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RESEARCH ARTICLE

The reversible impairment of behavioral variant frontotemporal brain sagging syndrome: Challenges and opportunities

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Abstract

Introduction: Due to loss of brain buoyancy, spontaneous spinal cerebrospinal fluid (CSF) leaks cause orthostatic headaches but also can cause symptoms indistinguishable from behavioral variant frontotemporal dementia (bvFTD) due to severe brain sagging (including the frontal and temporal lobes), as visualized on brain magnetic resonance imaging. However, the detection of these CSF leaks may require specialized spinal imaging techniques, such as digital subtraction myelography (DSM).

Methods: We performed DSM in the lateral decubitus position under general anesthesia in 21 consecutive patients with frontotemporal dementia brain sagging syndrome (4 women and 17 men; mean age 56.2 years [range: 31–70 years]).

Results: Nine patients (42.8%) were found to have a CSF-venous fistula, a recently discovered type of CSF leak that cannot be detected on conventional spinal imaging. All nine patients underwent uneventful surgical ligation of the fistula. Complete or near-complete and sustained resolution of bvFTD symptoms was obtained by all nine patients, accompanied by reversal of brain sagging, but in only three (25.0%) of the twelve patients in whom no CSF-venous fistula could be detected ($P = 0.0011$), and who were treated with non-targeted therapies.

Discussion: Concerns about a spinal CSF leak should not be dismissed in patients with frontotemporal brain sagging syndrome, even when conventional spinal imaging is normal. However, even with this specialized imaging the source of the loss of spinal CSF remains elusive in more than half of patients.

KEYWORDS
behavioral variant frontotemporal dementia, brain sagging, cerebrospinal fluid leak, frontotemporal dementia, spontaneous intracranial hypotension

1 | INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is an early-onset dementia characterized clinically by progressive changes in social behavior, personality, and cognition.[1–7] It is a devastating condition for both patients and their families and there is no cure.[1–9] Both sporadic and familial cases have been reported.[1–7] FTD is the most common cause of early-onset dementia, that is, in patients aged 60 or younger.[1–7]

It is important for the practicing neurologist and psychiatrist to recognize that symptoms indistinguishable from bvFTD also can be caused by severe brain sagging due to a spontaneous spinal cerebrospinal fluid (CSF) leak and associated loss of brain buoyancy, an imaging finding on magnetic resonance imaging (MRI) that may be missed even by experienced neuroradiologists. Brain sagging was first described in 1975 on pneumoencephalography[10] and it is pathognomonic for spontaneous intracranial hypotension (SIH).[11] SIH is an increasingly recognized cause of headaches, but it may also cause a variety of other more or less serious neurologic manifestations such as hearing loss, diplopia, coma, brachial amyotrophy, and superficial siderosis.[12–15] The cause of SIH is a CSF leak at the level of the spine[16] and several types have been identified.[17] In 2002, Hong et al. were the first to report the association of symptoms of bvFTD and SIH in a patient who also had other features of SIH, including pachymeningeal enhancement and severe brain sagging on MRI and low CSF pressure.[18] Dozens of patients with brain sagging and symptoms of bvFTD have been reported since.[19–28] Wicklund et al. coined the term "frontotemporal brain sagging syndrome" to describe this population of patients.[21] The association of SIH with unusual manifestations often becomes in doubt when in spite of extensive evaluations, no underlying spinal CSF leak can be detected. This is especially true for behavioral variant frontotemporal brain sagging syndrome where in 46 patients reported worldwide between 2002 and June 2020[18–28] only 2 (4.3%) had a documented spinal CSF leak.[20,28] In our initial experience with 29 patients with behavioral variant frontotemporal brain sagging syndrome evaluated between 2004 and 2017, a CSF leak could not be detected in any of the patients.[25] However, SIH is a rapidly evolving field, particularly with regard to imaging, and current technology has greatly increased the yield of detecting CSF leaks, particularly type 3 CSF leaks, the CSF-venous fistula.[17] Spontaneous spinal CSF-venous fistulas were first described in 2014[29] and are unique among CSF leaks because they are not associated with extradural CSF on conventional spinal imaging, such as MRI or computed tomography (CT)-myelography.[29–38] The detection of CSF-venous fistulas requires more specialized imaging techniques that are not widely available, such as digital subtraction myelography (DSM) or dynamic CT-myelography.[29–38] We have been successful in identifying CSF-venous fistulas in patients with SIH using DSM, especially since we started performing DSM in the lateral decubitus position in April 2018.[36] We now report on a contemporary group of patients with behavioral variant frontotemporal brain sagging syndrome investigated with lateral decubitus DSM.

RESEARCH IN CONTEXT

1. **Systematic Review**: We conducted a comprehensive review of the literature using resources such as PubMed and Google Scholar. Evidence suggests that spontaneous spinal cerebrospinal fluid (CSF) leaks can cause symptoms of behavioral variant frontotemporal dementia (bvFTD) in the setting of severe brain sagging.
2. **Interpretation**: Our findings indicate that a type of spinal CSF leak, the CSF-venous fistula, is found in ≈two fifths of patients with bvFTD brain sagging syndrome. Specialized imaging is required to detect these fistulas and their treatment is associated with resolution of bvFTD symptoms.
3. **Future Directions**: This work confirms that magnetic resonance images should be examined for brain sagging in patients with bvFTD symptoms and may help identify pathways involved in bvFTD symptomatology. Even with specialized imaging the source of the loss of spinal CSF remains elusive in most patients and great efforts need to be made to enhance the detection rate of the CSF loss.

2 | METHODS

This study was approved by our medical center's institutional review board. Informed consent was not necessary.

Since January 2001, all patients with SIH evaluated by us in person at Cedars-Sinai Medical Center in Los Angeles, California, have been enrolled prospectively in a registry. Patients evaluated remotely with the use of telehealth were not included. Using this registry, we reviewed the medical records and radiographic studies of a group of consecutive patients with SIH and symptoms of bvFTD who underwent a lateral decubitus DSM at our institution during the 32-month period between April 2018 and December 2020. The diagnosis of SIH was based on the criteria of the International Classification of Headache Disorders, third edition (ICHD-3),[39] with minor modifications. These criteria require objective evidence of SIH, consisting of brain MRI showing stigmata of SIH (i.e., pachymeningeal enhancement, brain sagging, or subdural fluid collections), spinal imaging showing a CSF leak (i.e., the presence of extradural CSF or a CSF-venous fistula), or low CSF opening pressure (i.e., <6.0 cm H_2O).[39] The modification consists of also including patients who do not have headaches but whose symptoms are best explained by SIH.

The clinical diagnosis of bvFTD was based on the clinical criteria of the International Behavioural Variant FTD Criteria Consortium (FTDC).[5] These criteria require progressive deterioration of behavior and/or cognition and consist of the presence of at least three of the following symptoms: (1) behavioral disinhibition; (2) apathy or inertia; (3) loss of sympathy or empathy; (4) perseverative, stereotyped, or

compulsive/ritualistic behavior; (5) hyperorality and dietary changes; and (6) neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions.

All patients (or their family/caregivers) completed a modified Migraine Disability Assessment (MIDAS) questionnaire to assess the severity of the symptoms, before and after last treatment. The modification consists of substituting "symptoms of SIH" for "headaches." We refer to this modified questionnaire as the "SIHDAS (SIH Disability Assessment Score)" questionnaire.[25] A score of 0 to 5 (grade I) is considered to equate to little or no disability, a score of 6 to 10 (grade II) is mild disability, a score of 11 to 20 (grade III) is moderate disability, and a score of >20 (grade IV) is severe disability. For outcome assessment, grades I and II were considered a good outcome. Mini-Mental State Examination (MMSE) was performed in all patients.

The imaging protocol consisted of universal brain MRI and MRMyelography (heavily T2-weighted MRI) for all patients. The DSM technique as described by Hoxworth et al.[40] was used with some minor modifications.[36] Briefly, DSM is performed under general endotracheal anesthesia with deep paralysis and suspended respiration for maximal detail and temporal resolution. Patients are positioned in the lateral decubitus position in a biplane angiography suite, with tilt table capability. Pillows or foam padding are placed to optimize cervicothoracic alignment. A fluoroscopically guided lumbar puncture is performed at the L2–3 level with a 22-gauge needle. An opening pressure is obtained at this time. Then, accurate needle position is confirmed with an injection of 0.5 ml of Omnipaque. Patients are then further positioned based on the area of interest, tilting the table to achieve contrast flow to the cervicothoracic spine. Finally, contrast is injected manually 1 ml/s with suspended respiration for 40 to 100 seconds while acquiring biplane subtraction images at 2 frames/s.

TABLE 1 Frequency of diagnostic criteria of bvFTD in 21 patients with behavioral variant frontotemporal brain sagging syndrome.

A Behavioral disinhibition:	21/21	100%
B Apathy or inertia:	21/21	100%
C Loss of empathy:	15/21	71.4%
D Perseverative behavior:	15/21	71.4%
E Hyperorality:	16/21	76.2%
F Executive dysfunction:	14/15	93.3%

Note: Core diagnostic features using the International Behavioral Variant Frontotemporal Dementia Criteria Consortium revised guidelines.[5]

TABLE 2 Neurologic manifestations of SIH in 21 patients with behavioral variant frontotemporal brain sagging syndrome

Hypersomnolence	21/21 (100%)
Dysequilibrium/gait dysfunction	19/21 (90.5%)
Headache	17/21 (81%)
Orthostatic	11/17 (64.7%)
Non-positional	3/17 (17.6%)
Reverse orthostatic	3/17 (17.6%)
Dysphagia/dysarthria	14/21 (66.7%)
Tremors	9/21 (42.9%)
Incontinence	7/21 (33.3%)
Orofacial dyskinesia	5/21 (23.8%)
Dysgeusia	4/21 (19.0%)
Hiccupping	4/21 (19.0%)
Hallucinations	3/21 (14.3%)
Impotence/erectile dysfunction	3/21 (14.3%)

2.1 | Statistical analysis

Differences in patient level–factors and clinical characteristics were compared with chi-square and the Wilcoxon–Mann–Whitney tests for categorical and continuous variables, respectively. All analyses were conducted with SAS software (version 9.2; SAS Inc.).

3 | RESULTS

Twenty-one patients (17 men [81%] and 4 women [19%]) met both the ICHD-3 criteria for SIH and clinical FTDC criteria and were included in this study. The mean age at the onset of SIH was 49.9 years (range: 24–66 years), at the onset of bvFTD symptoms was 51.1 years (range: 29–67 years), and at the time of the DSM was 56.2 years (range: 31–70 years).

The distribution of symptoms of bvFTD is shown in Table 1. The most common was behavioral disinhibition and apathy/inertia (100%) and the least common was perseverative, stereotyped, or compulsive/ritualistic behavior (71.4%). Behavioral disinhibition usually consisted of socially inappropriate comments and loss of decorum. Disability was high for all patients (SIHDAS score of IV in all). The clinical characteristics of SIH not only included headache, but also less typical symptoms, all associated with severe brain sagging, such as hypersomnolence, dysarthria, dysphagia, tremors, orofacial dyskinesias, disequilibrium/gait dysfunction, and incontinence (Table 2). Of note, all 21 patients had daytime hypersomnolence—usually coinciding with the symptoms of bvFTD. A history of headache was common and was reported in 17 patients (81%). The headache had orthostatic features in 11 patients (65%), but 3 patients (18%) had clearly reverse orthostatic headaches being unable to lie down, and the headache was rarely the main complaint. The most common scenario, present in 16 patients (76%), was headache as the initial manifestation of SIH followed by the insidious onset of symptoms of bvFTD. The symptoms of bvFTD were progressive in all, but by the time of evaluation in our institution headache had completely or mostly resolved in 13 (76.5%) of the 17 patients with a history of headache. In addition, symptoms of bvFTD were the initial manifestations of SIH in five patients (24%), four of whom never developed a headache.

Prior to presentation to our institution, 17 patients (81%) had undergone one or more epidural blood patches, seven patients (33%)

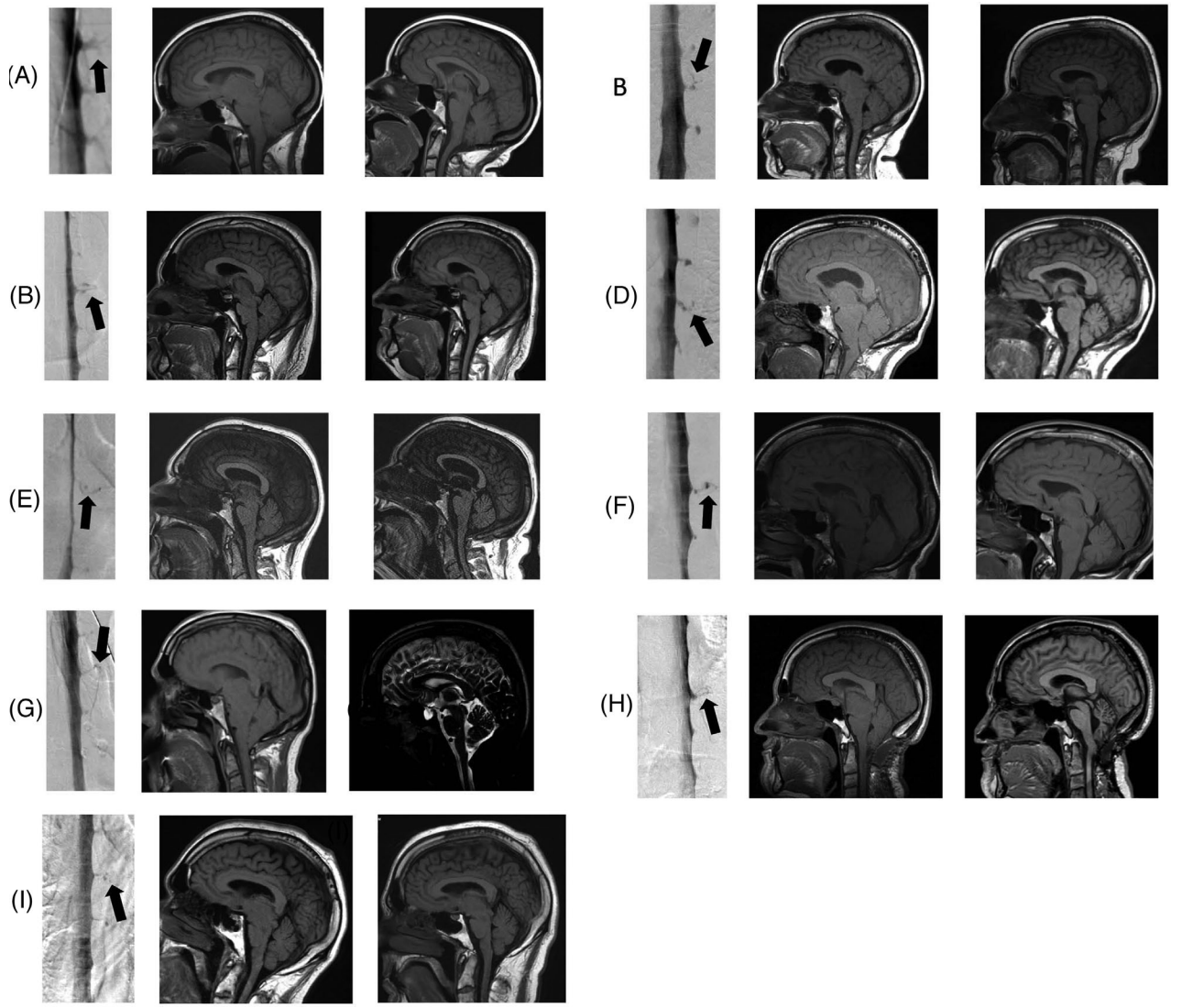

FIGURE 1 Digital subtraction myelograms (left panel) showing a spontaneous spinal cerebrospinal fluid-venous fistula (arrow) in nine patients (A–I) with behavioral variant frontotemporal brain sagging syndrome and pre- (middle panel) and post- (right panel) operative sagittal magnetic resonance imaging scans showing resolution of brain sagging. Patients B[49] and F[50] were reported in part by their initial treating physicians, patient F without our knowledge

had undergone percutaneous fibrin glue injections, and five patients (24%) had undergone suboccipital craniotomies and C1 laminectomies for Chiari decompression.

MMSE showed mild (score: 21–24) to moderate/severe (score: 10–20) cognitive impairment in eight patients. Formal neuropsychological testing was performed in 15 patients and showed poor executive function in 14 patients (93%). The following tests were administered to evaluate executive functioning: Trail Making Test part B, Wisconsin Card Sorting Test—64 card version, verbal fluency test, Brixton test, facial emotion recognition test, design fluency test, Tower of London test, faux-pax test, and backward digit span test.

MRI of the brain showed severe brain sagging in all patients. Brain sagging involved the temporal lobes, the midbrain, and the brainstem in all patients (Figure 1). None of the patients had frontotemporal brain atrophy. Other MRI findings typically seen in SIH were common and included meningeal enhancement (48%), pituitary enlargement (33%), subdural fluid collections (14%), and venous engorgement (5%).

Using DSM in the lateral decubitus position, spinal CSF-venous fistulas were detected in 9 (42.8%) of these 21 patients with behavioral variant frontotemporal brain sagging syndrome (Figure 1). The mean age of these nine patients (two women and seven men) was 51.4 years at the onset of SIH (range: 24–66 years), 54.8 years at the onset of bvFTD symptoms (range: 38–66 years), and 58.8 years at the time of DSM (range: 48–68 years). All CSF-venous fistulas were located in the thoracic spine and multiple CSF-venous fistulas were not encountered. Clinical and radiographic characteristics of the patients are shown in Table 3. Patients with CSF-venous fistulas were more likely to have an underlying spinal meningeal diverticulum (89% vs. 33%, $P = 0.0244$),

TABLE 3 Demographics of study cohort

Variable	All (n = 21)	Fistula N = 9 (42.9%)	No Fistula N = 12 (57.1%)	p value
Age in years				
FTD				0.3484
Mean (SD)	51.1 (12.0)	54.8 (10.0)	48.4 (13.0)	
Median (IQR)	52 [45-61]	56 [48-64]	50 [39-57]	
Range				
DSM				0.6236
Mean (SD)	56.2 (11.6)	58.8 (7.7)	54.3 (13.8)	
Mean (IQR)	60 [50-64]	60 [50-65]	60 [42-64]	
Range				
Headache*				0.7403
Mean (SD)	49.9 (13.4)	51.4 (10.0)	48.3 (13.9)	
Median (IQR)	51 [45-61]	52 [47-61]	50 [39-59]	
Range				
Sex				1.0000
Male	17 (80.9)	7 (77.8)	10 (83.3)	
Female	4 (19.1)	2 (22.2)	2 (16.7)	
BMI				0.2153
Mean (SD)	31.4 (8.1)	28.5 (5.8)	33.7 (9.1)	
Median (IQR)	31 [26-34]	27 [26-31]	32 [28-38]	
Range				
MMSE				0.5738
Mean (SD)	24.2 (5.0)	24.6 (6.3)	24.0 (4.1)	
Median (IQR)	26 [21-28]	27 [25-28]	25 [21-28]	
Range				
Location of Patients				0.1856
California	3 (14.3)	2 (22.2)	1 (8.3)	
U.S.	16 (76.2)	5 (55.6)	11 (91.7)	
International	2 (9.5)	2 (22.2)	0 (0)	
Characteristic MRI Findings				
Sagging	21 (100.0)	9 (100.0)	12 (100.0)	1.0000
Enhancement	10 (47.6)	4 (44.4)	6 (50.0)	1.0000
Engorged Veins	1 (4.7)	1 (11.1)	0 (0)	0.4286
Pituitary Enlargement	7 (33.3)	5 (55.6)	2 (16.7)	0.1588
Subdural	3 (14.3)	1 (11.1)	2 (16.7)	1.0000
Cyst	12 (57.1)	8 (88.9)	4 (33.3)	0.0244
Maximum cyst size**				0.2818
Mean (SD)	6.8 (4.1)	7.6 (4.5)	5.2 (2.9)	
Median (IQR)	6 [4-10]	7 [4-10]	4 [3-6]	
Range	3-15	3-15	3-10	
Opening pressure				0.1064
Mean (SD)	10.7 (5.2)	9.4 (5.7)	13.2 (2.9)	
Median (IQR)	11 [6-13]	10 [6-12]	13 [13-14]	
Range	0-21	0-21	9-17	

(Continues)

TABLE 3 (Continued)

Variable	All (n = 21)	Fistula N = 9 (42.9%)	No Fistula N = 12 (57.1%)	p value
Cognitive Impairment***				0.314
Intact	13 (61.9)	7 (77.9)	6 (50.0)	
Mild	3 (14.3)	0 (0)	3 (25.0)	
Moderate/severe	5 (23.8)	2 (22.2)	3 (25.0)	
Outcome				0.0011
Good	12 (57.1)	9 (100.0)	3 (25.0)	
Poor	9 (42.9)	0 (0)	9 (75.0)	

Abbreviation: BMI, body mass index; DSM, digital subtraction myelography; FTD, frontotemporal dementia; IQR, interquartile range; MMSE, Mini-Mental State Examination; SD, standard deviaition.
*Excludes 4 patients who did not experience a headache.
**among those with a cyst.
***based on minimental status exam score; minimental status exam score (Intact: 25 or greater; Mild: 21-24; Moderate/Severe: 10-20).

but there were no statistically significant differences in, for example, body mass index, CSF opening pressure, brain MRI findings, MMSE scores, or duration of symptoms.

Only two patients had a low CSF opening pressure (<6 cm CSF) at the time of the lateral decubitus DSM.

Clinical follow-up was complete for all 21 patients, for a total follow-up since onset of symptoms of 152 patient-years (range: 19–313 months; mean: 86.9 months) and since last treatment of 26.8 patient-years (range: 3–31 months; mean: 15.3 months).

All nine patients with a spinal CSF-venous fistula underwent a laminoforaminotomy for clip ligation of the CSF-venous fistula. There were no post-operative complications and post-operative MRI showed resolution of brain sagging in all nine patients (Figure 1). All 12 patients without a CSF-venous fistula underwent one or more surgical procedures after percutaneous procedures failed. Eight patients underwent a lumbar laminectomy for dural reduction surgery, five patients underwent laminoforaminotomies to repair meningeal diverticula, five patients underwent placement of a ventral dural patch graft at the site of a compression fracture or calcified disc herniation, two patients underwent placement of a wearable epidural spinal infusion system, two patients underwent a craniotomy for release of the tentorium cerebelli (allowing an incarcerated brain to resume a normal position), one patient underwent endovascular paraspinal vein embolization with a plastic polymer, one patient underwent resection of the styloid process and endovascular stent placement of the internal jugular vein for severe internal jugular vein stenosis, and one patient underwent endovascular stent placement of the inferior vena cava for mild inferior vena cava stenosis. One patient with recalcitrant symptoms died of aspiration pneumonia at age 36 secondary to severe dysphagia 6 months after surgical repair of spinal meningeal diverticula.

Overall, a good outcome was achieved by 12 (57.1%) of the 21 patients (Table 3), including 9 (100%) of 9 patients who underwent surgical clip ligation of the CSF-venous fistula compared to 3 (25%) of the 12 patients in whom the DSM failed to demonstrate a CSF leak (P = 0.0011).

4 | DISCUSSION

4.1 | Spontaneous spinal CSF-venous fistulas in frontotemporal brain sagging syndrome

In this study we were able to detect a spinal CSF-venous fistula in ≈two fifths of patients with behavioral variant frontotemporal brain sagging syndrome who underwent DSM in the lateral decubitus position. This, for the first time, shows that indeed spinal CSF leaks are responsible for at least a significant proportion of cases of behavioral variant frontotemporal brain sagging syndrome. In our prior study, wherein 26 patients with behavioral variant frontotemporal brain sagging syndrome underwent DSM in the prone position, we were not able to detect any CSF-venous fistulas.[25] Since the completion of that study, but prior to us performing DSM in the lateral decubitus position, we were able to detect a CSF-venous fistula in only one patient with behavioral variant frontotemporal brain sagging syndrome when the DSM was performed in the prone position,[41] corresponding to a detection rate of 2.9% (1/34 patients). This sizeable discrepancy is similar to the situation among patients with SIH in general, in which CSF-venous fistulas can be detected in ≈three fourths of patients when DSM is performed in the lateral decubitus position compared to only 15% when DSM is performed in the prone position.[36]

A flow diagram of the evaluation and treatment of patients with behavioral variant frontotemporal brain sagging syndrome is shown in Figure 2.

Identifying a CSF-venous fistula is important because it allows directed and effective treatments, such as surgical ligation of the fistula. The present study underscores the importance of being able to identify and treat the spinal CSF leak because all patients with behavioral variant frontotemporal brain sagging syndrome and a CSF-venous fistula had a good outcome compared to only one fourth of patients with frontotemporal brain sagging syndrome who did not have an identifiable CSF leak.

Similar to a recent study of patients suspected of SIH but with normal brain imaging,[42] the present study shows that the presence of

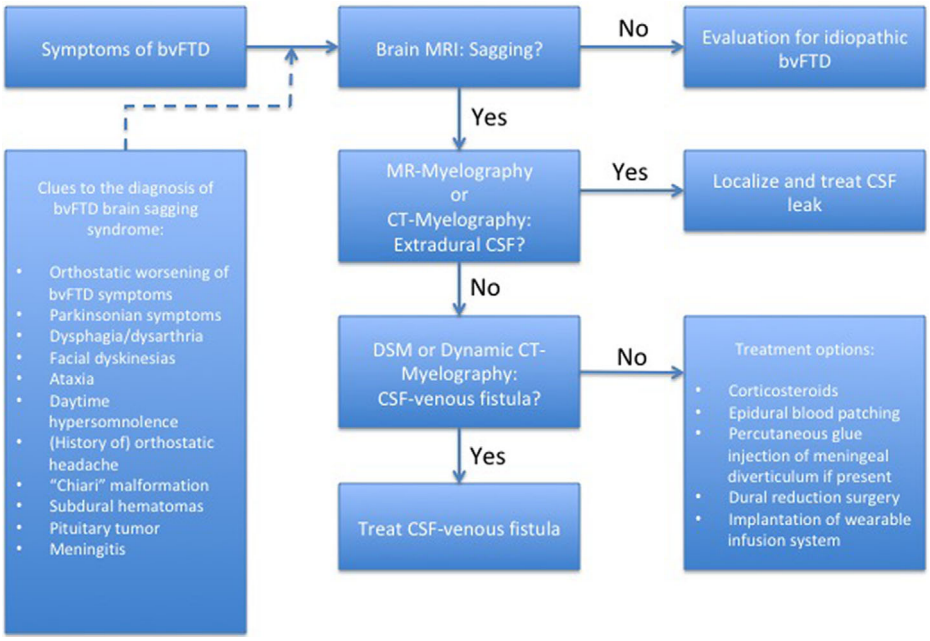

FIGURE 2 Flow diagram of the evaluation and treatment with behavioral variant frontotemporal brain sagging syndrome. bvFTD, behavioral variant frontotemporal dementia; CSF, cerebrospinal fluid; CT, computed tomography; DSM, digital subtraction myelography; MRI, magnetic resonance imaging

spinal meningeal diverticula is an important predictor of detecting a spinal CSF-venous fistula. This likely reflects the presence of a systemic underlying duropathy.

Although we were able to detect a CSF-venous fistula in a significant proportion of patients with frontotemporal brain sagging syndrome, this patient population remains the most challenging of all SIH patients with regard to identifying the underlying spinal CSF leak, significantly limiting treatment options. Great efforts need to be made to enhance the detection rate of the underlying spinal pathology in this patient population. We have developed non-targeted treatments for SIH patients without a detectable CSF leak, such as dural reduction surgery[22,43] and a wearable implantable spinal infusion system.[44] We have used these treatments in patients with frontotemporal brain sagging syndrome[22,25] but as this study shows the effectiveness of these treatments is much less than when a CSF leak is detected.

4.2 | Clues to the diagnosis of frontotemporal brain sagging syndrome—clinical

Although it is not possible to confidently diagnose frontotemporal brain sagging syndrome based purely on clinical characteristics, there are some clinical clues that should increase the level of suspicion among patients with symptoms of bvFTD (Figure 2). Orthostatic worsening (or, improvement with recumbency) of bvFTD symptoms has been reported in some patients with frontotemporal brain sagging syndrome and this is not a feature of idiopathic bvFTD. The current and previous studies have shown that hypersomnolence is a ubiquitous feature of behavioral variant frontotemporal brain sagging syndrome.[25] However, the hypersomnolence often is orthostatic and may not manifest itself until later in the day when the patient has been upright for hours.[25] In addition, Parkinsonian symptoms (such as tremor), dysphagia, dysarthria, facial dyskinesias, and ataxia are common among patients with behavioral variant frontotemporal brain sagging syndrome, but only hypersomnolence[45] and tremors[46,47] are seen with any frequency in patients with idiopathic bvFTD. A history of new-onset headaches can be elicited in a majority of patients with behavioral variant frontotemporal brain sagging syndrome, but it is rarely the most important symptom, it is often non-orthostatic particularly with the passage of time, and may be completely absent. Headaches have been found to be significantly more common in patients with idiopathic bvFTD in general compared to patients with Alzheimer disease.[48]

The neuropsychological profile of bvFTD is characterized by deficits in executive tasks with relative sparing of episodic memory and visuospatial functions. Neuropsychological testing has the potential to detect differences between idiopathic bvFTD and frontotemporal brain sagging syndrome, but because of the quaternary referral pattern of our practice, neuropsychological testing was performed at the referring institutions resulting in a heterogeneous battery of tests performed.

4.3 | Clues to the diagnosis of frontotemporal brain sagging syndrome—radiographic

Obtaining a brain MRI is usual practice in the evaluation of patients suspected of bvFTD to look for frontotemporal brain atrophy. However, patients with symptoms of bvFTD due to brain sagging and SIH

have been diagnosed erroneously not only with normal brain findings, but also with midbrain glioma and congenital midbrain dysplasia, because of the unusual slumping appearance of midbrain structures. Brain sagging often, but not invariably, involves the cerebellar tonsils and patients with frontotemporal brain sagging syndrome have been misdiagnosed with Chiari malformation and undergone unnecessary Chiari decompression surgery.[25,38] Other potential radiographic misdiagnoses include "meningitis" or "neoplasm" based on the typical pachymeningeal enhancement, "pituitary tumor" based on the presence of pituitary hyperemia, and "trauma" based on the detection of subdural fluid collections that can mimic traumatic acute on chronic subdural hematomas. A history of any of these diagnoses should increase the level of suspicion for frontotemporal brain sagging syndrome among patients with symptoms of bvFTD.

4.4 | Brain sagging

Brain sagging is the paramount feature of frontotemporal dementia brain sagging syndrome and deserves some further identification. Brain sagging is identifiable on a single mid-sagittal brain MRI showing one or more of the following features: effacement of perichiasmatic cisterns with bowing of the optic chiasm over the pituitary fossa, decreased ponto-mamillary distance, effacement of the prepontine cistern with flattening of the pons against the clivus, and cerebellar tonsillar herniation. Temporal lobe sagging manifests itself by temporal lobe herniation over the tentorium cerebelli and is best seen on a coronal plane. The degree of brain sagging in patients with frontotemporal dementia brain sagging syndrome is invariably profound and subtle abnormalities requiring exact measurements do not need to be sought.

4.5 | Disease mechanisms

Brain sagging could cause the symptoms of bvFTD by mechanical forces (stretching) on the frontal and temporal cortices and (or) their circuits. In a prior study, we have shown that approximately three fourths of patients with frontotemporal dementia brain sagging syndrome have frontotemporal hypometabolism on positron emission tomography examination and that intrathecal infusion of preservative-free normal saline restores brain sagging and results in significant improvement of bvFTD symptomatology.[25] Also, brain sagging involving the deep midline structures, cerebellum, or brain stem could explain the commonly associated neurological symptoms such as hypersomnolence, dysarthria, dysphagia, tremors, unsteady gait, ocular abnormalities, and movement disorders.

4.6 | Study limitations

Several limitations of this study should be noted. First, this is a highly selected group of patients referred to a quaternary referral center for SIH and the generalizability of our findings is unknown. For example, it is possible that a sizeable proportion of patients with behavioral variant frontotemporal brain sagging syndrome have a benign and self-limiting course. Second, only two thirds of the presently reported patients underwent formal neuropsychological testing and post-operative testing has not (yet) been performed. However, the bvFTD symptomatology was clearly defined in our patients and met the well-established clinical criteria for bvFTD. Third, behavioral variant frontotemporal brain sagging syndrome is a rarely diagnosed disorder and although this is the only series of such patients with identifiable CSF leaks, the total number of patients was relatively low.

5 | CONCLUSIONS

Detecting spontaneous spinal CSF-venous fistulas in patients with behavioral variant frontotemporal brain sagging syndrome requires specialized imaging that is invasive and not widely available. However, pursuing the detection of CSF-venous fistulas is worthwhile because treatment of the fistula is effective and associated with low risk, while there are no disease-modifying treatments available for the devastating symptoms of bvFTD. Even with this specialized imaging the source of the loss of spinal CSF remains elusive in more than half of patients.

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None

CONFLICTS OF INTEREST

The authors report no disclosures. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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