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Detection rate of MR myelography without intrathecal gadolinium in patients with newly diagnosed spontaneous intracranial hypotension

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AIM: To evaluate the detection rate of magnetic resonance (MR) myelography without intrathecal gadolinium for cerebrospinal fluid (CSF) leakage in patients with newly diagnosed spontaneous intracranial hypotension (SIH) and to validate a published scoring system for predicting CSF leakage.

MATERIALS AND METHODS: This retrospective, observational, single-institution study included patients with newly diagnosed SIH between March 2015 and April 2021. Patients were included if they (a) had newly diagnosed SIH and (b) underwent initial brain MR imaging and preprocedural MR myelography with two- and three-dimensional turbo spin-echo sequences. Patients who underwent spine surgery or procedures including epidural injection and acupuncture were excluded. The detection rate was defined as the proportion of patients with a true-positive MR myelography result among all patients with confirmed CSF leakage. The interobserver agreement for the MR myelography results between two radiologists was analysed using weighted kappa statistics.

RESULTS: A total of 136 patients (mean age, 48 years; 70 women) with suspected SIH were included. Of these patients, 120 (88%, 120/136) were confirmed to have CSF leakage. Of the patients with confirmed CSF leakage, 90 (75%, 90/120) had epidural fluid collection. The detection rate of MR myelography for CSF leakage was 88% (105/120). The interobserver agreement between the two readers for detecting CSF leakage ($\kappa = 0.76$) or epidural fluid collection ($\kappa = 0.76$) on MR myelography was high. Among 24 patients with normal brain MR imaging results, 16 had CSF leakage (67%, 16/24).

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CONCLUSIONS: Non-invasive MR myelography without intrathecal gadolinium should be considered to detect CSF leakage in patients with suspected SIH.

Introduction

Spontaneous intracranial hypotension (SIH) is a condition in which the fluid pressure inside the skull is lower than normal. Currently, the standard method for diagnosing cerebrospinal fluid (CSF) leakage in patients with SIH is computed tomography (CT) myelography. However, magnetic resonance (MR) myelography without gadolinium injection has recently been suggested as another option for detecting CSF leakage in patients with SIH, owing to its non-invasive characteristic and non-inferiority to CT myelography.[1–3] The diagnostic yield of MR myelography without gadolinium injection in previous studies was 67–100%[3–13]; however, these studies had several limitations, such as a small sample size, lack of interobserver agreement, or retrospective study and single-centre design.

Recently, a scoring system for MR imaging (MRI) findings in patients with SIH has been suggested.[14] In this scoring system, typical signs such as pachymeningeal enhancement, engorgement of the venous sinus, and effacement of the suprasellar cistern ≤4 mm are given 1 or 2 points each. If these signs are not found on brain MRI, CSF leakage is likely absent; however, the scoring system has not been validated externally in other institutions. Moreover, it has also been reported that CSF leakage may be present despite negative brain MRI findings.[12]

The aim of the present study was to evaluate the detection rate for CSF leakage of MR myelography without gadolinium injection in patients with newly diagnosed SIH and to validate a published scoring system for predicting CSF leakage.

Materials and Methods

Study design

This retrospective, observational, single-institution study was approved by our local ethics committee and institutional review board. The requirement for informed consent was waived owing to the retrospective study. This study was conducted in accordance with the guidelines of the Standards for Reporting of Diagnostic Accuracy Studies.[15,16]

We reviewed the medical records and images of patients with suspected SIH who underwent preprocedural MR myelography at Asan Medical Center between March 2015 and April 2021. SIH was diagnosed by the International Classification of Headache Disorder (3rd edition) when the CSF pressure is low (<60 mm) or there is evidence of CSF leakage on the imaging.[17]

Patients

Overall, 159 consecutive patients with suspected SIH underwent preprocedural MR myelography. Patients were included in this study if they (a) had clinically diagnosed SIH based on symptoms and (b) underwent initial brain MRI and preprocedural MR myelography with two-dimensional (2D) and three-dimensional (3D) turbo spin-echo sequences. Patients who underwent spine surgery or any procedure including epidural injection and acupuncture were excluded. The clinical characteristics of the patients are summarised in Table 1.

MR myelography

MR myelography was performed using a 3 T MRI unit (Ingenia or Achieva, Philips Healthcare, Best, Amsterdam, Netherlands). The routine MR myelography protocol included sagittal T2-weighted images, 2D and 3D heavily T2-weighted turbo spin-echo pulse sequences with fat saturation. The entire spine was scanned at three separate levels (i.e., cervical, thoracic, and thoracolumbar areas), which overlapped at the margins. The 2D turbo spin-echo sequence is made by reconstructing the maximum intensity projection images with a single slap by imaging scan in the coronal orientation. Axial and sagittal images and coronal maximum intensity projection images with thin sections were

Table 1
Characteristics of the study population (n=136).

Characteristics	No. (%)
Age[a] (years)	48 ± 12
Sex	
Female	70 (51%)
Male	66 (49%)
Symptoms	
Orthostatic headache	120 (88%)
Nausea or vomiting	80 (67%)
Neck pain or stiffness	57 (42%)
Dizziness	45 (33%)
Other ear-related symptom	42 (31%)
Tinnitus	39 (29%)
Non-orthostatic headache	12 (9%)
Photophobia	9 (7%)
Hearing disturbance	8 (6%)
Cognitive symptom	8 (6%)
Movement disorders	7 (5%)
Back pain	6 (5%)
Other visual symptoms	6 (5%)
Diplopia	3 (2%)
Vertigo	3 (2%)
Reduced consciousness level	0 (0%)
Symptom improvement	122 (89%)

[a] Data are mean ± standard deviation.

Table 2
Detailed protocols of magnetic resonance myelography.

	Sagittal T2-weighted image	2D heavily T2-weighted turbo spin-echo sequence	3D heavily T2-weighted turbo spin-echo sequence
TR/TE (ms)	2,462/120	5,456/1,000	3,000/600
Flip angle	90	90	90
Matrix size	412 × 258	512 × 512	512 × 512
FOV (mm^2)	200 × 300	270 × 270	270 × 270
Section thickness (mm)	4	50	1
TSE factor	32	256	128
Total time (min:sec)	1:28	1:32	3:27

TR, repetition time; TE, echo time; FOV, field of view; TSE, turbo spin-echo; 2D, two-dimensional; 3D, three-dimensional.

reconstructed from coronal MR myelography in a 3D turbo spin-echo sequence. The detailed MR myelography acquisition protocols are summarised in Table 2.

All MR myelography images were evaluated independently by two neuroradiologists (S.J.K. and S.J.L., with 35 and 5 years of experience in neuroradiology, respectively). Both were blinded to the clinical information and all other imaging studies evaluations performed. In addition, all MR myelography images were analysed by another neuroradiologist (C.H.S. with 10 years of experience in neuroradiology), as a mediator who was aware of the clinical information of patients and other imaging evaluations performed (e.g., radionuclide cisternography). The mediator combined the results of clinical evaluations, radionuclide cisternography, and MR myelography and established a reference standard.[4,6]

Analysis

The primary outcome was the detection rate of MR myelography for CSF leakage in patients with newly diagnosed SIH. The detection rate was defined as the proportion of patients with a true-positive MR myelography result among all patients with newly diagnosed SIH with confirmed CSF leakage (number of true-positive results divided by all SIH patients with CSF leakage).

For all included patients, brain MR images that were sufficient for analysis were evaluated blindly by two neuroradiologists (C.H.S. and S.J.L.), and discordant interpretations were resolved by consensus. Five brain MRI findings were assessed in patients with suspected SIH, as previously reported[18]: diffuse pachymeningeal enhancement, engorged venous sinus, brain sagging, enlarged pituitary gland, and subdural fluid collection. In addition, three quantitative signs (size of the suprasellar cistern, size of the prepontine cistern, and mamillopontine distance) were assessed with good discriminative power, as reported by Dobrocky *et al.*[14] Effacement of the suprasellar cistern, effacement of the prepontine cistern, and decreased mamillopontine distance can be observed in patients with SIH. For validation, the scoring system of Dobrocky *et al.*[14] was applied to the patients included in this study. The scores were calculated for all patients. Pachymeningeal enhancement, engorgement of the venous sinus, and effacement of the suprasellar cistern ≤4 mm were all given 2 points each. Subdural fluid collection, effacement of the prepontine cistern ≤5 mm, and mamillopontine distance ≤6.5 mm were given 1 point each. The patients were divided into three groups based on the estimated score: low grade (≤2), intermediate grade (3–4), and high grade (≥5).

Statistical analysis was performed using MedCalc version 20.023 (MedCalc Software, Ostend, Belgium). Data were analysed descriptively as frequencies and percentages for categorical variables and mean (± standard deviation) for continuous variables. The interobserver agreement for the MR myelography results between the two radiologists was analysed using weighted kappa statistics. Statistical significance was set at a *p*-value of 0.05, which was considered to be significant.

Results

Patient characteristics

Between March 2015 and April 2021, a total of 159 patients were assessed for initial eligibility. Patients who underwent procedures, such as lumbar puncture, acupuncture, and epidural injection (n=15), and those who had a previous operation (n=8) were excluded. Fig. 1 shows the flow diagram of the patients in this study. A total of 136 patients with clinically diagnosed SIH were included to determine the detection rate of MR myelography for CSF leakage. Patient characteristics are shown in Table 1. The mean patient age was 48 years, and 70 patients (51%) were women. Among the 136 patients, orthostatic headache was the major symptom (88%, 120 of 136). Other symptoms included nausea or vomiting (59%, 80 of 136), neck pain or stiffness (42%, 57 of 136), and dizziness (33%, 45 of 136). The most common

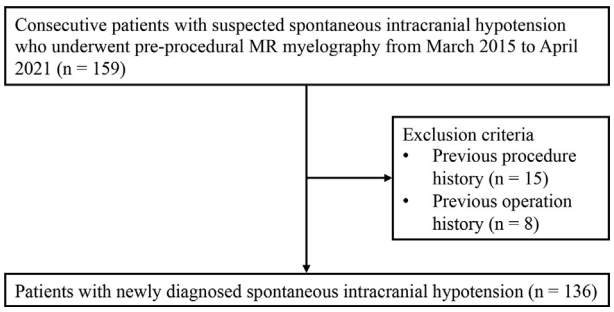

Figure 1 Flow diagram of patients.

symptoms in patients without orthostatic headache were: non-orthostatic headache (n=7), nausea or vomiting (n=6), and neck pain (n=5). The number of patients who showed symptom improvement during the follow-up was 122 (90%). Of the 136 patients included in this study, 106 (78%) underwent radionuclide cisternography.

Brain MRI findings

In total, 128 patients (94%, 128/136) with sufficient brain MR images were analysed. On brain MRI, venous engorgement was the most common finding (65%, 83/128), followed by enlarged pituitary gland (63%, 80/128), diffuse pachymeningeal enhancement (57%, 73/128), brain sagging (42%, 54/128), and subdural fluid collection (21%, 27/128; Table 3). In addition, 24 patients (19%, 24/128) had normal brain MRI findings. Of the 27 patients with subdural fluid collection, 25 patients (93%, 25/27) had bilateral subdural fluid collection and two patients had left subdural fluid collection. The mean values of the quantitative signs were 2.85, 4.77, and 5.89 mm for the size of the suprasellar cistern, size of the prepontine cistern, and mamillopontine distance, respectively.

MR myelography

The interval between initial brain MRI and MR myelography was 5.3 ± 10.1 (standard deviation) days. Based on the reference standard, the number of patients with SIH with confirmed CSF leakage was 120 (88%, 120/136). Of these patients, 90 (75%, 90/120) had epidural fluid collection. Two patients with epidural fluid collection did not show CSF leakage on MR myelography.

The detection rate of MR myelography for CSF leakage was 88% (105/120, 95% confidence interval [CI], 80–93%) for reader 1 and 85% (102/120, 95% CI, 77–91%) for reader 2. The detection rate of MR myelography for epidural fluid collection was 91% (82/90, reader 1 and 2). Readers 1 and 2 detected epidural fluid collection on MR myelography in 94 (78%, 94/120) and 92 (77%, 92/120) patients, respectively.

The interobserver agreement between the two readers for the detection of CSF leakage on MR myelography was high (κ = 0.76; 95% CI, 0.63–0.89). For the detection of epidural fluid collection on MR myelography, the interobserver agreement between the two readers was also high (κ = 0.77; 95% CI, 0.65–0.88).

Table 3
Initial and follow-up brain MRI findings.

Brain MRI findings	No. of patients with initial MRI (%, total n=128)	No. of patients with follow-up MRI (%, total n=85)
Venous engorgement	83 (65%)	22 (26%)
Enlarged pituitary gland	80 (63%)	19 (22%)
Diffuse pachymeningeal enhancement	73 (57%)	37 (44%)
Brain sagging	54 (42%)	16 (19%)
Subdural fluid collection	27 (21%)	18 (21%)
Normal brain MRI findings	24 (19%)	36 (42%)

Data are number (%).
MRI, magnetic resonance imaging.

Regarding evaluation by reader 1, the frequencies of CSF leakage detection according to level were as follows: thoracic level, 64% (68/106); lumbar level, 52% (55/106); thoracolumbar level, 29% (31/106); cervical level, 28% (30/106); cervicothoracic junction, 28% (30/106); and craniocervical junction, 21% (22/106). Representative cases are illustrated in Figs 2 and 3 and Electronic Supplementary Material Fig. S1.

Validation of the published scoring system for CSF leakage

When the published scoring system was applied to the included patients, 25 patients were categorised as low grade; 25 patients, intermediate grade; and 78 patients, high grade. In the low-grade group, 19 patients (76%, 19/25) had CSF leakage. In the intermediate-grade group, 19 patients (76%, 19/25) had CSF leakage. In the high-grade group, 74 patients (95%, 74/78) had CSF leakage. Among all patients with SIH with normal brain MRI findings, 16 patients had CSF leakage (67%, 16/24).

Follow-up

Follow-up brain MRI was performed in 85 patients, of whom 57 (67%) showed improvement in symptoms. Nine patients showed worsened symptoms on brain MRI. The findings of the initial and follow-up brain MRI are summarised in Table 3.

The number of patients who underwent epidural blood patch was 116, of whom 112 showed improvements (97%, 112/116). Reader 1 detected the presence of CSF leakage in 106 patients during MR myelography. Epidural blood patch was performed in 96 of these 106 patients (91%), and symptom improvement was observed in 93 patients (87%, 93/106). Among 25 patients with normal brain MRI findings, 19 patients underwent epidural blood patch and 18 patients had symptomatic relief (95%, 18/19). Of the 31 patients with a negative MR myelography result, 20 patients underwent epidural blood patch and 19 of them showed improvement of symptoms (95%, 19/20).

Discussion

In the present study, the detection rate of MR myelography for CSF leakage by reader 1 and 2 were 88% (105 of 120, 95% CI, 80–93%) and 85% (102 of 120, 95% CI, 77–91%), respectively. The interobserver agreement between the two readers for the detection of CSF leakage (κ = 0.76) or epidural fluid collection (κ = 0.76) on MR myelography was high. Among 24 patients with normal brain MRI findings, 16 patients had CSF leakage (67%, 16/24). Therefore, MR myelography demonstrated a high detection rate in patients with SIH. The current findings suggest that MR myelography may be particularly useful for detecting CSF leakage and for guiding the treatment of patients with SIH.

The diagnostic yield of MR myelography without intrathecal gadolinium in previous studies was 67–100%.[3–13] The present study similarly showed a high detection rate

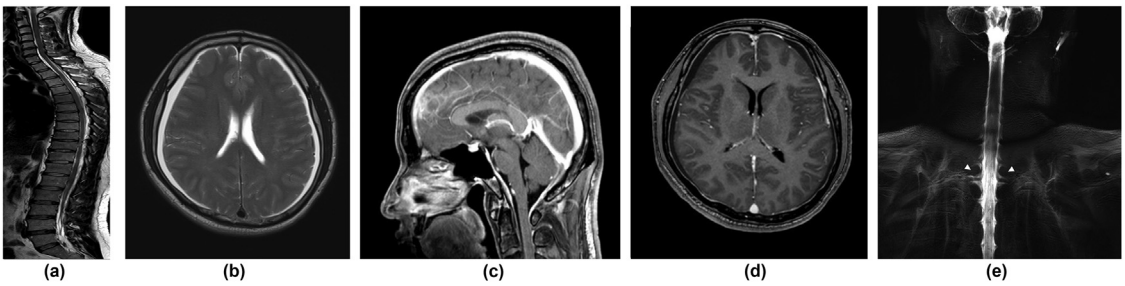

Figure 2 Representative case of a 45-year-old man with orthostatic headache, nausea, vomiting, dizziness, and tinnitus. (a) Sagittal spine MRI image showing epidural fluid collection within the ventral aspect of the spinal canal at cervicothoracic junction and the dorsal aspect of the spinal canal at thoracic level. (b) Axial T2-weighted brain MRI image showing bilateral subdural fluid collection. (c) Sagittal enhanced T1-weighted image showing venous engorgement, enlarged pituitary gland, and brain sagging. (d) Axial enhanced T1-weighted image showing diffuse pachymeningeal enhancement. (e) Maximum intensity projection 2D MR myelography images showing CSF leakage at cervicothoracic junction (arrowheads).

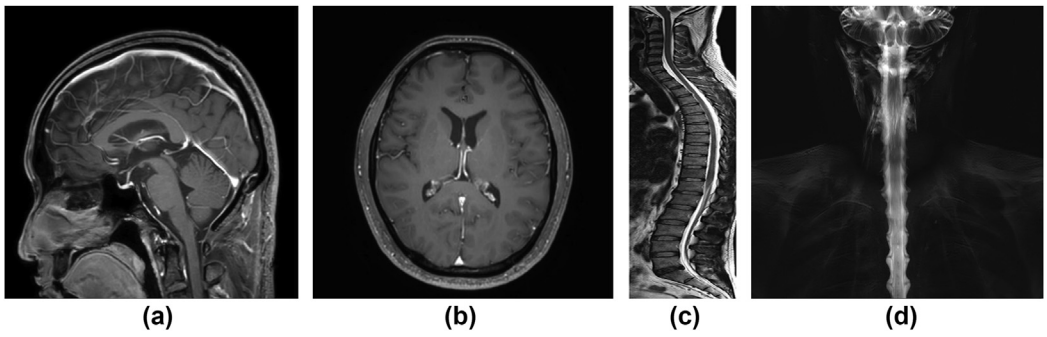

Figure 3 Representative case of a 39-year-old man with posterior neck pain. (a) Sagittal enhanced T1-weighted brain MRI image showing no definite venous engorgement, enlarged pituitary gland, or brain sagging. (b) Axial enhanced T1-weighted image showing no diffuse pachymeningeal enhancement. (c) Sagittal spine MRI image showing epidural fluid collection within the ventral aspect of the spinal canal at cervicothoracic junction and the dorsal aspect of the spinal canal at thoracolumbar junction. (d) Maximum intensity projection 2D MR myelography images showing extensive CSF leakage at the craniocervical junction, and upper C-spine levels.

comparable to that in previous studies. In previous studies, the diagnostic yield of CT myelography was 74%[5] and the diagnostic yield of MR myelography with intrathecal gadolinium was 14–100%.[1,2,6,7,19,20] The detection rate of MR myelography in the present study was 88%, which is high compared to that of other modalities. The interobserver agreement between the two readers for the detection of CSF leakage ($\kappa = 0.76$) in the present study was high. Only a few previous studies have analysed interobserver agreement. In the study by Yoo *et al.*,[4] the interobserver agreement of two readers for the detection of CSF leakage was moderate ($\kappa = 0.634$ and 0.444). In the study of Chen *et al.*,[21] the interobserver agreement between the two readers was good and similar to that in the present study ($\kappa = 0.74$ on MR myelography with thin-section axial multiplanar reconstruction and $\kappa = 0.72$ on 3D MR myelography with maximum intensity projection).

The main advantages of MR myelography without intrathecal gadolinium include its lack of invasiveness, radiation hazard, adverse effects from contrast agents, and requirement for lumbar puncture for contrast medium injection[1,3,6,12]; however, it is a static method that detect CSF pooling after leakage.[5,10] MR myelography with intrathecal gadolinium and CT myelography are dynamic methods that can detect CSF leakage accurately[22–24]; however, these are invasive procedures that require lumbar puncture,[6] which can exacerbate CSF volume depletion in patients with low CSF pressure.[25] Complications, such as encephalopathy or neurotoxic manifestations, including decreased mentality, global aphasia, and visual disturbance, may occur as adverse effects of contrast agents.[26,27] Moreover, CT myelography has a disadvantage radiation exposure.[4] Radioisotope cisternography is a dynamic study that can detect CSF leakage when an active leak is present at the time of the examination[10]; however, detecting the exact leakage site is difficult owing to poor resolution.[4,10,28,29] In addition, radioisotope cisternography is an invasive method that exposes the patient to radiation.

Theoretically, MR myelography without intrathecal gadolinium provides static rather than dynamic information. Slow CSF leakage is easy to trace using MR myelography without intrathecal gadolinium because it is a method of detecting CSF pooling after leakage; however, fast-flow CSF leakage can be difficult to detect.[5,10] Therefore, a negative MR myelography without intrathecal gadolinium may not be detected because they are probably cases of fast-flow CSF leakage. SIH has a variety of aetiologies, including CSF leakage and CSF venous fistula.[2,8,20,30] When epidural

CSF leakage is not detected, CSF venous fistula can be considered a cause of SIH.[31–34] CSF venous fistula can be detected using CT myelography or radioisotope cisternography.[12,32] Therefore, if non-invasive MR myelography without intrathecal gadolinium is performed as a screening test and the results are unclear, invasive methods, such as CT or MR myelography with intrathecal gadolinium, should be undertaken to determine the leakage site.

In the study by Tsai *et al.*,[12] four patients with negative brain MRI findings showed abnormal CSF collection on MR myelography (24%). In the present study, 24 patients had negative findings on the initial brain MRI and 16 of them had CSF leakage on MR myelography (67%). Based on the published scoring system by Dobrocky *et al.*,[14] 76% of low-grade patients in this study had CSF leakage on MR myelography. This suggests that CSF leakage can occur even when the brain MRI findings are nearly normal. Therefore, it may be necessary to attempt non-invasive methods such as MR myelography if the patient's symptoms are suspicious for SIH, even if the brain MRI findings are low grade or normal. The proportions of intermediate- and high-grade patients based on the published scoring system in this study were similar to those reported by Dobrocky *et al.*[14]

On the initial brain MRI, venous engorgement (65%), enlarged pituitary gland (63%), and pachymeningeal enhancement (57%) were the most common findings. On follow-up brain MRI, venous engorgement and enlarged pituitary gland were the most common symptoms that showed improvement. In the study of Dobrocky *et al.*,[14] pachymeningeal enhancement (83%) and venous engorgement (66%) were the most common imaging findings. The proportion of patients with normal brain MRI findings was 19% (24 of 128) in the present study, whereas it was 20% in a previous review article.[35] In this study, the frequency of detection of subdural fluid collection was 21% (27 of 128) on initial brain MRI in patients with SIH. If bilateral subdural fluid collection or subdural haemorrhage is observed in a patient in the absence of a history of trauma, SIH may be suspected, and the symptoms should be examined.

In general, conservative treatments such as bed rest, hydration, and use of an abdominal binder are applied. If the symptoms do not improve, epidural blood patch is performed. The main treatment for SIH is epidural blood patch, which, if successfully performed, improves symptoms within a few hours. Empirically, if the exact level of the leakage is not known, epidural blood patch can be performed.[29,36]. In this study, among 31 patients with a negative MR myelography result, 20 patients underwent epidural blood patch and the symptoms improved in 95% (19 of 20). Two patients had epidural fluid collection and no CSF leakage on MR myelography. In one patient, epidural blood patch was not performed. This patient, who complained of orthostatic headache and dizziness, was admitted to the hospital and showed improvement of symptoms after hydration. In the other patient, epidural blood patch was not performed and the symptoms did not improve.

The present study had several limitations. The main limitation was the retrospective and single-centre design. In addition, the detection rate of MR myelography was not compared with that of other techniques, such as CT myelography, owing to lack of data. Radioisotope cisternography was performed in 78% (106/136) of the patients. The recent trend at Asan Medical Center is not to perform radioisotope cisternography if characteristic findings of SIH are found on brain MRI or MR myelography.

In conclusion, the detection rate of MR myelography for CSF leakage in patients with newly diagnosed SIH was 88%, with a high interobserver agreement. Among patients with negative brain MRI findings, 67% had CSF leakage. Therefore, non-invasive MR myelography without intrathecal gadolinium should be considered to detect CSF leakage in patients with suspected SIH.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2022.06.018.

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