REVIEW

Brain Sagging Dementia—Diagnosis, Treatment, and Outcome

A Review

Aslan Lashkarivand, MD, and Per Kristian Eide, MD, PhD

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Correspondence
Dr. Eide
p.k.eide@medisin.uio.no

Abstract

Brain sagging dementia (BSD), caused by spontaneous intracranial hypotension (SIH), is a rare syndrome that is only recently recognized, mimicking the clinical findings of behavioral variant frontotemporal dementia (bvFTD). Being aware of its signs and symptoms is essential for early diagnosis and treatment in this potentially reversible form of dementia. Our objective was to identify cases of BSD in the literature and present its clinical characteristics, diagnostic workup, treatment options, and outcome. The review was reported according to PRISMA guidelines and registered with the PROSPERO database (CRD42020150709). MEDLINE, EMBASE, PsychINFO, and Cochrane Library were searched. There was no date restriction. The search was updated in April 2021. A total of 983 articles were screened and assessed for eligibility. Twenty-nine articles (25 case reports and 4 series) and 70 patients were selected for inclusion. No cranial leak cases were identified. BSD diagnosis should be made based on clinical signs and symptoms and radiologic findings. There is a male predominance (F:M ratio 1:4) and a peak incidence in the 6th decade of life. The main clinical manifestation is insidious onset, gradually progressive cognitive and behavioral changes characteristic for bvFTD. Headache is present in the majority of patients (89%). The presence of brain sagging and absence of frontotemporal atrophy is an absolute criterion for the diagnosis. CSF leak is identified with myelography and digital subtraction myelography. The treatment and repair depend on the etiology and extent of the dural defect, although an epidural blood patch is the first-line treatment in most cases. With treatment, 81% experienced partial and 67% complete resolution of their symptoms. This review highlights the most important clinical aspects of BSD. Due to the sparse evidence and lack of BSD awareness, many patients are likely left undiagnosed. Recognizing this condition is essential to provide early treatment to reverse the cognitive and behavioral changes that may otherwise progress and fully impair the patient. Moreover, patients with longstanding SIH must be assessed carefully for cognitive and behavioral changes.

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Page 786

From the Department of Neurosurgery (A.L., P.K.E.), Oslo University Hospital–Rikshospitalet; and Institute of Clinical Medicine (A.L., P.K.E.), Faculty of Medicine, University of Oslo, Norway.

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Glossary

BSD = brain sagging dementia; **bvFTD** = behavioral variant frontotemporal dementia; **EBP** = epidural blood patch; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SIH** = spontaneous intracranial hypotension.

Behavioral variant frontotemporal dementia (bvFTD) is an insidious, gradually progressive neurodegenerative disorder defined by behavioral changes and cognitive dysfunction and characterized by predominant frontal or anterior temporal atrophy.[1,2] Unlike other neurodegenerative disorders, bvFTD predominantly has a presenile onset (<65 years of age). Patients commonly present with changes in personality, decline in interpersonal conduct, emotional blunting, apathy, and inertia.[3] They also have poor executive function and a loss of insight and judgment early on. With impairment in daily activities, there is a significant burden on patients' families and caregivers.[4]

Recently a new syndrome with clinical resemblance to bvFTD has been recognized. Patients present with low CSF pressure, sagging of the brain, and characteristics mimicking those of bvFTD.[5-8] In 2002, Hong et al.[5] presented a middle-aged man with findings of spontaneous intracranial hypotension (SIH) and cognitive and behavioral changes similar to bvFTD that responded to SIH targeted treatment.

SIH is a syndrome characterized by low CSF pressure–related postural headaches associated with various other signs and symptoms, including nausea, vomiting, neck stiffness and pain, tinnitus, dizziness, and diplopia. CSF volume depletion leads to ventricular collapse and "sagging" of the brain that in rare cases cause distortion of the diencephalon and brainstem with subsequent stupor and coma.[9,10] In some patients, however, there are additional gradual and slowly evolving behavioral and cognitive changes similar to bvFTD. The constellation of signs and symptoms has been referred to as intracranial hypotension syndrome, frontotemporal brain sagging syndrome, behavioral variant frontotemporal dementia as a complication of SIH, or brain sagging syndrome. The aim of this review is to establish the current knowledge about this entity, which we refer to as brain sagging dementia (BSD). From the existing literature, we aimed at defining diagnostic criteria for BSD.

Methods

This review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and registered with the PROSPERO database (CRD42020150709) (see eTables 1–3, links.lww.com/WNL/B892).[11] The search strategy and methodology were designed in collaboration with a librarian experienced in literature searches for systematic reviews. We searched MEDLINE, EMBASE, PsychINFO, and Cochrane Library for all relevant synonyms and variations of the terms: SIH, brain sagging, dementia, and behavioral and cognitive changes. References of screened full-text articles were also considered for inclusion. There was no date limitation. Only articles in English language were included. The search was updated on April 21, 2021. The search strategy in its entirety is provided as supplementary material (see eTables 1–3, links.lww.com/WNL/B892).

The eligibility criteria were mainly based on the presence of SIH clinical findings and diagnosis, brain sagging on imaging, and the presence of cognitive and behavioral changes indicative of bvFTD (see eTable 1, links.lww.com/WNL/B892). Based on a preliminary search of current literature, the following broad inclusion criteria were used: patients with SIH (or CSF leak) and brain sagging, with dementia, or early-onset dementia, or frontotemporal dementia, or bvFTD, or any behavioral and cognitive changes characteristic for the condition. Our current understanding of the pathophysiology of this syndrome was considered when deciding the exclusion criteria (see Figure 1).

The data were screened and assessed for eligibility by the 2 authors independently in all steps. The CARE guidelines were used to assess the quality of case reports.[12] The JBJ critical appraisal tool was utilized by the authors.[13] Any discrepancies were discussed and resolved by consensus, although with a high threshold for exclusion. Due to the rarity of the disease and the phenomenon in question, we agreed on a predetermined strategy of low threshold for full-text review to identify articles that may describe the clinical and radiologic findings of brain sagging and bvFTD, but without the explicit labeling.

Results

The literature search identified 1,454 articles. After deleting duplicates, 983 articles remained and underwent screening and assessment for eligibility (see Figure 1; PRISMA flow diagram). Twenty-nine articles were included in the current study: 25 case reports (level 5 quality of evidence)[14,15] and 4 series (level 4 quality of evidence).[14,15] A total of 70 patients were selected for inclusion. Our results are summarized in eTable 4 (links.lww.com/WNL/B892; case reports) and Table 1 (case series).

Pathophysiology

CSF has a crucial function in providing mechanical buoyancy as a protective cushion for the brain. A CSF volume depletion by any means can disturb this function, causing a gravitational sink of the brain structures, resulting in the classical brain sagging seen in patients with SIH. Although the most common cause of intracranial hypotension is iatrogenic, caused by lumbar puncture, many cases lack a known etiology or a history of traumatic puncture responsible for the disease, hence denoted as "spontaneous."

Regardless of the etiology, the brain's gravitational downward displacement causes traction in meningeal pain fibers, resulting in the classical orthostatic headache in SIH.

In rare cases, the CSF hypovolemia and ensuing brain sag is so severe and progressive that it distorts brainstem reticular formation function, with subsequent alteration in level of consciousness and eventually coma.[9,10] In patients with BSD, however, this process seems to evolve slowly and over a more extended time. The main mechanism responsible for the cognitive and behavioral changes in BSD is not fully understood. Because the prototypical frontotemporal atrophy seen on imaging in bvFTD is lacking in patients with BSD, other pathophysiologic mechanisms must be sought. Several theories have been postulated. One concept is based on the stretching and mechanical forces upon frontotemporal cortical structures or their circuits.[6,16,17] This may also explain the development of accompanying signs and symptoms of deep midline and brainstem structures seen in most patients with BSD. Another theory builds on the decreased perfusion observed in the frontotemporal, parietal, and cerebellar cortical areas caused by venous stagnation due to stenosis at the confluence of the vein of Galen into the straight sinus.[18,19] The reason behind this theory is twofold. One, according to the Monro-Kellie doctrine,[20] the loss of CSF volume will subsequently lead to venous engorgement in order to compensate for the volume loss, resulting in brain swelling and sagging at the level of tentorial incisura. Two, the brain swelling is itself caused by the sagging, causing reduced venous drainage due to stenosis at vein of Galen confluence into straight sinus. These 2 processes are naturally not mutually exclusive.

Clinical Presentation

The classic clinical presentation of a patient with BSD is a man in his 50s seeking medical attention either voluntarily or at request of his family members complaining of headache (mostly orthostatic), insidious onset of cognitive decline, and progressive behavioral alteration.

Although the female:male ratio in SIH is 2:1, only 16/70 (23%) of the BSD cases presented in the literature are female patients. Also, BSD's peak incidence seems to be about 10 years older than in SIH. The median age at either presentation or disease onset for case reports were 55 years (range 38–66). One case report presented the patient as "in his mid-50s."[7] The median age for the 4-case series was between 50.6 and 57 years (range 34–65).

The majority of patients (62/70 [89%]) reported some form of headache, ranging from mild to severe, positional and nonpositional, and occurring early or at a later stage of the disease. Unlike SIH, many patients with BSD have their first clinical evaluation due to cognitive or behavioral changes and not headaches, although often headache is an additional burden. Interestingly, in some patients, the headache may be absent or may not occur until in later stages of the disease.[8,16,19,21-23]

Although signs and symptoms mimicking bvFTD were an inclusion criterion, most cases with an insidious onset and gradual progression,[1] without an acute event that triggered immediate medical attention (more than 3–4 weeks), were included in the analysis. Some common characteristics were outlined in most reports: antegrade amnesia,[22,24-26] distractibility and impersistence,[23,24,27-30] preservative and stereotyped behavior,[7,8,21,30-33] and altered speech output.[8,16,21,27-33] A decline in social and interpersonal conduct, including bizarre behavior and social and sexual inappropriateness, was a prominent future in most reports.[5-8,16,17,29-37] In contrast to bvFTD, 60% of patients with BSD also presented with cerebellar symptoms such as ataxia, gait disturbance, and dysarthria.[6-8,16,17,21,22,24,25,27-30,32,36-39] Therefore, the clinical pictures of BSD and bvFTD differ. Nevertheless, although rare, one should be aware of bvFTD mimicking signs and symptoms that may as well occur in the autosomal dominant disorder spinocerebellar ataxia type 17.[40]

Assessment and Diagnosis

The diagnosis of BSD should be made based on clinical findings and neuroimaging. The primary diagnostic tools for assessment and diagnosis of BSD are shown in Table 2. Patients should fulfill the clinical diagnostic criteria for bvFTD based on signs and symptoms. Although not necessary for manifesting a diagnosis, a thorough neuropsychological assessment is often performed to gain insight into patients' behavioral changes and serve as an objective measure during the follow-ups. A careful interview with the patients and their relatives is crucial to detect subtle behavioral and personality changes. Moreover, signs and symptoms of SIH, predominantly orthostatic headache, and low lumbar puncture opening pressure support the diagnosis. Nevertheless, their absence does not exclude a possible BSD.[41-43]

Brain MRI is the gold standard to rule out imaging findings of bvFTD, such as atrophy of frontal and anterior temporal cortices, and to confirm the presence of brain sag.[1,2,17,18,33] MRI findings of intracranial hypotension are shown in Figure 2. In addition, patients with BSD may demonstrate pachymeningeal enhancement (reported in 44/70 patients [63%]) and subdural effusion (reported in 15/70 patients [22%]) as well as pituitary hyperemia and venous engorgement. A decreased angle between vein of Galen and straight sinus (normal value = 73° ± 12°) measured in a midline sagittal section is highly suggestive of brain sagging.[18,19] Hypoperfusion in the frontotemporal, parietal, and cerebellar cortical regions may be seen in SPECT studies.[19]

Although PET has been performed only in a few patients, there is evidence of hypometabolism in the frontal and temporal lobe in these patients.[6,16] Schievink et al.[16] performed PET on 8 patients with BSD, of whom 6 showed hypometabolism in the frontotemporal region.

A systematic search for the CSF leakage site is essential not only for diagnosing BSD but also for the treatment approach. The

imaging should start with a craniospinal contrast-enhanced MRI searching for evident traces of CSF leak.[44] This step should be followed by myelography (either CT or MRI) to further identify and localize the CSF leak.[45] Nonetheless, in the current review, a CSF leak was detected in only 9/70 (13%) patients. The majority of leaks were located at the thoracic level[24,27,28,31,38,46]; only 2 lumbar/sacral[6,28] and 1 at the cervical level[8] were noted. No cranial CSF leak cases were identified.

If no extradural CSF leaks are identified, one should look for indirect findings suggestive of a possible leak, such as spinal meningeal diverticula. In 1 series, a spinal meningeal diverticulum (type 2a CSF leak[47]) was found in 15/29 (52%) patients.[16] During recent years, digital subtraction myelography has also been added to the diagnostic armamentarium of SIH in case of possible direct CSF–venous fistulae.[39,48]

Treatment

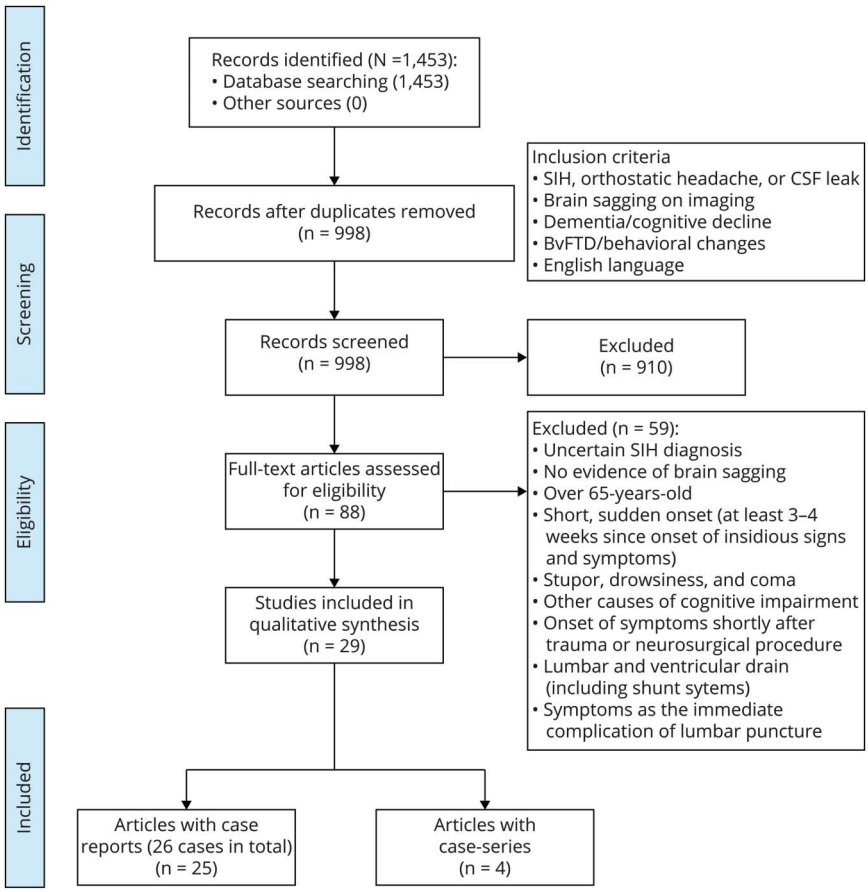
The traditional conservative treatment regimen usually prescribed for SIH, with hydration, bed rest, caffeine, theophylline, and analgesics, seems to have no effect on BSD. The first-line treatment in BSD should therefore be a lumbar epidural blood patch (EBP). Only a transient improvement is achieved the majority of times, and the lumbar EBP should therefore be repeated. If a CSF leak site is identified, a targeted blood patch can replace the second lumbar EBP. In case of structural abnormality or a focal CSF leak site that indicates surgical repair, then this should be pursued. The surgical approach depends entirely on the cause of the CSF leak and the magnitude of the dural defect.[35,49] Although many surgical techniques targeting the underlying cause of the leak have been described in the literature, most times the dural tear can be sutured or concealed by dural patch graft. Blood patch has not shown to be successful in the treatment of CSF–venous fistulae; surgical disruption of these fistulae is necessary.[39,48]

A course of steroids has shown to be successful in some patients and may be tried in case of failed EBP.[5,7,22,35] Intrathecal saline infusion has been tried and may be beneficial; however, its effect is only temporary.[8,24,38]

Prognosis

With treatment strategies mentioned in the previous section, 47 of 70 patients (67%) with BSD in the literature had a good outcome with complete resolution of their symptoms (Table 1 and eTable 4, links.lww.com/WNL/B892). An additional 10 patients (14%) experienced transient effect of the treatment. Therefore, as many as 81% of patients had some form of effect of the treatment, either transient or complete.

Figure 1 PRISMA 2009 Flow Diagram[55]



bvFTD = behavioral variant frontotemporal dementia; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SIH = spontaneous intracranial hypotension.

The transient treatment responses reported vary from a few days to months to several years.[6] In these cases, a repeat EBP or course of steroid treatment was usually required to boost the treatment effect.

Discussion

BSD is a form of dementia that for many years has been unrecognized and underreported in part because of its complex and obscure pathophysiologic mechanisms and lack of proper diagnostic workup and in part due to its insidious progression with a broad specter of signs and symptoms. Therefore, the reported cases in the literature are limited, with the first report from just about 2 decades ago.[24] This review provides insight into this condition.

Dementia, especially when occurring in presenile age, has a significant disease burden for patients and their families.[4] BvFTD is the most common type of FTD and has no cure. A fraction of these patients, however, might have BSD that can be cured. Most patients with bvFTD are in presenile age (before 65 years of age).[2,50] In 2011, Rascovsky et al.[2] showed that the criteria for possible bvFTD were significantly more sensitive in early onset disease (<65 years of age). Likewise, in our preliminary search, we found that all patients with certain signs of BSD had an early onset disease. The 2 largest cohort studies about bvFTD as a serious complication of SIH did not report any patients with late disease onset (>65 years of age).[6,51] Moreover, in elderly patients, several factors may contribute to cognitive changes mimicking bvFTD, making the BSD diagnosis more challenging and at risk of bias.[2,52]

Recognizing the signs and symptoms of BSD and being able to differentiate it from bvFTD is of utmost importance as the 2 conditions have different outcomes and prognoses. However, the insidious and subtle behavioral changes in patients with SIH can be easily overlooked and not infrequently related to a reduced level of consciousness due to collection of subdural effusion, resulting in consequent burr-hole surgery with variable outcomes.[9,53] The fact that most articles in the literature refer to the case reported by Hong et al. in 2002[5] as the first report on BSD illustrates how easily this condition is overlooked.[7,8,16] In the current review, we found that the first report on a patient with findings of BSD was in 1998 by Pleasure et al.[24]

In contrast to patients with SIH, in whom the symptoms are predominated by orthostatic headache, BSD is mainly dominated by behavioral and cognitive changes indistinguishable from bvFTD. In BSD, however, about 90% of patients report some form of headache, although its gravitational component

Table 1 Summary of the Included Series

Reference	Patients with dementia, n	M/F	Age, y, median (range)	Headache and other symptoms, duration, median (range)	Behavioral/cognitive changes	Diagnosis and treatment
Vetrugno et al.[23] (2008)	3/3	2/1	57 (49–60)	No orthostatic headache, 11 mo (6–48 mo)	Hypoactive-hypoalert behavior (psychic akinesia); chronic state of decreased behavioral initiative, persistent somnolence, impaired attention, and stereotyped motor activity; mild impairment on attention or memory tasks	BS 3/3, PME 0/3, SDH 0/3; no CSF leak identified; EBP resulted in transient improvement in 2/3 and repeated EBP resulted in complete resolution in 1/3
Wicklund et al.[6] (2011)	8/8	7/1	53 (45–59)	Headache, with onset occurring either before or concurrently with the behavioral changes; 4/8 with orthostatic headache (significant in 1/8); symptoms related to deep midline, cerebellum, and brainstem dysfunction, in various degrees	Behavioral changes characterized by disinhibition and apathy; all had cognitive impairment, although behavioral disturbance was always more prominent; 4/8 exhibited inappropriate sexual behavior	BS 8/8, PME 3/8, SDE 1/8; CSF leak site found in only 1/8 (lumbar spine); nerve root diverticula in 5/8; treatment in 4/8; surgery, EBP, and steroids with various effect, but none with complete resolution
Capizzano et al.[17] (2016)	4/8	4/0	54 (48–64)	Orthostatic headache in 3/4 (2 only mild), 1/4 with brainstem and cerebellar symptoms; hypersomnia in all; tics in 2/4; 30 mo (12–48 mo)	Behavioral change and disinhibition in 3/4; cognitive deficit in forms of memory impairment in all	Complete resolution in 2/4; 1 improved with targeted EBP and another with spinal surgery
Schievink, W. I. 2018[16]	29/29	21/8	50.6 (34–65)	Headache 27/29 (20/29 orthostatic), auditory symptoms 21/29, disequilibrium/gait dysfunction 19/29, tremor 15/29, dysphagia/dysarthria 9/29	Disinhibition and apathy/inertia 29/29, exhibited inappropriate sexual behavior 14/29, impulsive purchase 11/29; memory impairment 22/29; mild/moderate impairment on MMSE (mean 22.4/30; SD 2.1)	BS 29/29, PME 20/29, SDE 3/29; no leak identified in any patient; spinal meningeal diverticula found in 15/29; single EBP in 29/29, complete resolution in 1/29, and transient improvement in 24/29; steroids improved symptoms in 2/6; surgery with good outcome in 12/26 overall good outcome in 21/29

Abbreviations: BS = brain sagging; EBP = epidural blood patch (lumbar level if not otherwise specified); MMSE = Mini-Mental State Examination; PME = pachymeningeal enhancement; SDE = subdural effusion.

Table 2 Diagnostic Criteria for Brain Sagging Dementia

Absolute clinical and imaging criteria
Signs and symptoms of bvFTD[1,2,a]
Absence of bvFTD imaging findings; frontotemporal atrophy[b]
Imaging findings of brain sagging
Insidious onset, slowly progressing (>3/4 wk)
No history of recent trauma or lumbar puncture
Symptom onset before 65 years of age
Symptoms cannot be explained by altered level of consciousness alone
At least 1 of the supporting clinical criteria (SIH) or 3 of the additional criteria
Supporting clinical criteria
Orthostatic headache[41]
Low lumbar puncture opening pressure
Improvement of symptoms after blood patch
Additional criteria
Headache
Cerebellar signs and symptoms
Hypersomnolence
Choreiform movements
Pachymeningeal enhancement on imaging
Subdural effusion on imaging
Evidence of CSF leak on myelogram

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; SIH = spontaneous intracranial hypotension.
[a] Signs and symptoms must meet the diagnostic criteria of bvFTD.
[b] Frontotemporal atrophy must be ruled out; findings on PET and SPECT will not alter the diagnosis.

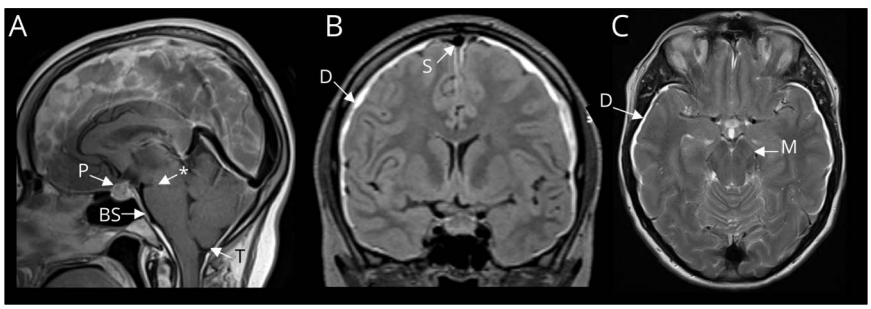
may be lacking. Upon further scrutiny, one may reveal that the symptoms started with severe headaches several months to years before cognitive decline.[22,27,29,30,35] Like patients with SIH who may feel worsening of headaches towards the end of the day, patients with BSD may feel behavioral and cognitive decline towards the evening.[16] However, we are not sure whether an acute (within minutes) positional worsening and improvement of behavioral and cognitive symptoms are related to BSD.[16] In these cases, a reduced level of consciousness due to disruption of the reticular formation and acute compression of the brainstem should be considered.[9,10]

Nevertheless, the signs and symptoms alone are not enough to distinguish BSD from bvFTD. Although lumbar puncture can be informative about the opening pressure and the CSF content to rule out infection and other degenerative diseases, such as Alzheimer disease, it cannot confirm a BSD diagnosis.[42,43] In case of high clinical suspicion for BSD, one should be cautious with using lumbar puncture as the primary diagnostic workup. It may lead to an iatrogenic CSF leak, causing confusion in localizing the main leak. This is perhaps more important in these patients than in patients with SIH, as only a minority (13%) of leaks are successfully localized.

To establish the diagnosis, an IV contrast-enhanced craniospinal MRI should be obtained. The presence of brain sag is absolute for the diagnosis. The accompanying pachymeningeal enhancement (present in the majority) and subdural effusion (present in the minority) are supportive, but their absence does not alone exclude the diagnosis. Moreover, the radiologic characteristics of FTD, namely frontotemporal atrophy on MRI, must be ruled out.[1,2] Frontotemporal hypoperfusion or hypometabolism on PET or SPECT, on the other hand, should be evaluated carefully in conjunction with other BSD findings because these changes might be present in patients with BSD as well.[19] The frontotemporal findings may be absent in the early stages of bvFTD.[54]

The first-line treatment, that is, conservative measures, used in the treatment of SIH should be skipped when treating BSD. In the latter condition, the intracranial hypotension has persisted for so long that its reversal with conservative measures seems unlikely. Also, these patients have a more severe illness. Although their minor complaints of headache may mask the seriousness of the disease, patients with BSD have behavioral changes and lack of insight that can lead to poor decision-making with serious actions such as sexual assault and felony.[5-7,16,32,34,35,37]

Figure 2 Neuroimaging Findings of Brain Sagging Dementia



Brain MRI T1-weighted images of a middle-aged person with spontaneous intracranial hypotension and brain sagging show in (A) sagittal, (B) coronal, and (C) axial planes typical signs of intracranial hypotension, such as pituitary (P) enlargement, sagging brainstem (BS) towards the clival bone, downward tonsillar (T) ectopy, smaller pontomesencephalic angle (indicated by an asterisk), enhancement of the dura (D), which may be accompanied by subdural effusions and eventually hematoma, dural venous engorgement (here indicated by rounding of the cross-section of the dural venous sinuses [S]), and reduced space for the mesencephalon (M).

Some limitations to this review should be noted. First, given the rarity and limited awareness of BSD among physicians, reports might have been missed or excluded due to lack of proper case presentation, especially regarding behavioral and cognitive changes and duration of the symptoms. Deciphering actual cognitive impairment from a reduced level of consciousness based on the reports can sometimes be demanding. Second, most studies included are case reports and retrospective series with a limited number of patients and a low quality of evidence. Third, the case presentations' retrospective nature limits a thorough neuropsychological assessment before and after treatment. Thus, the reversibility of BSD is unknown.

BSD is a newly recognized syndrome mimicking bvFTD with treatment possibilities and cure potential with an excellent outcome. Early recognition and diagnosis allow effective intervention before disease progression to fulminant dementia with tragic costs for patients and their families. Despite the rarity, it is essential to have the signs and symptoms of SIH in mind when evaluating a patient for bvFTD. The current study should raise awareness so patients with SIH undergo a thorough neuropsychological assessment and follow-up.

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Appendix Authors

Name	Location	Contribution
Aslan Lashkarivand, MD	Department of Neurosurgery, Oslo University Hospital–Rikshospitalet, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Per Kristian Eide, MD, PhD	Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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Aslan Lashkarivand and Per Kristian Eide

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