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MAJOR PAPER

Relationship between Parasagittal Perivenous Cysts and Leakage of Gadolinium-based Contrast Agents into the Subarachnoid Space around the Cortical Veins after Intravenous Administration

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Purpose: The purpose of this retrospective study was to investigate the relationship between the number and size of cystic structures around the cortical veins near the superior sagittal sinus and the leakage of gadolinium-based contrast agent (GBCA) around the cortical veins.

Methods: Of 190 patients (91 male and 99 female), that were scanned at 4 h after an intravenous injection of GBCA as a diagnostic examination for endolymphatic hydrops, 6 patients with GBCA leakage were younger than the previously proposed threshold age of 37.3 years for leakage. Six age-matched patients without leakage were also included for reference. In addition, we included 8 cases without leakage that were older than the hypothesized threshold of 37.3 years, as well as 8 age-matched patients with GBCA leakage into the cerebrospinal fluid space. The number of cysts was counted and the sizes were measured in these 28 patients (age: 32–60 years old, 13 men and 15 women).

Results: The mean number of cysts surrounding the cortical veins in the parasagittal region was 4.29 ± 1.77 vs. 1.79 ± 1.05 ($P = 0.0001$) in the subjects with and without GBCA leakage, respectively. The mean size of the largest cysts was at 8.89 ± 3.49 mm vs. 5.69 ± 2.29 ($P = 0.009$) in the subjects with and without GBCA leakage, respectively.

Conclusion: The number and size of the perivenous cystic structures near the superior sagittal sinus is greater in subjects with GBCA leakage into the subarachnoid space compared with those without leakage. Future research regarding the histological and functional details of these parasagittal cystic structures is needed.

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

Introduction

Although it had long been believed that the brain has no lymphatic vessels, they have been recently identified *in vivo*.[1] Meningeal lymphatic vessels exist along the superior sagittal sinus and have been visualized in human subjects by contrast-enhanced MRI.[2] The details of the drainage pathway from the cerebrospinal fluid (CSF) in the subarachnoid space to the meningeal lymphatic vessels are still unknown, but the following studies using gadolinium-based contrast agents (GBCAs) have elucidated part of this drainage pathway.

Serial 3D-real inversion recovery (IR) imaging revealed the distribution over time of the GBCA in the subpial space around the cortical veins at 5 min after intravenous (IV) injection. At 4 h after the injection of GBCA, the leakage into the surrounding subarachnoid space was seen mostly in subjects over the age of 37.[3,4] Furthermore, imaging findings have indicated that the subpial space around the cortical veins seems to be continuous with the meningeal lymphatic vessels along the superior sagittal sinus.[5]

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Color-coded images generated from decomposed data into various T_2 components using non-contrast enhanced multi-echo imaging suggested that interstitial fluid with a higher protein concentration was distributed around the cortical veins.[6] It was recently also reported that there was gadolinium deposition in the pia-ensheathed leptomeningeal vessels in the histology of a human patient that had received repeated IV-GBCA.[7] In other words, this accumulating evidence suggests that the subpial space around the cortical veins is a part of the drainage pathway for the interstitial fluid of the brain, i.e., the downstream part of the glymphatic system.

We have observed many cases of delayed 3D-real IR imaging of the whole brain that were obtained at 4 h after IV-GBCA in patients with a suspicion of endolymphatic hydrops.[3,8,9] In patients showing GBCA leakage into the subarachnoid space around the cortical veins, we have frequently encountered cystic structures surrounding the cortical veins near the superior sagittal sinus. Therefore, we hypothesized that these parasagittal cystic structures might be storage cysts that are formed when there is an obstruction or stenosis in the drainage pathway, which could occur if the subpial space around the cortical vein was continuous with the meningeal lymphatic vessels around the superior sagittal sinus.[5]

The purpose of this retrospective study was to investigate whether or not there was a relationship between the number and size of the cystic structures around the cortical veins near the parasagittal sinus and the presence or absence of leakage of gadolinium contrast agent around the cortical veins.

Materials and Methods

The subjects included 190 patients (91 male and 99 female), who were scanned at 4 h after an intravenous injection of GBCA as a diagnostic examination for endolymphatic hydrops. This patient cohort was identical to the previously reported study that evaluated the relationship between the patient's age and GBCA leakage around the cortical veins.[4] The patients' age ranged from 14 to 81 years and the median age was 50 years. In all cases, the estimated glomerular filtration rate was 60 mL/min/1.73 m^2 or greater. There were no cases with brain tumors or large cerebral infarctions and no apparent history of subarachnoid hemorrhage, head trauma or central nervous system infection.

Of these, 6 patients had apparent GBCA leakage, but were younger than the previously proposed age threshold for leakage (i.e., 37.3 years old).[4] We also selected 6 age-matched patients without leakage for comparison. In addition, we included 8 patients without GBCA leakage that were older than the age threshold of 37.3 years and 8 age-matched patients with GBCA leakage. For the analysis, if there were multiple candidates of the same age, the one with the closest birthday to the patient of interest was selected. The number of cysts was counted and the size of each cyst was measured in all 28 patients (age: 32–60 years old, 13 men and 15 women) according to the criteria and methods indicated below. The ethical committee of our institution approved this retrospective study with a waiver of consent from the patients.

Magnetic resonance imaging

The axial 3D-real IR images covering the entire brain were obtained at 4 h after an intravenous injection of a single dose (0.1 mmol/kg) of macrocyclic GBCA (gadobutrol; Bayer, Osaka, Japan). A 3T MR scanner (Skyra; Siemens Healthineers, Erlangen, Germany) with a 32-channel array coil was used. The detailed parameters for the 3D-real IR imaging were the same as the previous study.[4] Briefly, a TR of 15130 ms, TE of 549 ms, TI of 2700 ms, pixel size of 0.5 × 0.5 mm^2, with 1 mm thickness, phase sensitive reconstruction (real reconstruction), and scan time of 10 min were applied.

Image evaluation

The presence of GBCA leakage around the cortical veins was determined in a manner similar to our previous report.[4] Briefly, a high signal intensity in the subarachnoid space around the cortical veins with a signal intensity value of 30 or greater, 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. On a picture archiving and communication systems (PACS) viewer (RapideyeCore; Canon Medical Systems, Tochigi, Japan), the 3D-real IR images were displayed 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 the previous study.[4] Two experienced neuroradiologists (S.N. and T.T. with 31 and 29 years of experience, respectively) independently reviewed all 256 axial, 1 mm thick, slices for each patient to determine if GBCA leakage around the cortical veins was present. Any discrepancies between the two observers were discussed and a consensus was obtained.

Two board certified radiologists (R.N. and R.I. with 7 and 10 years of experience, respectively) counted the number of cysts and, if there was a discrepancy, agreed after discussion.

The method and criteria for determining a cyst were as follows:

1. The 3D-real IR obtained at 4 h after an intravenous injection of gadolinium contrast agent was displayed at a Window level of 20 and Window width of 200, and the number of cysts satisfying the following conditions was calculated.
2. Only the slices above the superior edge of the lateral ventricle were reviewed. The number of 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 counted. Those with a long axis diameter of 3 mm or longer on the axial images were also included.

3. Arachnoid granulations protruding into the superior sagittal sinus were not counted as cysts. Nodular structures with thick walls were not counted as cysts if the thick wall covered more than half of the nodular area. These are thought to be arachnoid granulations. Structures that mostly protruded into the bone were also considered to be arachnoid granulations and not counted as cysts. Cysts involved in the remodeling of the inner table of the skull were not excluded.
4. Irregularly shaped cystic structures surrounded by very thin membranous trabeculae in the subarachnoid space were presumed to be caused by arachnoiditis and not counted 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 counted as cysts.
5. Multiplanar reconstruction function was used to characterize the relationship between the surrounding brain parenchyma, vessels, and the remodeling of the skull.

Finally, the long axis length of the largest cyst from each patient on the axial slice was also measured by an experienced neuroradiologist (S.N.).

Statistical analysis

Intraclass correlation coefficients (ICC 2,1) for the agreement of the number of the cysts between the two radiologists were calculated. The average number of cysts and the size of the cysts were compared between patients with and without GBCA leakage around the cortical veins. A Welch's *t*-test was used for comparison. A Spearman's rank correlation coefficient was calculated between age and the number of cysts, and between age and the size of the cysts. The statistical software used was SPSS Statistics version 24 (IBM Japan, Tokyo, Japan), and $P < 0.05$ was set as the threshold for significant differences.

Results

Representative images are shown in Figs. 1–4. Table 1 indicates the patient age, gender, presence or absence of the GBCA leakage, and the number of cysts. The long axis length of the largest cyst is also indicated in Table 1.

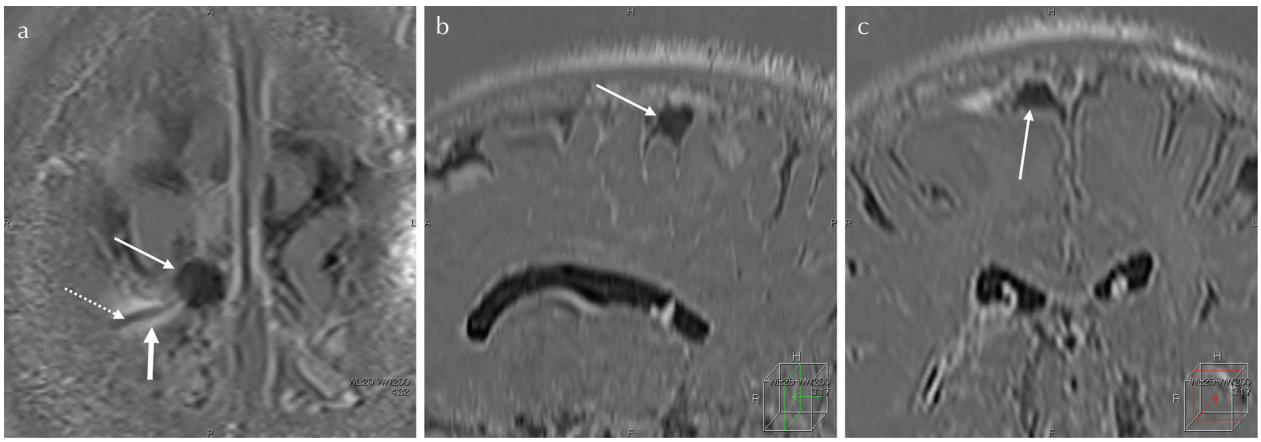

Fig. 1 A 52-year-old woman. The axial (**a**), sagittal (**b**) and coronal (**c**) views of 3D-real IR images obtained at 4 h after intravenous administration of GBCA. A cystic area with a long diameter of 10.7 mm (arrows, **a**–**c**) is seen adjacent to the cortical vein (dotted arrow, **a**) and the superior sagittal sinus. GBCA leakage along the cortical vein is visualized (**a**, bold arrow). The cyst is slightly compressing the adjacent brain parenchyma (**a**–**c**). Signal of the cysts are similar to that of cerebrospinal fluid without apparent GBCA distribution. GBCA, gadolinium-based contrast agent.

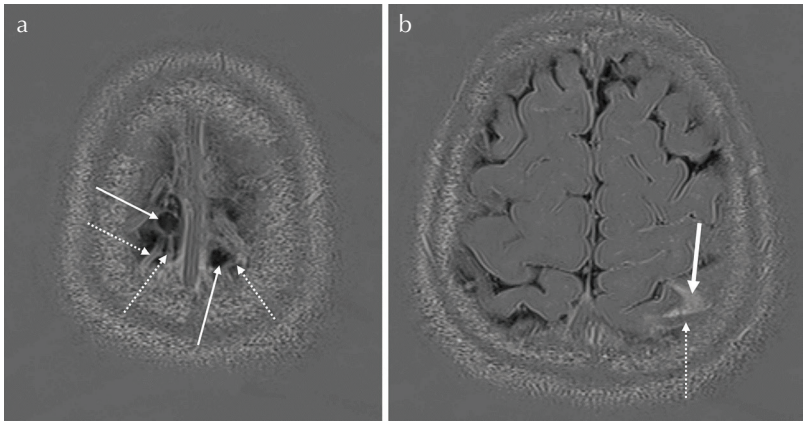

Fig. 2 Axial 3D-real IR images (**a** and **b**) obtained at 4 h after intravenous administration of GBCA in a 32-year-old man with GBCA leakage around the cortical vein. Cystic structures (arrows, **a**) close to the cortical veins (dotted arrows, **a**) are visualized bilaterally near the superior sagittal sinus. At a lower slice (**b**), the GBCA leakage (bold arrow, **b**) along the cortical vein (dotted arrow, **b**) is visualized. GBCA, gadolinium-based contrast agent.

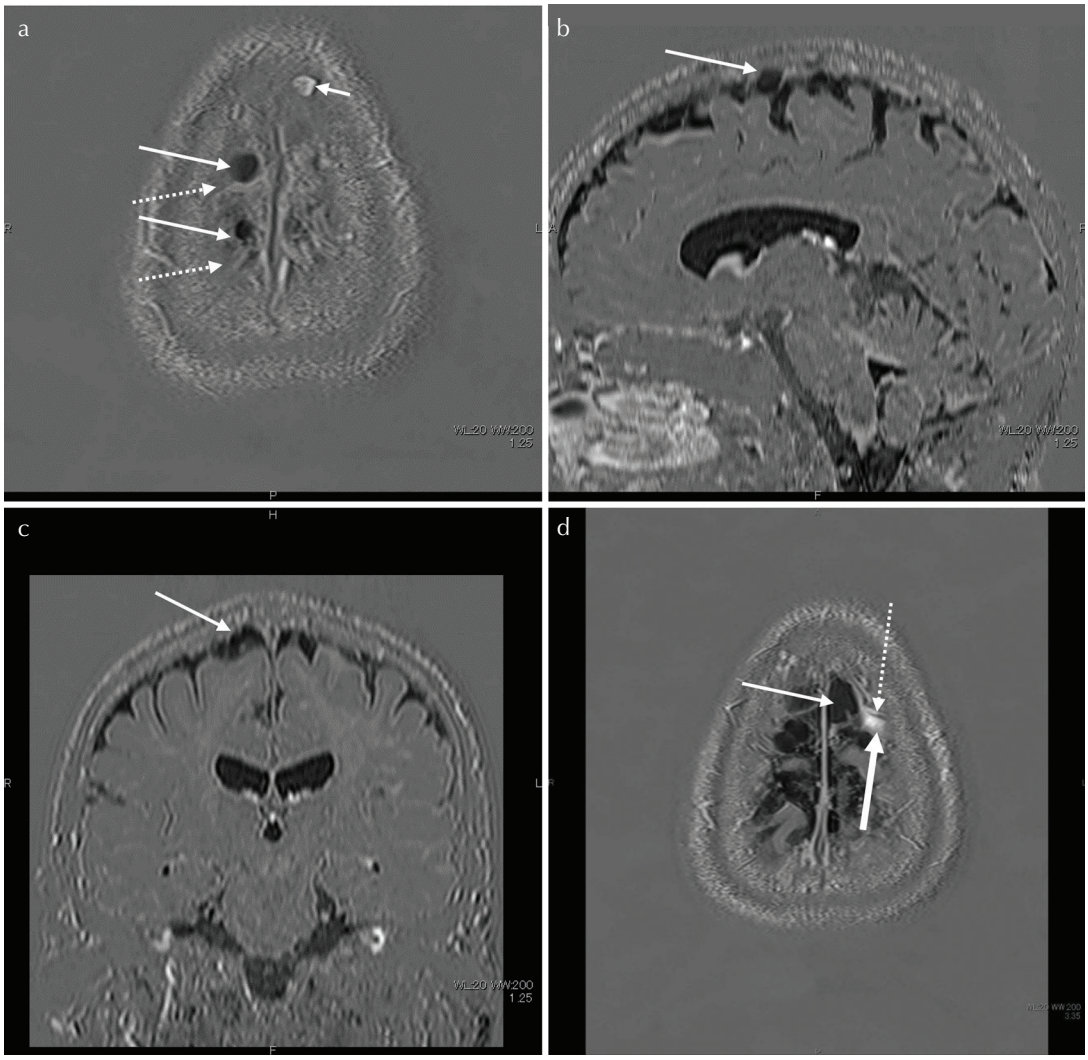

Fig. 3 A 60-year-old man. The axial (**a**), sagittal (**b**) and coronal (**c**) views of 3D-real IR images obtained 4 h after intravenous administration of GBCA. A lower level of the axial image (**d**) is also shown. Cystic structures (arrows, **a**–**c**) are seen adjacent to the cortical vein (dotted arrows, **a**) and the superior sagittal sinus. A cyst is slightly compressing the adjacent inner table of the skull (arrows, **b** and **c**). A nodular structure with high signal intensity (short arrow, **a**) protruding into the skull was identified as an arachnoid granulation. GBCA leakage along the cortical vein (dotted arrow, **d**) is visualized (bold arrow, **d**). Another cyst (arrow, **d**) is seen near the leakage. GBCA, gadolinium-based contrast agent.

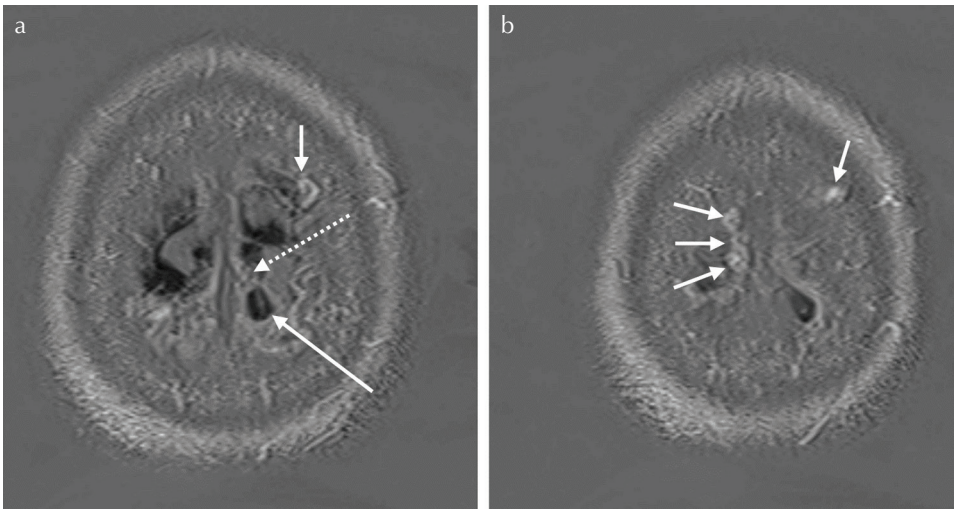

Fig. 4 An axial 3D-real IR image obtained at 4 h after intravenous administration of GBCA (**a**) in a 60-year-old woman without GBCA leakage. An upper level of the axial image (**b**) is also shown. A small cystic structure (arrow, **a**) is visible close to the cortical vein (dotted arrow, **a**) and the superior sagittal sinus. Nodular structures with high signal intensity (short arrows, **a** and **b**) protruding into the skull or aligned along the superior sagittal sinus were identified as arachnoid granulations. GBCA, gadolinium-based contrast agent.

Table 1 Age, gender, number of cysts, and size of the largest cyst in the leakage positive and negative group

Age	Leak positive			Leak negative		
	Gender	Number of cysts	Size of the largest cyst	Gender	Number of cysts	Size of the largest cyst
32	M	3	9.7	M	1	6.9
33	M	3	5.6	F	2	4.7
34	M	7	8.7	F	2	4.0
34	M	4	6.5	F	2	5.1
35	M	2	7.8	M	4	8.3
36	M	3	6.3	F	1	6.1
39	F	6	7.7	F	1	3.1
46	M	4	8.2	M	3	5.4
46	M	3	7.2	F	1	8.2
47	F	3	7.6	F	2	7.2
48	F	5	7.2	M	3	5.4
49	F	7	11.8	F	0	0
52	F	3	10.7	F	2	7.3
60	M	7	19.5	F	1	7.9
Average		4.29	8.89		1.79	5.69
Standard deviation		1.77	3.49		1.05	2.29

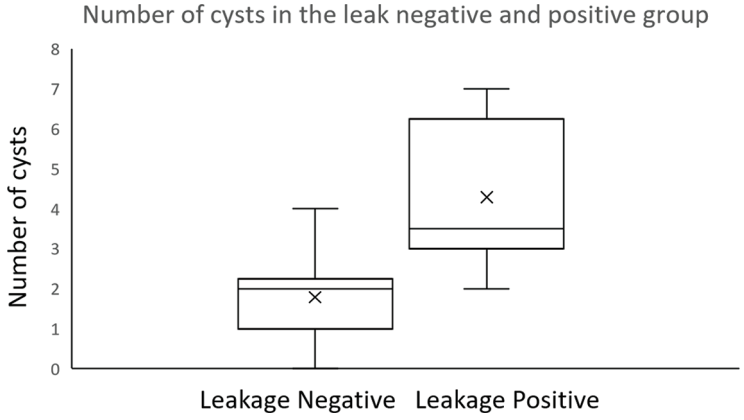

Fig. 5 A box-and-whisker plot of the number of cysts in the GBCA leakage negative and positive patients. The lower side of the rectangle is the first quartile (25th percentile value) and the upper side is the 75th percentile value. The horizontal line in the rectangle is the median. The horizontal line under the whisker indicates the 10th percentile value, and the horizontal line above the whisker indicates the 90th percentile value. The cross sign in the rectangle is the mean. There is a significant difference between the groups (P = 0.0001). GBCA, gadolinium-based contrast agent.

The ICC between the two radiologists for the number of cysts was very high at 0.981 (95% confidence level 0.956–0.991). The mean number of cysts around cortical veins in the parasagittal region was 4.29 ± 1.77 vs. 1.79 ± 1.05 (mean ± standard deviation) (P = 0.0001) for patients with and without GBCA leakage, respectively at 4 h after administration. There was a significantly greater number of cysts in the group with GBCA leakage than in the group without leakage (Fig. 5).

The mean long axis diameter of the largest cyst around the cortical veins in the parasagittal region was 8.89 ± 3.49 vs. 5.69 ± 2.29 mm (mean ± standard deviation) (P = 0.009) for patients with and without GBCA leakage. The mean long axis diameter of the cysts was significantly larger in patients with leakage than in those without leakage (Fig. 6).

The Spearman's rank correlation coefficient (R_s) was 0.109 between age and the number of cysts and 0.333 between age and the long axis diameter of the cysts. Both are smaller than the R_s significance threshold of 0.375 (Fig. 7).

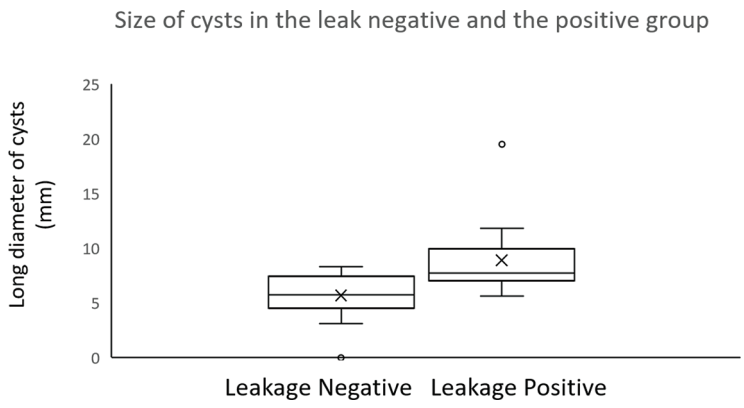

Fig. 6 A box-and-whisker plot of the long diameter of the largest cyst in the GBCA leakage negative and positive patients. The lower side of the rectangle is the first quartile (25th percentile value) and the upper side is the 75th percentile value. The horizontal line in the rectangle is the median. The horizontal line under the whisker indicates the 10th percentile value, and the horizontal line above the whisker indicates the 90th percentile value. The cross sign in the rectangle is the mean. There is a significant difference between the groups (P = 0.009). GBCA, gadolinium-based contrast agent.

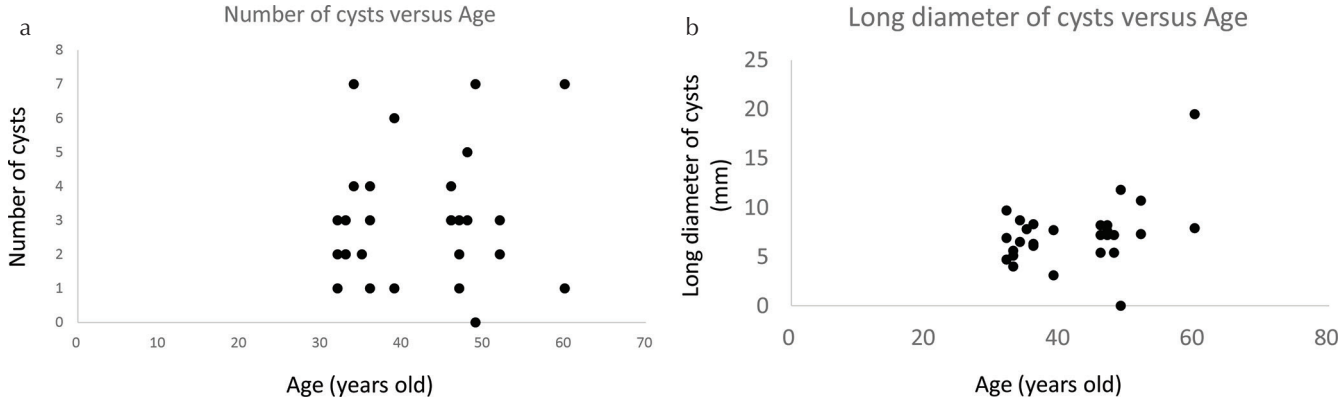

Fig. 7 A scatter plot of the number of cysts vs. patient age (**a**). There was no significant correlation (R_s = 0.109). Significance level for R_s was 0.375. A scatter plot of the number of cysts vs. patient age (**b**). Although there appears to be a small correlation, it was not statistically significant (R_s = 0.333). Significance level for R_s was 0.375. R_s, Spearman's rank correlation coefficient.

Discussion

The glymphatic system has attracted much attention as a mechanism for the excretion of waste products from the brain,[10–14] and has been actively studied for its association with Alzheimer's disease,[15,16] normal pressure hydrocephalus,[17,18] and sleep.[19] Some investigators have performed studies to better understand this system, focusing on upstream, middle and downstream processes of the glymphatic system as indicated below.

Research of the upstream part of the glymphatic system has focused on the production of cerebrospinal fluid (CSF) and has indicated that the choroid plexus may not be the main production site for CSF. Alternatively, the brain capillaries were found to be the main site for CSF production, and there was very little separation between the interstitial fluid and the cerebrospinal fluid in the brain.[20,21] It was also noted that blood-brain barrier (BBB) permeability was enhanced in Alzheimer's disease.[22,23]

For the mid-portion of the glymphatic system, the CSF in the subarachnoid space migrates deep into the brain from the perivascular space around the arteries, enters the brain parenchyma via aquaporin 4 in the astrocytic foot process, drains waste products, and exits from the perivenous space.[24] This part of the system has been studied by the intrathecal administration or the intraparenchymal administration of tracers,[18,25–28] and the visualization of water movement in the brain parenchyma using diffusion tensor-based imaging techniques without tracers has been also attempted.[29,30] In addition, the intra-arterial perivascular drainage (iPAD) pathway,[31] which drains in the direction opposite to the blood flow in the arterial wall itself, has also been proposed as an important alternative drainage route. Details of the relative capacities and roles of the glymphatic versus iPAD pathways remain unclear.

For the downstream portion of the glymphatic system, two subparts have been described.[32] One is the path, by which CSF flows out of the perivenous space around the veins in the brain parenchyma to the subpial space in the subarachnoid space around the vessels.[33] The other is the drainage pathway called the parasagittal dura complex, which contains the arachnoid granulations, intradural channels, and meningeal lymphatics along superior sagittal sinus.[26,34] The connection

between these 2 subparts remains unclear. We speculate that the connection between the subpial space around the cortical veins to the parasagittal dura complex might be an important factor in this missing link.[5] In addition to studies using the intravenous administration of tracers, there are studies examining GBCA transport into the parasagittal dura after intrathecal administration.[26]

Age is a predicting factor for GBCA leakage around the cortical veins.[3,4] The number of arachnoid granulations protruding into the venous sinus was not a good indicator for GBCA leakage around the cortical veins.[4] In this study, we examined the pathological or aging conditions in the downstream part of the glymphatic system from the perspective of the relationship between intravenously administered tracer leakage around the cortical veins and parasagittal cyst formation. This study found that the number of cystic structures around the cortical veins in the parasagittal area was significantly different between patients with and without GBCA leakage.

In other words, cystic structures may be storage cysts that are formed when the subpial space around the cortical vein is occluded or stenotic and the drainage of interstitial fluid to the meningeal lymphatic vessels around the superior sagittal sinus is restricted. The results of the study are consistent with this hypothesis. Also, our speculation that incidental cysts (i.e., arachnoid cysts) could be compressing the subpial space around the cortical veins might be compatible with these findings. This study found no significant correlation between age and the number of the cysts or age and the size of the cysts. The size and age were slightly correlated, although not significant. One might also speculate that some cysts exist from a younger age and these grow as the patient ages. Further studies are needed to elucidate the pathophysiological mechanisms of parasagittal cysts.

There are some limitations to this study. The number of patients was small and all patients had a suspicion of endolymphatic hydrops. No histological evidence was obtained for the cystic structures near the parasagittal sinus and cortical veins or for the continuity of the subpial space around cortical veins. Detailed histological studies of the parasagittal dura do not mention the cystic structures observed in this study.[34] Naturally, the CSF signal intensity in the parasagittal area might be higher in the patients with GBCA leakage than in those without leakage. This difference might have biased the identification of the cystic areas. However, the identification of the cysts was mostly based on the presence of the cyst wall and the displacement of the cortical veins or brain parenchyma, as well as skull remodeling. Therefore, the degree of enhancement in the surrounding CSF might not be a key factor in the identification of cysts. Furthermore, even in patients with positive GBCA leakage, sometimes the CSF around cyst was not enhanced, due to the uneven distribution of the GBCA in the subarachnoid space of the parietal area (Figs. 1–3). To clarify the relationship between the total amount of GBCA in CSF space and number of parasagittal perivenous cysts might be an interesting future research theme.

There is an another limitation. The only confounding factor that could be eliminated in this study was age. Other confounding factors such as gender, the presence of cerebral white matter lesions, and comorbidities such as hypertension could not be excluded. To clarify the contribution of these factors to the findings, we must wait for larger prospective studies.

It has recently been reported that GBCAs may be found in the parasagittal dura after intrathecal administration.[26] Whether CSF migrates directly through the dura itself to the channels in the parasagittal dura, or CSF permeates through small arachnoid granulations, or through the stomata in the pial-sheath around the cortical veins is unknown.[34,35] Parasagittal dura might be a complex of meningeal lymphatics, lateral lacuna, a large number of channels, and small arachnoid granulations. It could be the "primary organ" of the excretory pathway, which may be termed the "parasagittal dura unit". Further histological examination and tracer studies will elucidate the anatomy, physiology, and pathology of the parasagittal dura unit, which will be an important future area of research.

Conclusion

The number and size of cystic structures around the parasagittal sinus and cortical veins is associated with GBCA leakage into the subarachnoid space from the subpial space around the cortical veins. Future research regarding the histological and functional details of parasagittal cystic structures is needed.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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