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RESEARCH SUBMISSIONS

Patterns of clinical and imaging presentations in patients with spontaneous intracranial hypotension due to spinal cerebrospinal fluid venous fistula: A single-center retrospective cross-sectional study

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Abstract

Objective: To identify distinct clinical or imaging subtypes of spontaneous intracranial hypotension (SIH) due to spinal cerebrospinal fluid (CSF) venous fistula (CVF).

Background: Spontaneous intracranial hypotension is classically understood to present clinically with an orthostatic headache and stereotyped brain magnetic resonance imaging (MRI) findings; however, most prior literature examining clinical and brain MRI features of SIH has focused on all types of spinal CSF leaks concurrently. This study aimed to evaluate whether data support the possibility of internally consistent subtypes based on brain imaging features and clinical symptoms analogous to those seen in primary headache syndromes.

Methods: This retrospective cross-sectional single-institution study included 48 consecutive patients meeting the International Classification of Headache Disorders, 3rd edition criteria for SIH due to CVF. Clinical symptoms, pre-treatment brain MRI, and symptom duration were analyzed. Clinical and MRI data were analyzed to identify patterns and associations between symptoms and imaging findings.

Results: A total of 20 males and 28 females were evaluated, with a mean (standard deviation) age of 61 (10) years. In all, 44/48 (92%) patients experienced headaches, though 18/48 (40%) did not endorse relief when flat, including six of the 48 (13%) with worsening symptoms when flat. In all, 19/48 (40%) patients reported at least one migraine symptom, and six of the 48 (13%) presented with at least one migraine symptom and had no relief when flat. Clinical symptoms clustered primarily into a "classic" presentation consisting of relief when flat, occipital head pain, comorbid neck pain, a

Abbreviations: BMI, body mass index; CI, confidence interval; CSF, cerebrospinal fluid; CVF, CSF venous fistula; ICHD-3, International Classification of Headache Disorders, 3rd edition; MRI, magnetic resonance imaging; OR, odds ratio; SD, standard deviation; SIH, spontaneous intracranial hypotension.

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pressure/throbbing headache quality, and an "atypical" presentation that was characterized by having several differences: less relief when flat (nine of 22 (41%) vs. 20/23 (87.0%), $p=0.002$; odds ratio [OR] 0.110, 95% confidence interval [CI] 0.016–0.53), more frontal head pain (14/22 (64%) vs. one of 23 (4%), $p<0.001$; OR 35.0, 95% CI 4.2–1681.0), less neck pain (two of 21 (4.5%) vs. nine of 13 (69.6%), $p<0.001$; OR 0.023, 95% CI 0.0005–0.196), and more stabbing/sharp headache quality (nine of 22 (41%) vs. two of 23 (9%), $p=0.017$; OR 7.0, 95% CI 1.18–75.9). Brain MRI findings clustered into three groups: those presenting with most imaging findings of SIH concurrently, those with brain sag but less pachymeningeal/venous engorgement, and those with pachymeningeal/venous engorgement but less brain sag.

Conclusion: This study highlights the clinical and imaging diversity among patients with SIH due to CVF, challenging the reliance on classic orthostatic headache alone for diagnosis. The findings suggest the existence of distinct SIH subtypes based on clinical and imaging presentations, underscoring the need for comprehensive evaluation in patients with suspected CVF. Future research should further elucidate the relationship between clinical symptoms and imaging findings, aiming to refine diagnostic criteria and enhance understanding of SIH's pathophysiology.

Plain Language Summary

This study explored the variety of symptoms and brain magnetic resonance imaging (MRI) characteristics among patients with spontaneous intracranial hypotension (SIH) due to spinal cerebrospinal fluid venous fistula (CVF). We studied the clinical symptoms and brain scans of 48 patients with CVF, and we found distinct "classic" and "atypical" symptom patterns and varied MRI findings that suggest different subtypes of the condition. These findings suggest that we should not rely only on the usual signs of orthostatic headache for diagnosis and indicate the need for a thorough diagnostic approach to better understand and treat SIH.

KEYWORDS
brain magnetic resonance imaging, cerebrospinal fluid venous fistula, orthostatic headache, spontaneous intracranial hypotension

INTRODUCTION

Spontaneous intracranial hypotension (SIH) was first understood to be caused by a ventral spinal dural defect or ruptured spinal meningeal diverticulum/nerve root sleeve with cerebrospinal fluid (CSF) leakage into the epidural space, resulting in a spinal epidural fluid collection, referred to as Type 1 and Type 2 CSF leaks, respectively.[1] This understanding was broadened when it was reported that some patients with SIH who demonstrated no spinal epidural fluid collection were actually losing CSF directly into an epidural vein, a pathogenic mechanism of CSF loss named a CSF venous fistula (CVF), or Type 3 CSF leak.[2] Subsequent work demonstrated that CVF could only be effectively detected with myelography performed in the lateral decubitus position and that such imaging finds CVF to account for up to 50% of cases of new orthostatic headache with brain imaging features of SIH.[3–5]

Published studies on CVF since 2019 have continued to challenge our understanding of SIH. For example, it has been shown that CVF can cause orthostatic headache without brain findings of SIH on magnetic resonance imaging (MRI), and spinal opening pressure is normal in most cases of CVF.[6–9] The discovery of this important class of CSF leak as a major cause of SIH that had been hitherto undetectable has called into question to what extent CVF resemble or differ from Type 1 and 2 CSF leaks, and consequently to what extent prior published literature on CSF leak can accurately guide us from clinical presentation to CVF discovery.

Many CSF leaks are first suspected when a patient reports an orthostatic headache, whereby patients experience symptomatic relief when lying flat, and the prevalence of orthostatic headache in SIH has been estimated to range from 93% to 98% in large cohort studies.[10,11] However, these studies have included patients experiencing all major types of spinal CSF leak, and both how and

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where CSF is lost from the subarachnoid space may drive key clinical and radiologic features. For example, it is believed that CSF leaks from the skull base cause neither the brain changes on MRI associated with SIH, nor the clinical syndrome of postural headaches.[12] There is less published literature on whether the symptoms associated with CVF show the same high rates of orthostatic headache as other types of CSF leak. One report describing the features of a cohort of 44 patients with CVF noted an unexpectedly high rate of 31% with non-orthostatic headaches; however, this has not been replicated.[9] In this context, the clinical features associated with spinal CVF merit dedicated evaluation. We hypothesized that many patients with CVF do not present with a typical orthostatic headache; they frequently endorse other headache and non-headache symptoms, and clinical symptoms tend to cluster together. In addition, while several authors have noted the impressive clinical heterogeneity of patients with SIH, we hypothesized that there may be distinct subsets of patients with SIH who show internally consistent but distinct brain MRI findings and/or clinical phenotypes as are seen with primary headache syndromes such as migraine and trigeminal autonomic cephalgias.

Common features of SIH on brain MRI include pachymeningeal enhancement, venous engorgement, sagging of the posterior fossa structures, and subdural collections. These features have been encoded into a scoring system referred to as the Bern Score, which reflects the probability of localizing both CSF leaks and CVF on subsequent myelography.[8,13,14] Such a scoring system is useful as patients may present with all, some, or none of the characteristic SIH brain MRI findings. For example, some patients may present with "brain sag" predominant imaging findings without significant pachymeningeal enhancement or venous engorgement, while others can present with pachymeningeal enhancement and venous engorgement without significant brain sag (Figure 1).

There were two main purposes of this study. First, to describe and analyze the presenting clinical symptoms of patients meeting the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for SIH due to a CVF, with particular attention to those patients who did not present with a classic orthostatic headache. Second, to evaluate whether there was evidence of distinct internally consistent clinical or imaging subtypes of patient presentations.

METHODS

This was a retrospective, cross-sectional study of 48 consecutive patients meeting ICHD-3 criteria for SIH who were diagnosed with one or more definite CVF on dynamic computed tomography myelography at the University of Colorado School of Medicine between February 10, 2021 and March 10, 2024. All patients had a pre-procedural brain and total spine MRI available for review and were assessed by a provider within our healthcare institution. This is the primary analysis of these data, though many included patients have been assessed in prior work by our institution.[7,8,15–17] Approval from the University of Colorado Institutional Review Board was obtained, and written informed consent was waived due to the retrospective nature of the study design. Medical records were reviewed for patient demographic information, including age, sex, and body mass index (BMI). All available clinical progress notes for each patient at the time of presentation were reviewed, any symptoms endorsed or denied by each patient were recorded, as were the duration of symptoms prior to presentation. Each patient's pre-procedural brain MRI was assessed, and a Bern Score was recorded at the time of formal evaluation by a board-certified, subspecialty-trained neuroradiologist who was directly involved in the care of these patients. Patients underwent dynamic decubitus computed tomography myelography, and the spinal level, laterality, and number of CVF were recorded.

Statistical analyses

Descriptive statistics were calculated based on recorded patient characteristics, clinical symptoms, and imaging findings, including frequencies, mean, and standard deviation (SD). Cluster analysis was performed on clinical and MRI data using hierarchical clustering with the Jaccard distance. Given two binary variables, A and B, the Jaccard distance reflects the ratio of the intersection to the union of two variables, i.e., 1 − [(A and B)/(A or B)]. Heatmaps were generated to visually represent these relationships, with dendrograms illustrating the clusters of patients derived from the hierarchical relationships. When assessing the similarity between symptoms and imaging findings, pairwise Jaccard distances were calculated between each finding, followed by Euclidean distance for subsequent clustering. Statistical power for clustering was evaluated by calculating the cluster separation distance using Cohen's *d* effect size as described by Dalmaijer et al.[18] Two-tailed Fisher's exact tests were performed to explore symptom associations in patients who presented with no relief when lying flat, as well as symptom associations in patients who presented with no headache. The Fisher's exact test was also performed to explore associations between brain MRI findings that tended to present concurrently, as well as to explore potential relationships between clinical and imaging findings. A multiple logistic regression model was used to explore the relationship between symptom duration and the presence or absence of headache. For Fisher's exact tests, observations were assumed to be independent. For logistic regression, in addition to independence of observations, we assumed that the predictor and outcome variables were not collinear and that the log odds of predictor variables have a linear relationship with the outcome variable. A $p < 0.05$ was considered statistically significant. No statistical power calculation was conducted prior to the study; the sample size was based on the available data. There was no missing data for the studied variables. All analyses were performed using R version 4.3.0.

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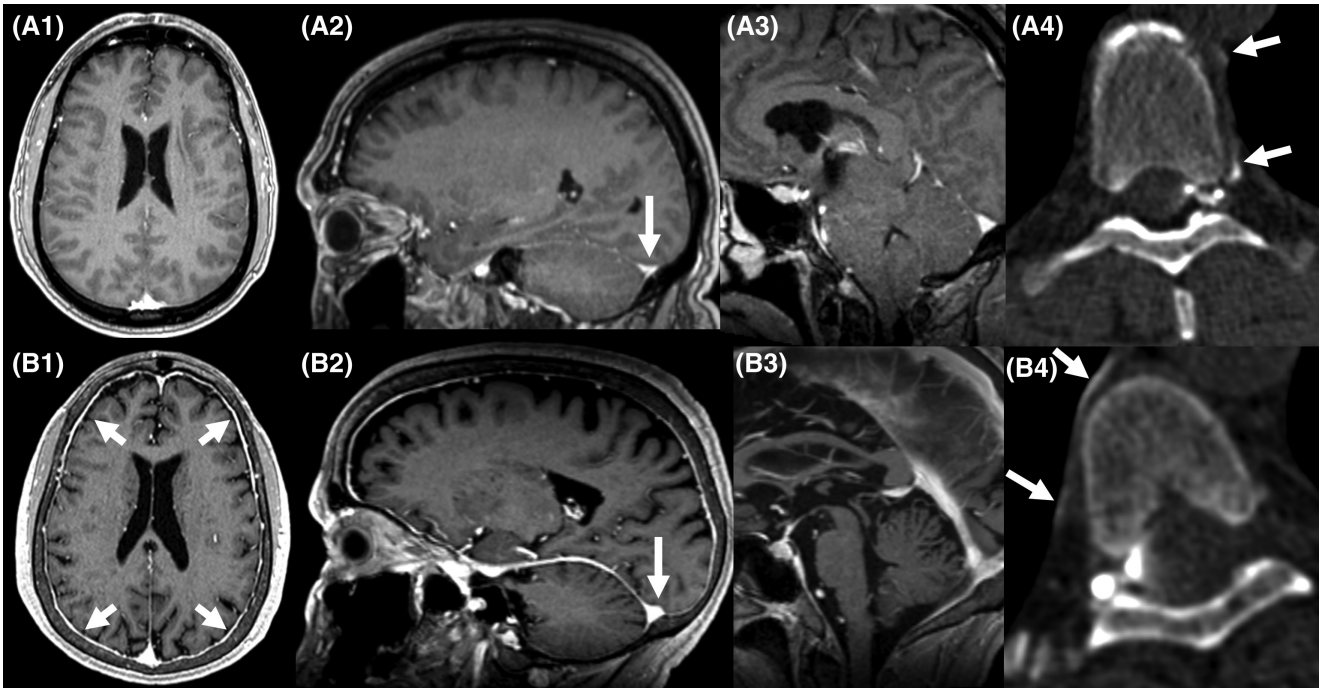

FIGURE 1 Examples of two patients with cerebrospinal fluid venous fistula (CVF) and different magnetic resonance imaging (MRI) brain presentations. (A) A man in his 50s with spontaneous intracranial hypotension. (A1) Axial T1 post-contrast MRI brain demonstrates no significant pachymeningeal enhancement. (A2) Sagittal paramedian T1 postcontrast MRI of the brain demonstrates no significant engorgement of the transverse venous sinuses (arrow). (A3) Sagittal T1 postcontrast MRI of the brain at midline demonstrates severe downward displacement of the posterior fossa structures (brain sag). (A4) Left decubitus dynamic computed tomography myelography demonstrates a CVF at the T7–8 level (arrows). (B) A woman in her 60s with spontaneous intracranial hypotension. (B1) Axial T1 postcontrast MRI demonstrates diffuse pachymeningeal thickening and enhancement (arrows). (B2) Sagittal paramedian T1 postcontrast MRI demonstrates engorgement of the transverse venous sinuses with an upward convex margin (arrow). (B3) Sagittal T1 postcontrast image at midline demonstrates no significant downward displacement of the posterior fossa structures. (B4) Right decubitus dynamic computed tomography myelography demonstrates a CVF at the T4-5 level (arrows).

RESULTS

Patient and CVF characteristics are reported in Table 1. The mean (SD, range) patient age was 61.0 (10.3, 34–81) years, and 20 men and 28 women were evaluated. The mean (SD, range) BMI was 28.0 (4.7, 21.4–41.2) kg/m^2. The mean (SD, range) opening pressure was 13.0 (4.6, 4–26) cm CSF, with two patients having an opening pressure <6 cm CSF and one patient having an opening pressure >25 cm CSF. Six patients had two CVFs and 42 patients had one CVF each. In all, 52 CVFs were in the thoracic spine, one was in the cervical spine, and one was in the lumbar spine; 38 CVFs were on the right and 16 CVFs were on the left.

Clinical findings

Symptom characteristics and frequencies are reported in Figure 2. In all, 44 of the 48 patients (92%) endorsed a headache, and four (8%) described no headache. In all, 30 of the 48 patients (63%) described improvement of their symptoms when they were flat, and 18 (37%) reported no symptom improvement when flat. Six of the 48 patients (13%) described worsening of their symptoms when they were flat. Thus, the total of patients who presented without a "classic orthostatic headache", specifically no symptomatic relief when flat, symptoms which were worse when flat, and/or no head pain at all, was 19/48 patients (40%).

The mean (SD, range) symptom duration preceding CVF localization was 5.1 (9.4, 0.01–36) years. In a multiple logistic regression model for the presence or absence of headache, with covariates of age, BMI, symptom duration, and Bern Score, the absence of headache was associated with longer symptom duration ($p = 0.045$; odds ratio [OR] 1.10, 95% confidence interval [CI] 1.00–1.22), while the remaining variables were not significantly associated with the absence of headache.

Of the 18 patients who did not experience relief when flat, 11 (61%) reported worsening of symptoms with Valsalva, 10 (56%) reported dizziness, eight (44%) reported tinnitus, seven (39%) reported worsening with position transitions, six (33%) reported an exertional headache, five (28%) reported worsening when flat, and four each (22%) reported difficulty sleeping, memory issues, difficulty concentrating, or nausea. No relief when flat was associated with symptom worsening when flat ($p = 0.022$; OR 10.6, 95% CI 1.04–543.4), worsening with position changes ($p = 0.003$; OR 17.3, 95% CI 1.9–854.9), and the absence of neck pain ($p = 0.005$; OR 8.7,

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TABLE 1 Patient and cerebrospinal fluid venous fistula characteristics.

Characteristic	Value
Sex, *n*	
Male	20
Female	28
Age, years, mean (SD, range)	61.0 (10.3, 34–81)
BMI, kg/m^2, mean (SD, range)	28.0 (4.7, 21.4–41.2)
CVFs per patient, *n*	
One	42
Two	6
CVF level, *n*	
Thoracic spine	52
Cervical spine	1
Lumbar spine	1
CVF side, *n*	
Right	38
Left	16
Symptom duration, years, mean (SD, range)	5.1 (9.4, 0.01–36)
Bern Score	
Mean (SD, range)	6.2 (2.1, 1–9)
Low, 0–2, *n* (%)	2/48 (4)
Intermediate, 3–4, *n* (%)	10/48 (20)
High, 5–9, *n* (%)	36/48 (75)

Abbreviations: BMI, body mass index; CVF, cerebrospinal fluid venous fistula.

95% CI 1.6–91.7). In all, 19 of the 48 patients (39.6%) reported at least one migraine symptom (photophobia, phonophobia, and/or nausea) and six (12.5%) presented with at least one migraine symptom and had no relief when flat.

Of the four patients who reported no headache, one presented with memory issues and syncope; one presented with memory issues, difficulty concentrating, hearing loss, and tinnitus; one presented with radicular pain/paresthesia; and one presented with isolated neck pain.

Of the 44 patients with headache, 29/44 (66%) described a pressure/throbbing quality, 7/44 (16%) described a sharp/stabbing quality, 4/44 (9%) reported both headaches qualities, and 4/44 (9%) described their headache neither as sharp/stabbing or pressure/throbbing. In all, 25 of the 44 patients (57%) described their headache location as occipital, 15 (34%) described a frontal location, 12 (27%) described a temporal location, and eight (18%) described holocephalic pain. In all, 12 of the 44 patients (27%) reported periorbital pain, three (7%) reported facial pain, and 18 (38%) reported neck pain. Patients described several vestibulocochlear symptoms, including dizziness or loss of balance (30/48 [63%]), tinnitus (24/48 [50%]), and hearing loss (six of 48 [13%]). Several patients reported additional symptoms, including nausea (15/48 [31%]), difficulty concentrating (12/48 [25%]), fatigue (10/48 [21%]), photophobia (eight of 48 [17%]), blurry or double vision (eight of 48 [17%]), radicular pain or paresthesia (eight of 48 [17%]) or difficulty sleeping (seven of 48 [15%]).

Eight of the 48 patients (17%) described worsening of their symptoms during position transitions (moving from lying to sitting or sitting to standing). A common non-positional exacerbating factor was Valsalva/cough, present in 25 of the 48 patients (52%). Nine of the 48 patients (19%) reported worsening of symptoms with exertion or exercise, and eight (17%) also reported worsening symptoms with head movement.

Cluster analysis of the presenting symptoms suggested internally consistent sets of presentations (Figure 3). The largest symptom cluster, henceforth referred to as "classic," corresponded to 23 of the 48 patients (48%) and featured occipital head pain, comorbid neck pain, a high frequency of a pressure/throbbing headache quality, and a higher frequency of relief when flat. A second major cluster, referred to as "atypical," represented 22 of the 48 patients (46%). The cluster separation between these two was 3.58. Patients in the "atypical" cluster were characterized by higher frequencies of frontal head pain (14/22 (64%) vs. one of 23 (4%) [$p < 0.001$]; OR 35.0, 95% CI 4.2–1681.0), less neck pain (two of 21 (5%) vs. nine of 13 (70%) [$p < 0.001$]; OR 0.023, 95% CI 0.0005–0.196), a higher frequency of a sharp/stabbing quality of head pain (nine of 22 (41%) vs. two of 23 (9%) [$p = 0.017$]; OR 7.0, 95% CI 1.18–75.9) and a lower frequency of relief when flat (nine of 22 (41%) vs. 20/23 (87%) [$p = 0.002$]; OR 0.110, 95% CI 0.016–0.53).

Imaging findings

The Bern Score ranges from 0–9, with 0–2 reflecting low probability, 3–4 reflecting intermediate probability, and 5–9 reflecting high probability of CSF leak or CVF detection.[13,14] In our patients, the mean (SD, range) Bern Score was 6.2 (2.1, 1–9). Two of the 48 patients (4%) had a Bern Score of ≤2, 10 (21%) had a Bern Score of 3 or 4, and 36 (75%) had a Bern Score of ≥5. In all, 43 of the 48 patients (90%) had pachymeningeal enhancement, 37 (77%) had venous engorgement, 30 (63%) had suprasellar cistern narrowing, 33 (69%) had prepontine cistern narrowing, 29 (60%) had mamillopontine cistern narrowing, and 16 (33%) presented with subdural collections.

Cluster analysis of the brain MRI findings on a per-patient level segregated patients into three groups: Group 1, patients that demonstrated imaging findings of pachymeningeal enhancement, venous distension, and sagging of the brain evidenced by effacement of the basilar cisterns; Group 2, patients that demonstrated pachymeningeal enhancement and venous engorgement but less brain sag; and Group 3, patients that presented primarily with brain sag but only one or neither of pachymeningeal enhancement or venous engorgement (Figure 4).

Fisher's exact tests to explore the strength of the relationships illustrated by cluster analysis revealed that pachymeningeal enhancement was associated with presence of venous engorgement ($p = 0.007$; OR 18.7, 95% CI 1.57–1032.2), while suprasellar interval narrowing was associated with prepontine ($p = 0.004$; OR

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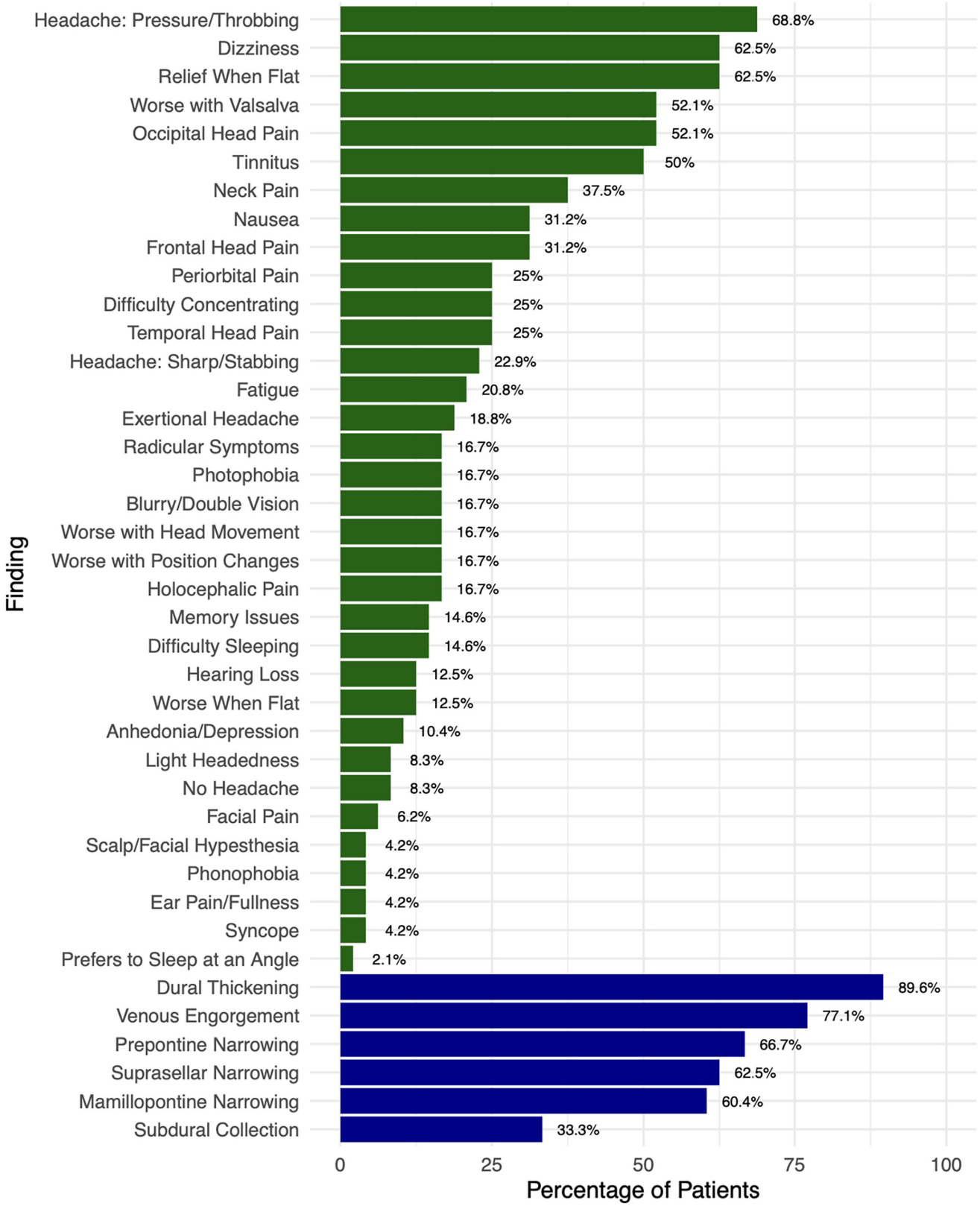

FIGURE 2 Bar chart illustrating distribution of clinical characteristics (green) and brain imaging findings (blue) in patients with cerebrospinal fluid venous fistula.

7.5, 95% CI 1.72–38.0) and mamillopontine narrowing ($p < 0.001$; OR 28.9, 95% CI 5.3–232.8). Similarly, the presence of prepontine narrowing was associated with mamillopontine narrowing ($p = 0.001$; OR 10.1; 95% CI 2.21–57.5). Conversely, pachymeningeal enhancement was not statistically significantly associated with prepontine ($p = 0.154$; OR 0.000, 95% CI 0.000–2.11),

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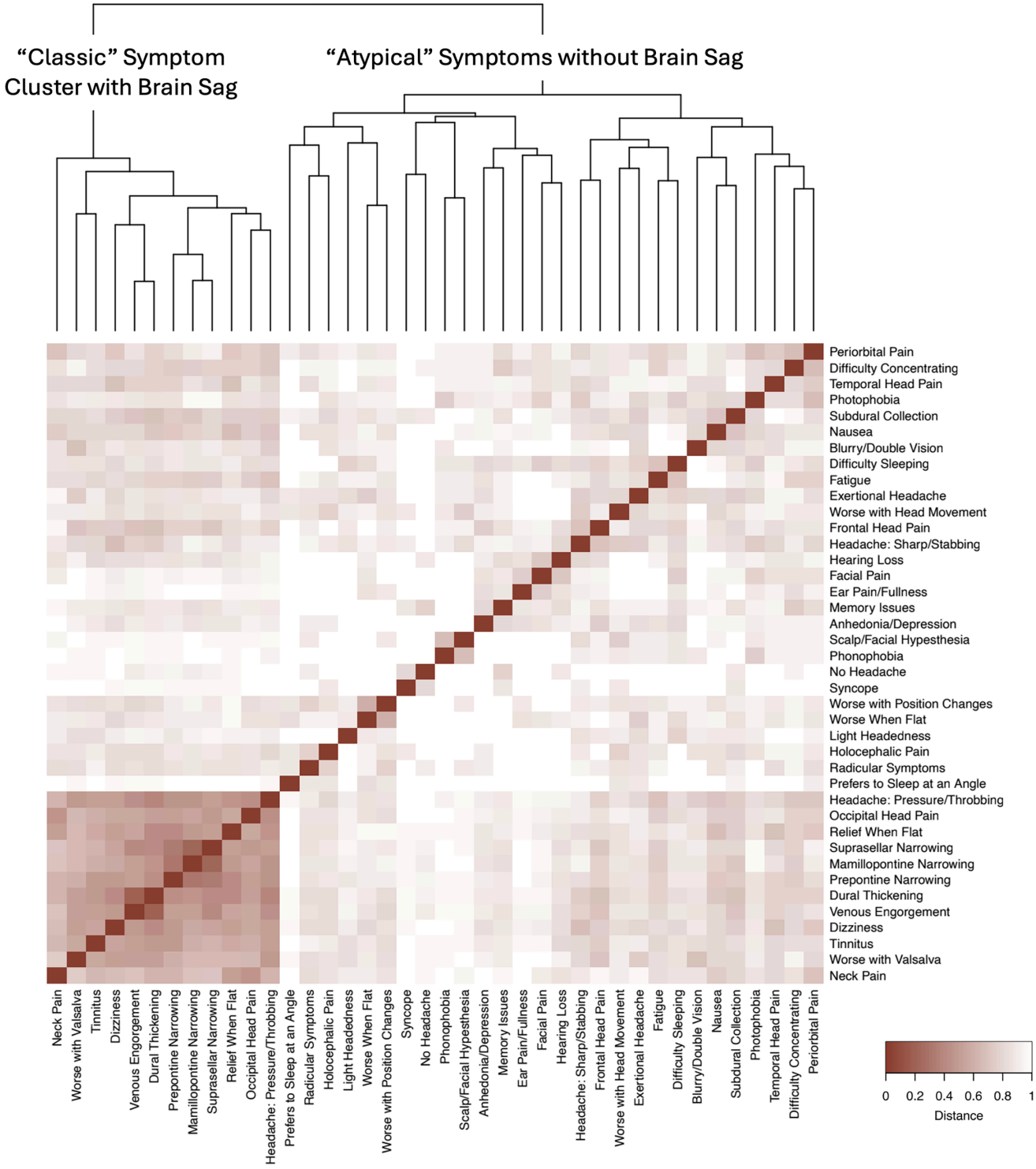

FIGURE 3 Heatmap illustrating hierarchical clustering of all symptom and imaging findings, where a darker color indicates higher similarity between findings. Two main clusters emerge, one that corresponds to "classic" symptoms (left) that cluster with brain sag imaging findings, and "atypical" symptoms that do not (right).

mamillopontine ($p = 0.635$; OR 0.35, 95% CI 0.007–3.98), or suprasellar narrowing ($p = 1.00$; OR 1.12, 95% CI 0.085–10.9), nor was venous engorgement statistically significantly associated with prepontine ($p = 0.293$; OR 0.372, 95% CI 0.034–2.19), mamillopontine ($p = 1.00$; OR 0.84, 95% CI 0.153–4.0), or suprasellar narrowing ($p = 0.288$; OR 2.5, 95% CI 0.51–12.5).

The relationship of clinical symptoms to imaging findings

Exploratory analysis was performed to evaluate potential relationships between imaging findings and clinical symptoms. The presence of brain sag, which clustered with the "classic" group, was

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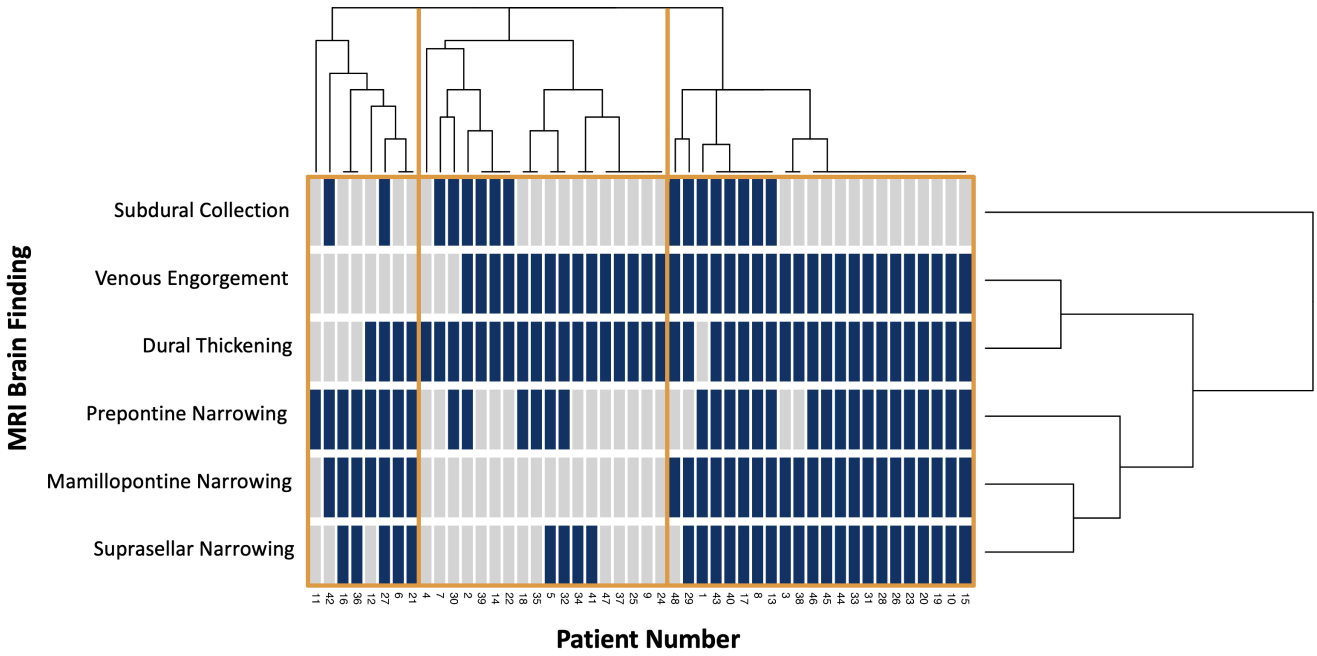

FIGURE 4 Similarity tilemap of brain magnetic resonance imaging findings (where the presence of a finding is indicated in blue) organized by Jaccard indices demonstrates that patients tend to cluster into three groups (orange boxes), with one group demonstrating more brain sag characteristics but less venous engorgement or dural thickening (left), one group demonstrating more venous engorgement and dural thickening but less brain sag (middle), and one group demonstrating most imaging features concurrently (right).

significantly associated with the absence of a "sharp/stabbing" quality of head pain ($p = 0.001$; OR 0.076, 95% CI 0.007–0.5). Conversely, the 'classic' clinical cluster of patients tended to group with imaging findings of brain sag (Figure 4). Cluster separation between patients with findings of brain sag versus those without was 7.0, indicating adequate power with the potential for generalizability to additional data.

DISCUSSION

In this retrospective study of 48 consecutive patients meeting ICHD-3 criteria for SIH due to a spinal CVF, we report distinct clusters of clinical symptom profiles and brain MRI findings with significant practical implications for the diagnosis of SIH and potential insights into its pathophysiology.

Importantly, orthostatic headache–the cardinal feature evoking consideration of CSF leak–was absent in nearly 40% of the patients with CVF. In addition, 13% had worsening of their symptoms when flat, a phenomenon that has been described in prior literature.[9,19] While nearly 48% of the patients presented in a cluster of classic symptoms characterized by pressure/throbbing, occipitally located head pain with comorbid neck pain and relief when flat, 46% fell into an "atypical" symptom cluster reporting more frontal and stabbing quality of head pain, less neck pain, and less relief when flat. Together, these elements of clinical heterogeneity challenge the assumption that even the most astute clinicians can readily recognize a CSF leak and have significant practical implications. If the presence of an orthostatic headache was used as a screening criterion for candidacy for SIH evaluation, nearly two in five patients would have been inappropriately excluded from further testing. Importantly, 19 of the 48 patients (40%) reported at least one migraine symptom, and six (13%) presented with at least one migraine symptom and had no relief when flat. We suspect that patients presenting in such a fashion are particularly susceptible to being excluded from further evaluation for SIH and instead might be inappropriately diagnosed with migraine. The difficulty of reaching a correct diagnosis in the setting of this clinical heterogeneity is highlighted by the prolonged delay between symptom onset and correct diagnosis in our patients, at a mean (SD) of 5.1 (9.4) years. Indeed, this delay may have influenced the relatively low rate of orthostatic headache in this cohort, as it is understood that the orthostatic nature of SIH symptoms may decrease with longer symptom duration.[20–22]

While several patients did not experience relief with recumbency, several other symptoms related to body position or movement were present. Specifically, eight of the 48 patients (17%) described symptom worsening during a position transition, but not necessarily when upright after the transition, and eight (17%) reported worsening of symptoms with head movement independent of body position. These findings advocate for providers caring for headache patients to be more specific in their clinical interviews. The question "Are your headaches positional?" can be interpreted in many ways, and simply asking, "Do you feel better when you lay down?" may ignore key clinical features of the patient with SIH due to a CVF. These findings argue for a detailed and structured SIH-specific review of systems with defined, closed-ended questions probing the diverse symptoms described in this study.

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Notably, several symptoms independent of body position or movement were present with high frequency. Specifically, more than half of patients (52%) reported symptoms worsening with cough or Valsalva, including 61% of those patients who did not experience relief when flat. This is in keeping with prior literature that has suggested that cough or Valsalva headache is a common clinical feature of CVF.[9]

The group of patients presenting with "classic" symptomatology tended to cluster with imaging findings of brain sag (Figure 3). The remaining patients did not present with such "typical" clinical features of SIH and had less associated brain sag on MRI. When brain sag was present, the odds of experiencing stabbing/sharp head pain was less than one-tenth the odds of experiencing that quality of pain when brain sag was absent. (OR 0.08, 95% CI 0.007–0.46; $p=0.001$). Prior authors have asserted that headache symptoms in SIH (and post-dural puncture headache) are due to traction on pain-sensitive intracranial and meningeal structures.[23,24] However, prior work has challenged this assertion by demonstrating a lack of association between the Bern Score and headache severity in SIH.[25] The finding of a strong inverse association between the presence of brain sag and sharp/stabbing pain further challenges this hypothesis and, to our knowledge, is the first to link specific clusters of radiological findings to clinical symptom profiles in SIH.

Analysis of brain MRI findings elucidated clustering into three groups: those who demonstrated most brain imaging findings concurrently, those who demonstrated more pachymeningeal thickening and venous engorgement but less brain sag, and those who demonstrated brain sag but less pachymeningeal thickening or venous engorgement. This finding builds on prior work aiming to understand the brain MRI findings in SIH. Choi et al.[26] advanced a conceptual framework for understanding the brain MRI findings in SIH: pachymeningeal enhancement, venous and pituitary engorgement reflecting an increase in intracranial blood in response to reduced intracranial CSF as predicted by the principles of the Monro–Kellie hypothesis; and downward displacement of brain structures, attributable to a loss of buoyancy. Our study reinforces this two-factor hypothesis of imaging findings: measures of venous engorgement were correlated with each other but not with measures of brain sag. Similarly, measures of brain sag were strongly correlated with each other but not with measures of venous distension. This data structure implies the presence of two independent but co-occurring underlying mechanisms by which loss of spinal CSF leak may affect the brain. This hypothesis is also supported by our previous report that spinal opening pressure and elastance are more strongly associated with venous/pachymeningeal engorgement than findings measuring caudal displacement.[8] Additionally, this finding adds the first empirical support for a concept first attributable to Mokri[27]–that pachymeningeal enhancement reflects a type of venous distension of the meninges or arises directly from it.

The existing classification schema proposed for CSF leaks is based on the nature of CSF loss (ventral dural tear, ruptured meningeal diverticula, or CVF). This schema is valuable and practical as each leak type calls for unique myelographic techniques and treatment strategies.[28] However, a classification schema based on clinical phenotype might improve the primary clinical recognition of SIH. We expand on this with additional preliminary empirical support for the identification of specific patient clusters within patients with CVF. If validated with future studies, the identification of internally cohesive but distinct patient subgroups with CVF may provide empirical support for a clinical categorization of this secondary headache disorder that parallels those used with primary headache disorders such as migraine or trigeminal autonomic cephalgias. If so, this might facilitate improved recognition of patients with SIH.

This study has several limitations. Principally, the retrospective nature of the study design and the reliance on symptoms recorded in clinical progress notes was a major limitation. Without a standardized questionnaire administered to all patients, it is likely that specific symptoms were not captured for every patient. For example, prior work evaluating clinical symptoms in patients with CVF noted frequent hyperacusis, though this was not present in our cohort, likely due to lack of elicitation and/or documentation during evaluation.[9] Additionally, the tempo of symptom onset was not routinely documented, which could theoretically help clinically distinguish SIH, with a sudden symptom onset, from other similar syndromes.[29] We encourage institutions caring for patients experiencing SIH to implement a structured review of symptoms in order to facilitate more standardized clinical research in the future on not only symptoms at presentation but also treatment responses. The study was further limited by a modest sample size and single-institution experience, as well as a single reader assessing each patient's Bern Score, though prior work from our institution has shown high inter-rater agreement for the Bern Score components.[8] Further, due to the small sample size and the limited number of events in each subgroup, the results from the exploratory logistic regression analyses should be confirmed with future research involving larger sample sizes. It is our hope that this study encourages other centers caring for patients with SIH to continue studying the nuanced clinical presentation of CVF in addition to directly comparing the clinical symptom profiles of patients with CVF to other CSF leak types.

CONCLUSION

In this retrospective cross-sectional study of 48 patients with CVF, only 63% had symptoms that improved when lying flat, and 8% had no headache upon presentation. A cluster analysis of symptoms identified three distinct presentations: classic, atypical, and acephalgic. Analysis of presenting brain MRI findings demonstrated clustering into three general groups: those with brain sag but less pachymeningeal/venous engorgement, those with pachymeningeal/venous engorgement but less brain sag, and those with both sets of findings. Clinical evaluation of patients with suspected CVF should include a thorough assessment of both cephalgic and acephalgic symptoms in order not to exclude patients with SIH from appropriate diagnostic testing. Finally, atypical symptoms, lack of orthostatic

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headache, and the presence of migraine symptoms were all common in patients with CVF and should not overly dissuade from pursuing this treatable cause of long-term morbidity.

AUTHOR CONTRIBUTIONS

Andrew L. Callen: Conceptualization; data curation; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Lichy Han:** Data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Samantha L. Pisani Petrucci:** Conceptualization; data curation; project administration; writing – review and editing. **Nadya Andonov:** Data curation; methodology; project administration; supervision; writing – review and editing. **Peter Lennarson:** Conceptualization; data curation; methodology; project administration; supervision; writing – review and editing. **Marius Birlea:** Conceptualization; data curation; methodology; project administration; writing – review and editing. **Chantal O'Brien:** Conceptualization; data curation; project administration; writing – review and editing. **Danielle Wilhour:** Conceptualization; data curation; methodology; project administration; writing – review and editing. **Abigail Anderson:** Conceptualization; data curation; methodology; project administration; writing – review and editing. **Jeffrey L. Bennett:** Conceptualization; data curation; methodology; project administration; writing – review and editing. **Ian R. Carroll:** Conceptualization; formal analysis; investigation; methodology; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Andrew L. Callen MD, Lichy Han MD, PhD, Samantha L. Pisani Petrucci MD, PhD, Nadya Andonov NP, Peter Lennarson MD, Marius Birlea MD, Chantal O'Brien MD, Danielle Wilhour MD, Abigail Anderson MD, Jeffrey L. Bennett MD PhD, and **Ian R. Carroll MD, MS** have no conflicts relevant to this work.

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