veins was present.

The method and criteria for determining the presence of a cyst and signal measurement of the cyst and CSF in the Sylvian fissure were as follows. Inclusion criteria of the cystic structure is similar that of the previous study.¹⁴

- 1) The 3D-real IR obtained at 4 hrs after IV-GBCA was displayed at a Window level of 20 and Window width of 200, and the cysts satisfying the following conditions were counted.
- 2) Only the slices containing the superior sagittal sinus above the superior edge of the lateral ventricle were reviewed. The cystic structures with thin walls that were within 15 mm on both the right and left sides of the anterior-posterior center line, and were in wide contact with the cortical veins were included. Those with a short axis diameter of 3 mm or longer on the axial images were included.
- 3) Arachnoid granulations protruding into the superior sagittal sinus were not included as cysts. Nodular structures with thick walls were not included as cysts

if the thick wall covered more than half of the nodular area. Those were thought to be arachnoid granulations. Structures that mostly protruded into the bone were also considered to be arachnoid granulations and not included as cysts. Cysts involved in the remodeling of the inner table of the skull were included.

- 4) Irregularly shaped cystic structures surrounded by very thin membranous trabeculae in the subarachnoid space were presumed to be caused by arachnoiditis and not included as cysts. Cystic areas apparently unrelated to the cortical veins, or incidental cyst-like CSF areas with indistinct walls in the cerebral sulcus due to brain shape were not included as cysts.
- 5) The multiplanar reconstruction function was used to characterize the relationship between the surrounding brain parenchyma, vessels, and the remodeling of the skull.
- 6) The signal intensity of each cystic structure was measured by placing a circular ROI as large as possible while avoiding the cyst wall.
- 7) We excluded five cases (4 men and 1 woman), in which no signal-measurable cystic structures of more than 3 mm in the short diameter could be identified.
- 8) The two cysts that were closest to the cortical vein were selected in each patient; when three or more cysts were candidates, the two that were closer to the midline were selected. In one case, it was difficult to select two cysts by the distance from the midline, so three cysts were selected. In four cases where only one cyst was identified, only one cyst was evaluated. In total, 51 cystic structures in 27 cases were evaluated.

In all included cases, the mean of the CSF signal intensity within the left and right Sylvian fissure was also measured by placing a circular 2-mm diameter ROI while avoiding the vessel. The signal intensity measurements of the cysts and CSF in the Sylvian fissure were performed by another neuroradiologist (S.N.).

Statistical Analysis

Comparisons of the signal intensity change from the pre-contrast images to each time point of 10 min, 4 hrs, and 24 hrs post-IV-GBCA of the cystic structures and Sylvian fissure CSF in the subjects with leakage (positive) and the subjects without leakage (negative) were performed using an ANOVA with Bonferroni correction for multiple comparisons.

For the cysts and the Sylvian fissure CSF, the comparison of the intensity at pre-contrast and that at 10 min post-IV-GBCA between the positive and negative groups was performed using a Mann–Whitney *U* test.

For the cysts and the Sylvian fissure CSF, the comparison between the positive and negative groups of the signal intensity at 24 hrs minus that at 4 hrs was also performed using a Mann–Whitney *U* test.

For the cysts and Sylvian fissure CSF, the comparison of the maximum contrast increase in the positive and negative groups was performed using a Mann–Whitney *U* test.

A Fisher's exact probability test (2×2 contingency table) was used to compare the maximum contrast-enhanced temporal phase of the cysts between the positive and negative groups.

We used 5% as a threshold to determine statistical significance. The software R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>) was used for the statistical analyses.

Results

Among the 27 cases (51 cysts) evaluated in this study, 20 cases (38 cysts) had leakage of GBCA into the subarachnoid space around the cortical veins and seven cases (13 cysts) did not. Representative MR images are shown in Fig. 1.

The time course of the mean signal intensity change in the cysts, which was calculated by subtracting the pre-contrast signal value from the values at 10 min, 4 hrs, and 24 hrs for the leakage positive and negative groups, is indicated in Fig. 2. In the leakage negative group, the mean signal increase in the cysts was significantly higher at 4 hrs than at 10 min or 24 hrs; there was no significant difference between 10 min and 24 hrs. In the leakage positive subjects, the mean signal enhancement in the cysts was significantly greater at 4 and 24 hrs compared to 10 min. However, although there was a trend of an increase from 4 to 24 hrs, the difference was not significant.

The change over time of the mean signal enhancement in the CSF of the Sylvian fissure in leakage positive and negative groups, respectively, is indicated in Fig. 3. The signal intensity increase in the Sylvian fissure CSF of the leakage positive group was the highest at 4 hrs and similar to that of the leakage negative group. There were significant differences in the mean values for all combinations except the between 10 min and 24 hrs in the leakage negative group. The signal intensity increase in the Sylvian fissure CSF was the highest at 4 hrs in the leakage positive group. There was a significant difference in the mean values for all time phase pairs.

The signal intensity at pre-contrast was not significantly different between the leakage positive and negative groups for both the cysts and the Sylvian fissure CSF. Also, at 10 min after IV-GBCA, neither the signal intensity of cysts nor Sylvian fissure CSF were significantly different between the leakage positive and negative groups. The signal intensity at pre-contrast and at 10 min post-IV-GBCA did not predict the leakage of GBCA around the cortical veins into the subarachnoid space.

The maximum signal intensity increase in the cysts was significantly higher in the positive group than the negative group. In the leakage positive group, the maximum signal intensity increase in the cysts was found in 10/38 and 28/38 cysts at 4 and 24 hrs after IV-GBCA, respectively. In the leakage negative group, the maximum signal intensity increase in the cysts was found in 10/13 and 3/13 cysts at 4

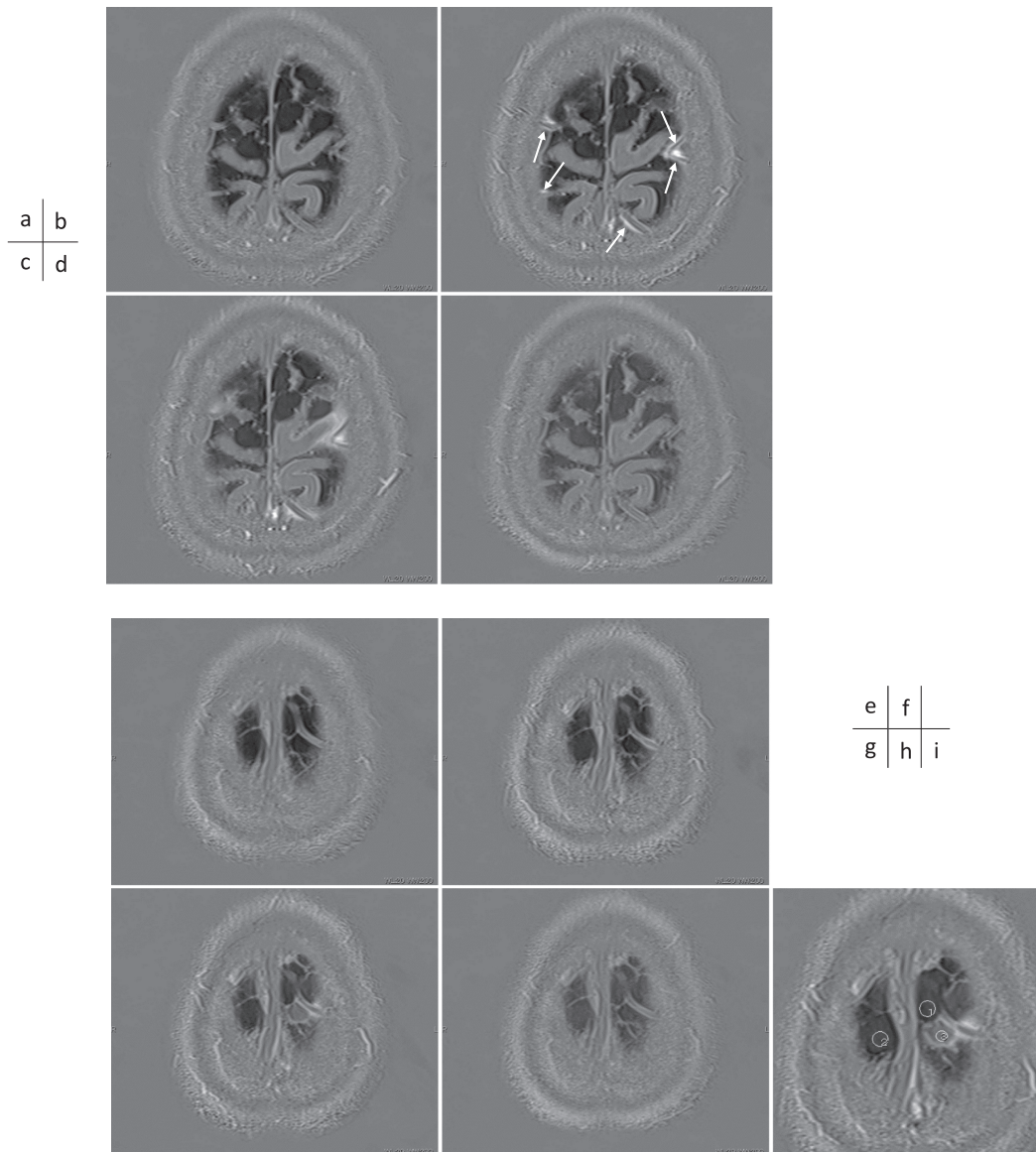


Fig. 1 3D-real IR images obtained in a 59-yr-old woman with suspected endolymphatic hydrops. The images were obtained at pre- (a) and 10 min (b), 4 hrs (c), and 24 hrs (d) after intravenous administration of IV-GBCA. Linear contrast enhancement along the cortical veins is visualized at 10 min after IV-GBCA (arrows, b). Increased signal intensity has spread into surrounding subarachnoid space by 4 hrs (c). Therefore, this patient was classified into the leakage positive group. The perivenous linear enhancement and surrounding cerebrospinal fluid enhancement decrease by 24 hrs after IV-GBCA (d). The 3D-real IR images obtained in the superior sagittal sinus at the level of the parietal area obtained at pre- (e) and 10 min (f), 4 hrs (g) and 24 hrs (h) post-IV-GBCA. (i) An enlarged view of the image obtained at 4 hrs. Examples of the circular ROI placement for the signal intensity measurement of the perivenous cysts are shown (i). In this patient, the distance from midline was similar in the cysts with ROI#2 and ROI#3. Therefore, all three cysts were included for the evaluation. Note that the signal intensity of the cyst at ROI#2 gradually increases up to 24 hrs (e–h), however the signal intensity of the cyst at ROI#3 peaks at 4 hrs (g) and decreases at 24 hrs (h) after IV-GBCA. 3D-real IR, 3D-real inversion recovery; IV-GBCA, a single dose of gadolinium-based contrast agent.

and 24 hrs, respectively. The peak time points for the maximum signal intensity increase in the cysts differed significantly between the leakage positive and negative groups ($P = 0.0019$).

The time point of the maximum signal increase for the Sylvian fissure CSF was at 4 hrs for all patients in both the

positive and negative groups. The maximum signal intensity increase for the Sylvian fissure CSF did not significantly differ between the groups ($P = 0.376$).

For the cystic structures, the signal intensity at 24 hrs after IV-GBCA minus that at 4 hrs was 4.9 ± 13.4 (mean \pm SD) for the leakage positive group and -8.7 ± 13.8 for the leakage

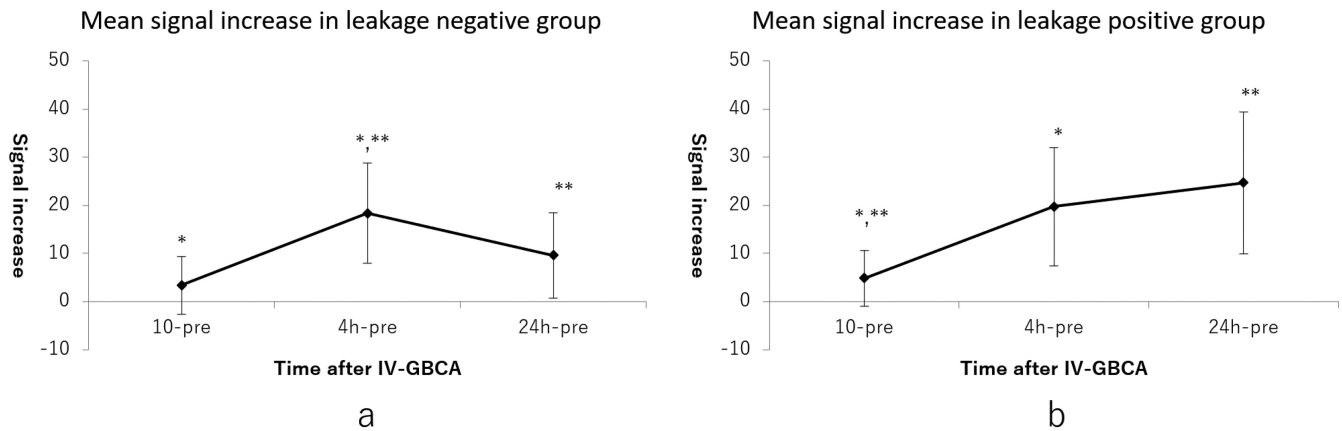


Fig. 2 The time course of the mean signal intensity increase of the perivenous cystic structures in the leakage negative (a) and positive groups (b). (a) In the leakage negative group, the intensity increase of the cysts at 4 hrs after IV-GBCA is significantly larger than that at 10 min and 24 hrs. (b) In the leakage positive group, the intensity increase of the cysts at 4 hrs and 24 hrs after IV-GBCA is significantly larger than that at 10 min. There was no significant difference between the signal change at 4 hrs and that at 24 hrs. The wash out of the content in the cysts seems to be delayed in the leakage positive group compared to the leakage negative group. IV-GBCA, intravenous of gadolinium-based contrast agent.

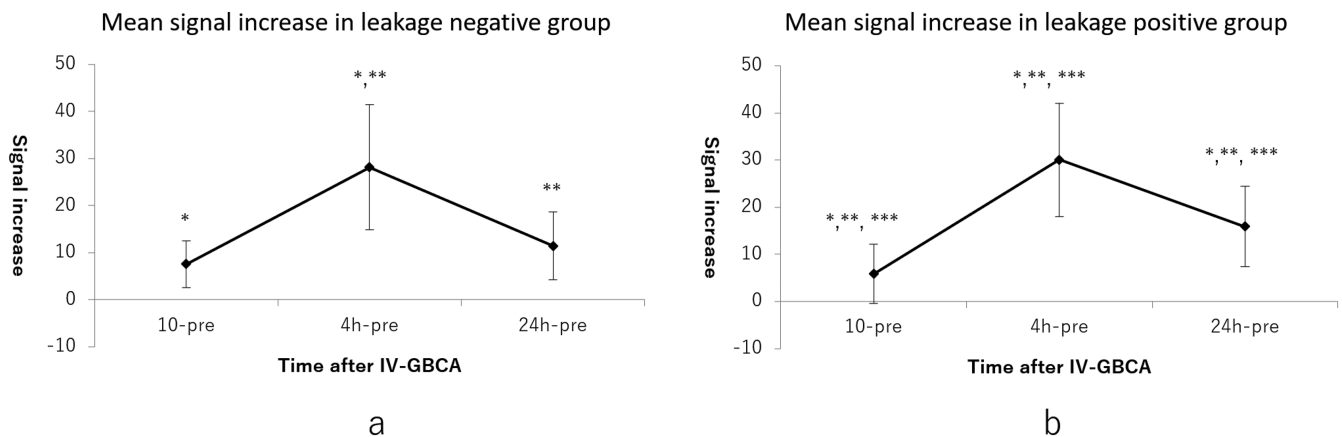


Fig. 3 The time course of the mean signal increase of the CSF in the Sylvian fissure of the leakage negative (a) and positive groups (b). (a) In the leakage negative group, the signal increase in the Sylvian fissure CSF at 4 hrs after IV-GBCA is significantly greater than that at 10 min and 24 hrs. (b) In the leakage positive group, the signal increase in the Sylvian fissure CSF at 4 hrs and 24 hrs after IV-GBCA is significantly greater than that at 10 min. There was a significant difference between all pairs. In both groups, the maximum signal increase was observed at 4 hrs after IV-GBCA. CSF, cerebrospinal fluid; IV-GBCA, intravenous of gadolinium-based contrast agent.

negative group. There was a significant difference between the groups ($P = 0.003$). For the Sylvian fissure CSF, the signal intensity at 24 hrs after the IV-GBCA minus that at 4 hrs was -14.2 ± 10.5 (mean \pm SD) for the leakage positive group and -16.7 ± 9.6 for the leakage negative group. There was no significant difference between the groups ($P = 0.401$).

Discussion

In the present study, there was no significant difference in the degree of increased signal intensity in the CSF of the Sylvian fissure between the positive and negative groups for leakage

of GBCA into the subarachnoid space around the cortical veins. The time point for the contrast peak of the CSF in the Sylvian fissure was 4 hrs after IV-GBCA in both groups. The Sylvian fissure is apart from parietal area, where perivenous leakage is frequently observed. The CSF signal of Sylvian fissure might not be mainly affected by the perivenous GBCA leakage in the parietal area.

The degree of an increase in signal intensity in the perivenous cysts peaked at 4 hrs and decreased significantly at 24 hrs in the negative group, whereas in the positive group the peak was indistinct and remained high until 24 hrs, with a tendency for the GBCA washout to be prolonged. Additionally, the

maximum degree of contrast enhancement in the cysts was significantly higher in the positive group than in the negative group.

For the first time, differences were found in the degree and time course of the GBCA distribution into the perivenous cysts between the leakage positive and negative groups. Currently, we can only speculate on the cause of these differences. We hypothesize that this result, together with previous morphological reports,¹ indicates an impaired communication between the perivenous cysts and the perivenous space, or a stagnation of the flow in the perivenous space in the leakage positive group. However, it is also possible to speculate differences in communication from the perivenous cysts and the subarachnoid space between the positive and negative groups, or that differences in the vascular permeability of the perivenous cyst walls between the positive and negative groups might be the cause.

It has been shown in animals that stimulation of the brain, which simulates a migraine aura, does not change the diameter of veins on the surface of the brain, but changes the size of the perivascular space around the veins on a minute-by-minute basis.¹⁵ In the images shown in the reported study, the perivascular space around the veins seemed to correspond to the perivenous space around the cortical veins as visualized on the 3D-real IR images in this study. The present data provide a basis for estimating the relationship between the perivenous cysts, the perivenous space and the meningeal lymphatic vessels. However, the present results are insufficient to further elucidate the role of the perivenous cysts in the dynamics of CSF and interstitial fluid. In the future, the degree of GBCA leakage for each cortical vein needs to be examined in detail to determine the pattern of signal intensity changes of the cysts in contact with that particular vein. Furthermore, a greater number of cases and imaging time points may be needed to fully elucidate the fluid dynamics of the cysts. Of course, it is also important to study the histology of perivenous cysts in various animal and human specimens of different ages.¹⁶

The parasagittal dura has been shown to play an important role in CSF drainage in humans using intrathecal administration of GBCA.¹⁷ The parasagittal dura has been a subject of research interest for some time,^{18,19} but the perivenous cysts in the vicinity of the parasagittal dura, which were studied here, have only been reported recently.¹⁴ Future studies of the glymphatic system and the meningeal lymphatics might also focus on the perivenous cysts, as well. The schematic diagram for the presumed anatomy of parasagittal area and cystic structure can be found in the recently published review article.²⁰

The limitations of the present study are as follows. Selection bias cannot be ruled out because the cases included were all patients with suspected endolymphatic hydrops and did not include perfectly healthy individuals. The determination of the presence or absence of leakage of GBCA into the subarachnoid space around the cortical veins was subjective,

although the criteria were determined quite carefully, and as described, similar to the previous studies.^{4,14} In the present study, we evaluated the perivenous leakage of GBCA just as positive or negative. The correlation between the degree of GBCA leakage and the signal change of cysts might be evaluated in the future study. The signal intensity measurements in the perivenous cysts were performed by manual placement of the ROIs, although the methods for the measurements were also defined in detail as indicated previously. The measurements utilized the 3D-real IR signal intensity itself, and because the signal intensity in the parenchyma of the brain, which is largely unaffected by the contrast agent, is close to zero, the ratio to a reference was not used. However, considering that the signal intensity of the cysts was measured in a nearly identical place near the superior sagittal sinus using a fixed receiver gain and the same head coil in all cases, we consider this measurement method to be sufficient, if not ideal. The use of an external phantom for a signal intensity reference may be considered for future studies in healthy subjects. The molecular weight of the GBCA used in this study was 604.71 g/mol, which is different from that of water molecules and other waste products. The dynamics of various waste products and that of GBCA are expected to be different. Considering these limitations, our results suggest that the perivenous cysts in the vicinity of the superior sagittal sinus might be associated with a mechanism of brain waste clearance, which has not received much attention until now, and may provide an opportunity for further research on the mechanisms of brain waste clearance in the future.

Conclusions

There was an association between signal changes over time after IV-GBCA in perivenous cystic structures near the superior sagittal sinus and the leakage of GBCA into the subarachnoid space in patients with suspected endolymphatic hydrops. Fluid turnover in the cystic structures of the leakage positive group seemed to be delayed compared to that of the leakage negative group. Signal intensity in the cystic structures in the pre-contrast images or images obtained at 10 min after IV-GBCA did not predict the GBCA leakage to the subarachnoid space. Further study to clarify the significance of these cystic structures in the waste clearance system of the brain is warranted.

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Conflicts of Interest

Toshiaki Taoka and Rintaro Ito are the professors in the Department of Innovative Biomedical Visualization

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The other authors declare that they have no conflicts of interest regarding this manuscript.

References

- Naganawa S, Ito R, Taoka T, et al. The space between the pial sheath and the cortical venous wall may connect to the meningeal lymphatics. *Magn Reson Med Sci* 2020; 19:1–4.
- Naganawa S, Ito R, Kato Y, et al. Intracranial distribution of intravenously administered gadolinium-based contrast agent over a period of 24 Hours: evaluation with 3D-real IR imaging and MR fingerprinting. *Magn Reson Med Sci* 2021; 20:91–98.
- Naganawa S, Nakane T, Kawai H, et al. Age dependence of gadolinium leakage from the cortical veins into the cerebrospinal fluid assessed with whole brain 3D-real inversion recovery MR imaging. *Magn Reson Med Sci* 2019; 18:163–169.
- Naganawa S, Ito R, Kawai H, et al. Confirmation of age-dependence in the leakage of contrast medium around the cortical veins into cerebrospinal fluid after intravenous administration of gadolinium-based contrast agent. *Magn Reson Med Sci* 2020; 19:375–381.
- Naganawa S, Nakane T, Kawai H, et al. Detection of IV-gadolinium leakage from the cortical veins into the CSF using MR fingerprinting. *Magn Reson Med Sci* 2020; 19:141–146.
- Da Mesquita S, Fu Z, Kipnis J. The meningeal lymphatic system: a new player in neurophysiology. *Neuron* 2018; 100:375–388.
- Absinta M, Ha SK, Nair G, et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *eLife* 2017; 6:e29738. doi:10.7554/eLife.29738.
- Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; 523:337–341.
- Albargothy NJ, Johnston DA, MacGregor-Sharp M, et al. Convective influx/lymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. *Acta Neuropathol* 2018; 136:139–152.
- Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med* 2012; 4:147ra111.
- Zhou Y, Cai J, Zhang W, et al. Impairment of the glymphatic pathway and putative meningeal lymphatic vessels in the aging human. *Ann Neurol* 2020; 87:357–369.
- Hershenhouse KS, Shauly O, Gould DJ, et al. Meningeal lymphatics: a review and future directions from a clinical perspective. *Neurosci Insights* 2019; 14:1179069519889027.
- Mestre H, Mori Y, Nedergaard M. The brain's glymphatic system: current controversies. *Trends Neurosci* 2020; 43:458–466.
- Naganawa S, Ito R, Nakamichi R, et al. Relationship between parasagittal perivenous cysts and leakage of gadolinium-based contrast agents into the subarachnoid space around the cortical veins after intravenous administration. *Magn Reson Med Sci* 2021; 20:245–252.
- Schain AJ, Melo-Carrillo A, Strassman AM, et al. Cortical spreading depression closes paravascular space and impairs glymphatic flow: implications for migraine headache. *J Neurosci* 2017; 37:2904–2915.
- Kutomi O, Takeda S. Identification of lymphatic endothelium in cranial arachnoid granulation-like dural gap. *Microscopy (Oxf)* 2020; 69:391–400.
- Ringstad G, Eide PK. Cerebrospinal fluid tracer efflux to parasagittal dura in humans. *Nat Commun* 2020; 11:354.
- Fox RJ, Walji AH, Mielke B, et al. Anatomic details of intradural channels in the parasagittal dura: a possible pathway for flow of cerebrospinal fluid. *Neurosurgery* 1996; 39:84–91.
- Johnston KD, Walji AH, Fox RJ, et al. Access to cerebrospinal fluid absorption sites by infusion into vascular channels of the skull. *J Neurosurg* 2007; 107:841–843.
- Naganawa S, Taoka T. The glymphatic system: A review of the challenges in visualizing its structure and function with MR imaging. *Magn Reson Med Sci* 2020 Nov 27. doi.org/10.2463/mrms.rev.2020-0122. [Epub ahead of print]