Spontaneous occult intracranial hypotension precipitating life-threatening cerebral venous thrombosis: case report

Avital Perry, MD,¹ Christopher S. Graffeo, MD,¹ Waleed Brinjikji, MD,² William R. Copeland III, MD,³ Alejandro A. Rabinstein, MD,⁴ and Michael J. Link, MD^{1,5}

Departments of ¹Neurologic Surgery, ²Radiology-Diagnostic, ⁴Neurology, and ⁵Otolaryngology–Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota; and ³Division of Neurosurgery, Department of Surgery, Tenwek Hospital, Bomet, Kenya

Spontaneous intracranial hypotension (SIH) is an uncommon headache etiology, typically attributable to an unprovoked occult spinal CSF leak. Although frequently benign, serious complications may occur, including cerebral venous thrombosis (CVT). The objective of this study was to examine a highly complicated case of CVT attributable to SIH as a lens for understanding the heterogeneous literature on this rare complication, and to provide useful, evidence-based, preliminary clinical recommendations. A 43-year-old man presented with 1 week of headache, dizziness, and nausea, which precipitously evolved to hemiplegia. CT venography confirmed CVT, and therapeutic heparin was initiated. He suffered a generalized seizure due to left parietal hemorrhage, which subsequently expanded. He developed signs of mass effect and herniation, heparin was discontinued, and he was taken to the operating room for clot evacuation and external ventricular drain placement. Intraoperatively, the dura was deflated, suggesting underlying SIH. Ventral T-1 CSF leak was identified, which failed multiple epidural blood patches and required primary repair. The patient ultimately made a complete recovery. Systematic review identified 29 publications describing 36 cases of SIH-associated CVT. Among 31 patients for whom long-term neurological outcome was reported, 25 (81%) recovered completely. Underlying coagulopathy/risk factors were identified in 11 patients (31%). CVT is a rare and potentially lethal sequela occurring in 2% of SIH cases. Awareness of the condition is poor, risking morbid complications. Evaluation and treatment should be directed toward identification and treatment of occult CSF leaks. Encouragingly, good neurological outcomes can be achieved through vigilant multidisciplinary neurosurgical and neurocritical care.

<https://thejns.org/doi/abs/10.3171/2017.10.SPINE17806>

KEYWORDS cerebral venous thrombosis; cerebrospinal fluid leak; spontaneous intracranial hypotension; epidural blood patch; neurocritical care

SPONTANEOUS intracranial hypotension (SIH) is an uncommon headache etiology, typically attributable to an unprovoked CSF leak.^{28,29,39,40} More than 80% of patients present with orthostatic headache, yet a wide swath of symptoms has been reported, ranging from cervical pain, meningismus, nausea/vomiting, and imbalance, to rare symptoms including gait disturbance, auditory or visual changes, Parkinsonism, ataxia, dementia, paralysis, radiculopathy, and cranial nerve deficits.^{4,29,39,42}

Diagnosis of SIH is frequently delayed while treatment of more common headache etiologies is attempted.³⁹ For most patients with SIH, this results in prolonged discomfort, but minimal clinical impact, as complications are rare, and the condition ultimately responds well to treatment via epidural blood patch (EBP).²⁹ However, severe complications of SIH have been reported, including cere-

bral venous thrombosis (CVT).^{12,21,22,25,42,43} Although estimated to occur in just 2% of SIH cases, CVT may quickly precipitate life-threatening complications including intracranial hemorrhage, seizures, brain herniation, venous infarction, and raised intracranial pressure.⁴² We report a complex and challenging case of CVT due to SIH arising from a spontaneous CSF leak at the cervicothoracic junction (CTJ), from which the patient ultimately made a complete neurological recovery; in parallel, we review the pertinent literature regarding this rare and dangerous entity.

Case Selection and Literature Review Methodology

We reviewed the chart of a patient who underwent treatment for complex SIH with CVT for case reporting.

ABBREVIATIONS CTJ = cervicothoracic junction; CVT = cerebral venous thrombosis; EBP = epidural blood patch; EVD = external ventricular drain; SDH = subdural hematoma; SIH = spontaneous intracranial hypotension.

SUBMITTED July 18, 2017. **ACCEPTED** October 10, 2017.

INCLUDE WHEN CITING Published online March 30, 2018; DOI: 10.3171/2017.10.SPINE17806.

Systematic review of the literature was initiated using PubMed, MEDLINE, Embase, and Google Scholar. Keywords and MeSH terms included “intracranial hypotension,” “cerebral venous thrombosis,” “venous sinus thrombosis,” and “CSF” or “cerebrospinal” together with “leak,” “hypotension,” or “hypovolemia.” Initial results after eliminating duplicates and performing bibliographic screening yielded 218 unique English-language publications. All cases or series describing clinically confirmed CVT attributable to SIH, with clear diagnostic evidence derived from radiographic, surgical, or therapeutic data, were included. Abstracts were screened independently by two authors (C.S.G. and W.R.C.) with instances of disagreement resolved by secondary review from the lead author (A.P.). Cumulatively, 29 articles describing 36 cases of CVT attributable to SIH were identified.

Included publications were reviewed in detail. Where available, individual patient characteristics and outcomes were captured, including: age; sex; presenting symptoms; evidence of SIH and/or CVT on initial imaging; treatments, including anticoagulation, EBP, surgical repair of CSF leak, or surgical treatment of an intracranial complication; resolution of symptoms (defined as complete vs incomplete return to presymptomatic baseline); complications; and findings on coagulopathy workup. STROBE guidelines were used as appropriate. Applicable components of this study were approved by our institutional IRB, which included an approved waiver of consent for minimal risk.

Case Report

History and Presentation

A 43-year-old man in excellent health presented to the emergency department complaining of new, intermittent, holocephalic non-orthostatic headaches, accompanied by dizziness and nausea, worsening over 1 week. The head CT scan was read as negative, neurology was not consulted, and the patient was referred to his primary care provider for a headache workup. Migraines were suspected, and sumatriptan and meclizine were initiated, with no relief. Subsequent outpatient MRI of the brain demonstrated smooth, diffuse dural and leptomeningeal enhancement, without tonsillar herniation or “brain sag” (Fig. 1A). The patient was referred to neurology, but while awaiting evaluation he experienced a severe headache and right-sided weakness, prompting a return to the emergency department.

Noncontrast head CT and CT venography demonstrated a large thrombus within the superior sagittal sinus overlying the frontal and parietal lobes, with extension into multiple bilateral cortical veins and no evidence of hemorrhage (Fig. 1B and C). Intravenous heparin was initiated with a bolus dose, and the patient was admitted to the neurosciences intensive care unit.

Three hours later, the patient experienced a generalized tonic-clonic seizure that self-limited after 45 seconds; lacosamide was administered using a loading dose, and emergency head CT demonstrated a 3.1 × 3.8 × 3.1-cm left posterior parietal hemorrhage overlying a thrombosed cortical vein (Fig. 1D). The patient became somnolent and

developed right gaze preference with right arm and leg paresis. As per American Heart Association/American Stroke Association guidelines, he was continued on intravenous heparin (last activated partial thromboplastin time prior to hemorrhage = 157 seconds, first after hemorrhage = 99 seconds).³⁵ Mannitol was initiated with marked improvement in his level of consciousness. Digital subtraction angiography demonstrated near-normal filling of the venous system, with evidence of contrast extravasation suggested by the presence of an “angiographic spot sign” (Fig. 1E). Twenty-four hours later, the patient developed recurrent somnolence and right hemiplegia; head CT demonstrated hemorrhage expansion (Fig. 1F). Heparin was discontinued, mannitol was increased, and 75 ml of 10% sodium chloride was initiated intravenously, resulting in restoration of the patient’s pre-expansion neurological examination.

Hypertonic saline was weaned successfully; however, 4 days later the patient became acutely somnolent with bilateral extensor posturing and a dilated, sluggish right pupil. He was emergently intubated and administered 100 ml of 23.4% sodium chloride intravenously, which immediately restored his level of consciousness.

Operation and Postoperative Course

Repeat angiography showed venous pooling and decreased right transverse sinus flow suggesting mass effect, for which the patient was taken to the operating room for a stereotactic left parietal craniotomy, clot evacuation, and external ventricular drain (EVD) placement (Fig. 1G and H). Evidence of CSF hypotension was immediately apparent following elevation of the craniotomy flap and direct exploration of the intracranial contents, as the dura appeared markedly deflated, without the expected turgor and with significant sag of the entire intradural contents. Samples of the hemorrhage were sent for pathologic analysis and confirmed to be negative for evidence of underlying tumor or vascular malformation.

Postoperatively, the patient was maintained in a 5° Trendelenburg position (i.e., supine with head declined relative to the feet) with the EVD threshold at 15 mm Hg. Hyperosmolar therapy was continued, but intracranial pressure remained low and EVD output was minimal. Once the patient was medically stable while tolerating flat positioning, the EVD was removed and the patient was taken for MRI of the cervical spine, which demonstrated a large T2 hyperintense epidural fluid collection, indicating a ventral CSF leak (Fig. 2A and B). A CT-guided myelogram confirmed pronounced contrast extravasation at T1–2 adjacent to a calcified osteophyte, which diagnosed a high-flow CSF leak (Fig. 2C–F). This was treated via a triple injection EBP in the prone Trendelenburg position, with 10 ml of autologous blood followed by 1–2 ml of fibrin glue infused into the bilateral T1–2 foramina, and an additional 10 ml of blood injected into the T1–2 dorsal epidural space (Fig. 3). Approximate target volumes for injection were derived from the standardized 30 ml thoracolumbar injection frequently used for occult-source SIH, adjusted for the difference in relative spinal canal and neuronal volumes between the high thoracic and thoracolumbar regions.³⁰

FIG. 1. **A:** Coronal T1-weighted contrast-enhanced MR image demonstrates diffuse smooth dural enhancement. **B and C:** Coronal noncontrast head CT image (**B**) demonstrates high attenuation in the superior sagittal sinus (*arrow*) as well as in an inflowing cortical vein (*arrowhead*), consistent with dural venous sinus thrombosis. This was subsequently confirmed via a 3D reformatted CT venogram (**C**), which demonstrated multiple superior sagittal sinus filling defects (*arrowheads*). **D:** Noncontrast head CT performed several hours later shows an acute left parietal intraparenchymal hematoma with associated effacement of the overlying sulci. **E:** Left internal carotid artery angiogram in the venous phase again demonstrates multiple superior sagittal sinus filling defects (*arrowheads*), as well as a pinpoint focus of contrast pooling in the region of the hematoma, consistent with an angiographic spot sign (*arrow*). **F:** Head CT acquired the next day shows expansion of the left parietal hematoma with increased vasogenic edema and mass effect. **G:** Repeat cerebral angiography with right internal carotid artery injection shows venous pooling and delayed contrast egress from the right transverse sinus (*arrow*), likely attributable to increased mass effect from the hematoma. **H:** Noncontrast head CT shows new postoperative changes of left parietal craniotomy for hematoma evacuation and EVD placement in the left lateral ventricle.

Flat positioning was maintained for 24 hours after EBP placement, followed by 48 hours of gradual elevation of the head of the bed to maximize fluid re-accumulation and promote scarring at the durotomy site. The patient's right-sided weakness and aphasia improved, although he reported a new horizontal diplopia that worsened on forced right gaze, suggesting incomplete right abducens palsy. He progressively recovered neurological function and was transferred to acute inpatient rehabilitation for residual right paresis.

Two weeks later, severe postural headaches recurred, and cervical imaging confirmed persistent high-flow CSF leak at T1–2, which was re-treated via epidural injection in the prone Trendelenburg position; after 4 ml was injected, the patient reported severe back pain and paresthesias, and the procedure was aborted. After the procedure, the positional headaches had resolved; however, at the 3-month follow-up, although neurological function had returned to near baseline, intermittent moderate postural headaches had returned. In consideration of the fact that the patient had two failed attempts at treatment via EBP (the second of which was poorly tolerated) and had an obvious underlying structural lesion causing the recurrences, it was decided to eschew a third EBP and proceed directly to open repair. Correspondingly, he was returned to the operating

room for a T1–2 laminectomy and intradural exploration, with exposure of the anterior elements via bilateral division of the T1–2 dentate ligaments. A persistent ventral durotomy was identified and repaired primarily using 6-0 permanent synthetic monofilament suture in a figure-of-eight fashion. The patient recovered uneventfully from this operation, and at last follow-up 6 months later reported definitive resolution of all headaches. Coagulopathy workup was nondiagnostic; although anticardiolipin immunoglobulin G antibodies were noted to be weakly positive on two discrete tests, both were significantly below the diagnostic threshold for antiphospholipid syndrome.

Literature Review

Twenty-nine publications describing 36 cases of CVT attributable to SIH were identified and reviewed in detail (Table 1). Mean and median ages were 41 years (range 29–75 years; Table 2), with a slight male predominance (54%). Postural headache was the most common presentation (83%), followed by nausea/vomiting (28%) and nonpositional headache (14%). Less prevalent symptoms including sensory changes (11%), auditory disturbance (11%), seizure (8%), disequilibrium (8%), altered mental status (8%), visual disturbance (3%), and plegia/paresis (3%). MRI

FIG. 2. **A and B:** Sagittal (A) and axial (B) T2-weighted MR images of the cervical spine demonstrate an expansive, CSF-isodense, ventral epidural fluid collection (*arrowhead*), extending from C1–2 inferiorly to beyond the CTJ. **C–F:** Obliquely angled, dynamic CT myelography without contrast identifies a calcified ventral osteophyte (C, *arrowhead*), adjacent to which frank extravasation of a large volume of contrast is observed in a time-dependent fashion (D–F, *arrowhead*). Figure is available in color online only.

studies of the brain at presentation contained evidence of SIH in 35 patients (97%) and CVT in 31 (86%), many of which were not initially recognized. Spinal imaging was performed in 13 patients (36%), all of which identified a CSF leak; among these, 46% were localized to the CTJ (defined as C7–T1), 39% to the thoracic spine, and 15% to the cervical spine.

CVT was treated with anticoagulation in 32 patients (89%). CSF leak was treated via EBP in 15 patients (42%), and open repair in 2 (6%). Three patients (8%) required cranial surgery for treatment of a CVT complication such as subdural hematoma (SDH). One death was reported (3%); major nonfatal complications included intraparenchymal hemorrhage in 8 (22%), seizure in 8 (22%), SDH

FIG. 3. CT fluoroscopic images from the EBP injection demonstrate three 20-gauge Tuohy needles, inserted into the dorsal epidural fat of T1–2 (A), and the perineural foraminal fat surrounding the bilateral exiting T-1 nerve roots (B and C). Ten milliliters of autologous blood was infused into each transforaminal needle, followed by 1–2 ml of fibrin glue; an additional 10 ml of blood was subsequently injected into the T1–2 dorsal epidural space.

TABLE 1. Reports and series documenting CVT attributable to SIH

Authors & Year	Age (yrs), Sex	Presenting Symptoms	Initial Imaging Evidence		Localization of CSF Leak	Surgery					Complications	Coagulopathy Workup
			SIH	CVT		Anticoagulation	EBP	CSF Leak Repair	Tx of ICC	Symptom Resolution		
Berriro et al., 2004	46, F	Postural HA, auditory disturbance	Yes	Yes	—	Yes	No	No	No	Complete	—	Negative
	32, F	Postural HA, nausea/vomiting, altered mental status	Yes	Yes	—	Yes	No	No	No	Complete	—	Hyperhomocysteinemia, homozygous C677T <i>MTHFR</i> gene mutation, heterozygous G20210A prothrombin gene mutation
Sopelana et al., 2004	56, M	Postural HA, nausea/vomiting	Yes	Yes	—	Yes	No	No	No	Complete	Subdural hygroma	Negative
Flemming & Link, 2005	31, F	Postural HA, eye pain, auditory disturbance	Yes	Yes	—	Yes	No	No	No	Incomplete	dAVF	—
Savioardo et al., 2006	31, M	Postural HA, nausea/vomiting	Yes	Yes	CTJ	Yes	No	No	No	Incomplete	—	Negative
	40, M	Nonpostural HA, hemibody paresthesia	Yes	Yes	—	Yes	No	No	No	Complete	Venous infarct	Negative
Lai et al., 2007	45, F	Postural HA, nausea/vomiting, rt leg paresthesia, Sz	Yes	Yes	—	Yes	Yes	No	No	Complete	Sz, venous infarct	Negative
Kataoka et al., 2007	36, M	Postural HA, postural auditory disturbance	Yes	Yes	CTJ	Yes	Yes	No	No	Complete	—	Negative
Albayram et al., 2007	45, M	Postural HA	Yes	Yes	Thoracic	Yes	Yes	No	No	Incomplete	—	Negative
Lan et al., 2007	36, M	Postural HA, nausea/vomiting	Yes	Yes	—	No	No	No	No	—	Sz, ICH, dAVF	Negative
Richard et al., 2007	38, M	Postural HA	Yes	Yes	—	Yes	No	No	No	Complete	—	—
	60, F	Postural HA, bilat tinnitus, hemiplegia	Yes	Yes	—	Yes	No	No	No	Complete	Hemiplegia, ICH	—
Wang et al., 2007	33, F	Postural HA, nausea/vomiting	Yes	No	Cervical	No	Yes	No	No	Complete	Sz	Negative
Takeuchi et al., 2007	32, M	Postural HA	Yes	Yes	—	No	Yes	No	No	Complete	—	Negative
Tan et al., 2008	46, F	Postural HA	Yes	Yes	—	Yes	No	No	No	—	—	Protein C deficiency
	40, M	Postural HA, disequilibrium	Yes	Yes	—	Yes	No	No	No	—	—	Protein C deficiency
Schievink & Maya, 2008	26, F	Postural HA, nausea/vomiting	Yes	Yes	Thoracic	Yes	Yes	Yes	No	Complete	—	Negative
	32, M	Postural HA	Yes	Yes	Thoracic	Yes	Yes	No	No	Complete	—	Negative
	43, M	Postural HA	Yes	No	CTJ	Yes	Yes	No	No	Complete	Sz, venous infarct	Negative

CONTINUED ON PAGE 674 »

» CONTINUED FROM PAGE 673

TABLE 1. Reports and series documenting CVT attributable to SIH

Authors & Year		Age (yrs), Sex	Presenting Symptoms	Initial Imaging Evidence		Localization of CSF Leak	Surgery					Symptom Resolution	Complications	Coagulopathy Workup
				SIH	CVT		Anticoagulation	EBP	CSF Leak Repair	Tx of ICC				
Haritanti et al., 2009	42, M	Postural HA	Yes	No	—	Yes	No	No	No	No	Complete	Sz, ICH	Negative	
Ivanidze et al., 2010	33, F	Postural HA	Yes	Yes	—	Yes	No	No	No	No	Complete	—	Protein S deficiency	
Nardone et al., 2010	44, F	Postural HA, transient homonymous hemianopsia, lt arm paresthesias	Yes	Yes	—	Yes	No	No	No	Burr holes	Complete	SDH	Negative	
Yoon et al., 2011	26, M	Postural HA	Yes	No	Cervical	No	Yes	No	No	No	Complete	Subdural hygroma	—	
Dangra et al., 2011	35, M	Postural HA, nausea/vomiting, altered mental status	Yes	Yes	—	Yes	No	No	No	No	Complete	SDH	Negative	
Mao et al., 2011	34, M	Postural HA	Yes	Yes	—	Yes	No	No	No	Yes (un-specified SDH Tx)	Complete	SDH	—	
Ferrante et al., 2012	59, M	Nonpostural HA, disequilibrium, incoordination	Yes	Yes	—	Yes	No	No	No	No	Complete	—	Negative	
Tian & Pu, 2012	41, F	Nonpostural HA	Yes	Yes	—	Yes	No	No	No	No	Complete	—	Autoimmune thrombocytopenia purpura	
Costa et al., 2012	48, F	Postural HA, nausea	Yes	Yes	—	Yes	No	No	No	No	Incomplete	Diplopia, blurred vision	B-cell lymphoma (in remission)	
Rozen, 2013	NA	Nonpostural HA, Sz	Yes	Yes	—	Yes	No	—	—	—	—	Sz, ICH	—	
Rice et al., 2013	75, M	Status epilepticus	Yes	Yes	—	Yes	No	No	No	No	Mortality	ICH, death	—	
Garcia-Carreira et al., 2014	29, F	Postural HA	No	Yes	Thoracic	Yes	Yes	No	No	No	Complete	—	Hyperhomocysteinemia, oral contraceptive pill	
	54, M	Postural HA, disequilibrium, lt arm & leg paresthesias, fall	Yes	No	Thoracic	Yes	Yes	No	No	No	Complete	SAH, ICH	Negative	
Ade & Moonis, 2013	54, F	Postural HA, nausea/vomiting	Yes	Yes	—	Yes	Yes	No	No	No	Complete	SDH	—	
Lin et al., 2013	43, F	Postural HA	Yes	Yes	CTJ	Yes	Yes	No	No	No	Complete	ICH	Protein S deficiency	
Theofanis et al., 2013	42, F	Sz, altered mental status	Yes	Yes	CTJ	Yes	Yes	No	No	No	—	Szs	Heterozygous G20210A prothrombin gene mutation, heterozygous C677T MTHFR gene mutation	
Present study	43, M	Nonpostural HA, weakness	Yes	Yes	CTJ	Yes	Yes	Yes	Yes	Craniotomy	Incomplete	Sz, ICH, hemiplegia, diplopia	Negative	

dAVF = dural arteriovenous fistula; HA = headache; ICC = intracranial complication; ICH = intracerebral hemorrhage; NA = not available; SAH = subarachnoid hemorrhage; Sz = seizure; Tx = treatment.

in 4 (11%), nonhemorrhagic venous infarct in 3 (8%), subdural hygroma in 2 (6%), dural arteriovenous fistula in 2 (6%), visual deficit in 2 (6%), and nonaneurysmal nontraumatic subarachnoid hemorrhage in 1 patient (3%).

Coagulopathy workup was completed in 28 patients (76%), of which 19 (68%) were negative. Positive risk factors or major complex coagulopathies included deficiencies of protein C or protein S in 2 (7%) each, hyperhomocysteinemia in 2 (7%), gene mutations in *MTHFR* or prothrombin in 2 (7%) each, and current oral contraceptive use or a history of B-cell lymphoma in 1 (4%) each.

Discussion

Although typically benign, SIH may precipitate lethal complications, including CVT and its sequelae. The occurrence of this rare condition is unpredictable and demonstrates a highly variable natural history, with outcomes ranging from complete resolution to severe disability or death. Our case and accompanying literature review—the first specifically surveying CVT in the setting of SIH—highlight the significant challenges inherent to managing complicated SIH.

Diagnosis presents the first and most important hurdle in SIH-associated CVT, as both are frequently misdiagnosed.^{38,42} Orthostatic headache should immediately raise suspicion, as should MRI abnormalities including leptomeningeal enhancement, pituitary hyperemia, flattening of the optic chiasm, anterior displacement of the pons against the clivus, or acquired Chiari malformation.^{39,40} A change in headache pattern heralds CVT in 40% of cases, but a high index of suspicion is warranted in any SIH patient with neurological changes, as delayed diagnosis or treatment is associated with worse outcomes.^{2,18,27,35,42}

The pathophysiology linking SIH to CVT is incompletely understood, and likely multifactorial. Schievink and Maya propose three major coincident mechanisms linking changes in flow dynamics between the CSF and venous compartments to thrombosis.⁴² First, as dictated by the Monro-Kellie doctrine, the loss of CSF results in a necessary expansion of the venous compartment, and the resultant venous engorgement slows flow through these vessels. This possibility is further supported by ultrasound-based studies that have demonstrated a decrease in flow through the straight sinus following CSF diversion via lumbar puncture.⁶ Simultaneously, the redirection of CSF through the durotomy into the epidural space, rather than into the venous system, causes an increase in dural venous blood viscosity. Finally, the downward sagging of intracranial structures puts traction on the thin-walled veins and sinuses, and this mechanical distortion leads to turbulence or stasis.

These concepts inform our treatment paradigm for CVT in SIH. Our patient responded dramatically to repositioning, including prolonged Trendelenburg with an EVD in place. This maneuver likely alleviated the impact of brain sag on venous anatomy, and decreased the rate of CSF egress through the thoracic durotomy. That the patient improved following administration of hyperosmolar therapy in the setting of intracranial hypotension seems counterintuitive at first glance; however, the effect of increased circulating osmoles is to mobilize more fluid

TABLE 2. Summary statistics of CVT attributable to SIH

Variable	Value
Demographics	
Median age, yrs	41
Mean age (range), yrs	41 (29–75)
Women, no. (%) [*]	16 (46)
Men, no. (%) [*]	19 (54)
Presenting symptoms, no. (%)	
Postural HA	30 (83)
Nausea/vomiting	10 (28)
Nonpostural HA	5 (14)
Sensory changes	4 (11)
Auditory disturbance	4 (11)
Sz	3 (8)
Disequilibrium	3 (8)
Altered mental status	3 (8)
Visual disturbance	1 (3)
Plegia/paresis	1 (3)
Treatment, no. (%)	
Anticoagulation	32 (89)
EBP	15 (42)
Operative repair of CSF leak	2 (6)
Operative treatment of ICC	3 (8)
Brain imaging, no. (%)	
SIH on presenting MRI	35 (97)
CVT on presenting MRI	31 (86)
CVT on subsequent imaging	36 (100)
Spinal imaging, no. (%)[†]	
CTJ CSF leak	6 (46)
Thoracic CSF leak	5 (39)
Cervical CSF leak	2 (15)
Complications, no. (%)	
Intraparenchymal hemorrhage	8 (22)
Sz	8 (22)
SDH	4 (11)
Venous infarct	3 (8)
Subdural hygroma	2 (6)
dAVF	2 (6)
Visual deficit	2 (6)
SAH	1 (3)
Death	1 (3)
Coagulopathy workup, no. (%)[‡]	
Negative workup	19 (68)
Protein C deficiency	2 (7)
Protein S deficiency	2 (7)
Hyperhomocysteinemia	2 (7)
<i>MTHFR</i> gene mutation	2 (7)
Prothrombin gene mutation	2 (7)
Oral contraceptive pill	1 (4)
B-cell lymphoma	1 (4)
Neurological outcome, no. (%)[§]	
Complete recovery	25 (81)
Incomplete recovery	5 (16)
Death	1 (3)

^{*} One study did not report the sex of the patient.

[†] n = 13.

[‡] n = 28.

[§] n = 31.

first into the venous compartment and then quickly out of the intracranial space, simultaneously reducing venous volume and stasis. A simultaneous decrease in parenchymal edema likely mitigated the effects of brain herniation. Interestingly, Stephen et al. approached treating SIH pathophysiology from a different direction, and infused intrathecal saline in a patient with SIH complicated by SDH.⁴⁹ Their patient improved significantly following the intervention, providing further proof of concept that normalization of the venous-CSF system is a central tenet in managing complicated SIH, although definitive treatment requires repair of the underlying leak.

This observation invites the question of how an EBP should be timed in the context of therapeutic anticoagulation for CVT. Clinical guidelines for the management of CVT of any cause are based on two small, randomized trials incorporating 79 patients, and a Cochrane review and meta-analysis of the same data.^{8,10,11,35} Although the authors ultimately conclude that anticoagulation is safe, potentially prevents thrombus propagation, and may facilitate recanalization, there is no unequivocal evidence mandating early implementation. In our review, 32 of 36 patients received anticoagulation; of the 32, 20 did not undergo EBP, 13 of whom made complete neurological recovery, comparable to 9 recoveries in 12 treated with anticoagulation and EBP (65% vs 75%). Three patients with CVT underwent EBP without preceding anticoagulation, all of whom made a complete recovery, suggesting that EBP may warrant consideration as first-line therapy.

This strategy finds further support in other reports that demonstrated persistent thrombus or SDH during the anticoagulation period, with subsequent resolution after EBP.^{2,20} The potential benefits of an EBP-first paradigm are underscored by the fact that active therapeutic anticoagulation prohibits EBP, and reversal of anticoagulation may be a risk factor for propagation of residual clot.^{23,45} An EBP-first framework would require a well-resourced clinical environment, early diagnosis of SIH-associated CVT, and a stable patient; more frequently, early imaging is limited to head CT/CT venography, and reflex initiation of anticoagulation is recommended over delayed care, particularly in critical cases.

Defining the optimal role for more aggressive interventions beyond EBP in the treatment of complicated SIH presents an even more ambiguous challenge. Clearly, the need for operative management is best decided on a case-by-case basis, governed by hemorrhage severity or refractoriness of CSF leak to EBP. Studies focused on uncomplicated SIH have suggested that EBP should be attempted at least 3 times before moving to open repair, and even then, surgery is generally advocated only in the presence of a definitive radiographic source.^{41,44,46} In the absence of a localized durotomy, large volume (≥ 30 ml) lumbar or thoracolumbar infusion is preferred for safety reasons, but given the predominance of cervicothoracic leaks, multiple treatments are often required. However, in the setting of an unambiguous lesion and a competent neurointerventionalist, we recommend targeted therapy, which has been successfully reported as proximal as C-2.³¹

The final key concept in managing SIH-associated CVT is avoidance of secondary complications via optimizing

neurointensive care, with recommendations derived from the broader literature on CVT of any etiology. Seizures are the most common CVT sequelae; previously reported to occur in 37% of adult cases, our literature review identified seizures in 8 (53%) of the 15 patients in whom complications were reported in detail.³ Treatment with antiepileptic medications is recommended after a single seizure, as is CT of the head to rule out hemorrhage, the most common precipitating factor.^{26,35} In parallel, dehydration is believed to contribute to both the initiation and propagation of CVT, and maintenance of normovolemia or moderate hypervolemia is recommended.^{14,37,48} This is particularly relevant in patients receiving hyperosmolar therapy, who are often in critical condition, and at highest risk for dehydration that may trigger a precipitous decline.

Our study is limited in several ways due to the restrictions of the available data. Both our case and the literature review are retrospective and collectively identified only 36 patients. Previously reported outcomes are heterogeneously and incompletely described, preventing formal statistical analysis, a particularly problematic issue with respect to complications and outcomes. However, in spite of these shortcomings, the present study marks the first systematic review focused on CVT as a complication of SIH, and a small but essential step forward in our understanding of this challenging and complex clinical entity.

Conclusions

CVT is a rare complication of SIH, which is itself a frequently undiagnosed cause of headache. CVT has the potential to precipitate devastating neurological consequences, and requires nuanced management that simultaneously targets the underlying cause while providing supportive neurointensive care. Further study aimed at optimizing an algorithm for early treatment of these patients is requisite, with a particular focus on the timing of EBP and anticoagulation. Perhaps even more importantly, physician education regarding SIH must be improved, as the condition is widely underdiagnosed, placing patients at risk for avoidable complications including CVT, dural arteriovenous fistula, intracranial hemorrhage, and a range of other potentially devastating injuries. Although CVT may result in significant morbidity and mortality, excellent recovery is possible even among critically ill patients through aggressive management by the neurosurgical and neurocritical care teams.

References

1. Ade S, Moonis M: Intracranial hypotension with multiple complications: an unusual case report. **Case Rep Neurol Med** 2013;913465, 2013
2. Albayram S, Tasmali KM, Gunduz A: Can spontaneous intracranial hypotension cause venous sinus thrombosis? **J Headache Pain** 8:200–201, 2007
3. Ameri A, Bousser MG: Cerebral venous thrombosis. **Neurol Clin** 10:87–111, 1992
4. Bassani L, Graffeo CS, Behrooz N, Tyagi V, Wilson T, Penaranda S, et al: Noninvasive diagnosis and management of spontaneous intracranial hypotension in patients with Marfan syndrome: case report and review of the literature. **Surg Neurol Int** 5:8, 2014

5. Berroir S, Grabli D, Hérán F, Bakouche P, Bousser MG: Cerebral sinus venous thrombosis in two patients with spontaneous intracranial hypotension. **Cerebrovasc Dis** 17:9–12, 2004
6. Canhão P, Batista P, Falcão F: Lumbar puncture and dural sinus thrombosis—a causal or casual association? **Cerebrovasc Dis** 19:53–56, 2005
7. Costa P, Del Zotto E, Giossi A, Volonghi I, Poli L, Frigerio M, et al: Headache due to spontaneous intracranial hypotension and subsequent cerebral vein thrombosis. **Headache** 52:1592–1596, 2012
8. Coutinho JM, de Bruijn SF, deVeber G, Stam J: Anticoagulation for cerebral venous sinus thrombosis. **Stroke** 43:e41–e42, 2012
9. Dangra VR, Sharma YB, Bharucha NE, Deopujari CE: An interesting case of headache. **Ann Indian Acad Neurol** 14:130–132, 2011
10. de Bruijn SF, Stam J: Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. **Stroke** 30:484–488, 1999
11. Einhäupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, et al: Heparin treatment in sinus venous thrombosis. **Lancet** 338:597–600, 1991
12. Fabricius J, Klotz JM, Hofmann E, Behr R, Neumann-Haefelin T: [Cerebral venous thrombosis and subdural haematoma: complications of spontaneous intracranial hypotension.] **Fortschr Neurol Psychiatr** 80:599–601, 2012 (Ger)
13. Ferrante T, Latte L, Abrignani G, Russo M, Manzoni GC, Torelli P: Cough headache secondary to spontaneous intracranial hypotension complicated by cerebral venous thrombosis. **Neurol Sci** 33:429–433, 2012
14. Ferro JM: Causes, predictors of death, and antithrombotic treatment in cerebral venous thrombosis. **Clin Adv Hematol Oncol** 4:732–733, 2006
15. Flemming KD, Link MJ: Spontaneous CSF leak complicated by venous thrombosis and dural arteriovenous fistula. **Cephalalgia** 25:751–753, 2005
16. Garcia-Carreira MC, Vergé DC, Branera J, Zauner M, Herrero JE, Tió E, et al: Cerebral venous thrombosis in two patients with spontaneous intracranial hypotension. **Case Rep Neurol Med** 2014:528268, 2014
17. Haritanti A, Karacostas D, Drevelengas A, Kanellopoulos V, Paraskevopoulou E, Lefkopoulou A, et al: Spontaneous intracranial hypotension: clinical and neuroimaging findings in six cases with literature review. **Eur J Radiol** 69:253–259, 2009
18. Idrissi AL, Lacour JC, Klein O, Schmitt E, Ducrocq X, Richard S: Spontaneous intracranial hypotension: characteristics of the serious form in a series of 24 patients. **World Neurosurg** 84:1613–1620, 2015
19. Ivanidze J, Zimmerman RD, Sanelli PC: Spontaneous intracranial hypotension followed by dural sinus thrombosis: a case report. **Clin Neurol Neurosurg** 112:498–500, 2010
20. Kataoka H, Tanizawa E, Ueno S: Spontaneous intracranial hypotension is associated with a risk of venous sinus thrombosis and subdural hematoma. **Cerebrovasc Dis** 23:315–317, 2007
21. Lai PH, Li JY, Lo YK, Wu MT, Liang HL, Chen CK: A case of spontaneous intracranial hypotension complicated by isolated cortical vein thrombosis and cerebral venous infarction. **Cephalalgia** 27:87–90, 2007
22. Lan MY, Chang YY, Liu JS: Delayed cerebral venous thrombosis in a patient with spontaneous intracranial hypotension. **Cephalalgia** 27:1176–1178, 2007
23. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B: Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. **Am J Hematol** 83:137–143, 2008
24. Lin CH, Chen YY, Hsieh YZ, Lo MC: Spontaneous intracranial hypotension complicated with cerebral venous thrombosis and intracerebral hemorrhage in a patient with protein S deficiency: a case report. **Changhua J Med** 11:48–53, 2013
25. Mao YT, Dong Q, Fu JH: Delayed subdural hematoma and cerebral venous thrombosis in a patient with spontaneous intracranial hypotension. **Neurol Sci** 32:981–983, 2011
26. Masuhr F, Busch M, Amberger N, Ortwein H, Weih M, Neumann K, et al: Risk and predictors of early epileptic seizures in acute cerebral venous and sinus thrombosis. **Eur J Neurol** 13:852–856, 2006
27. Mea E, Chiapparini L, Savoirdo M, Franzini A, Bussone G, Leone M: Clinical features and outcomes in spontaneous intracranial hypotension: a survey of 90 consecutive patients. **Neurol Sci** 30 (Suppl 1):S11–S13, 2009
28. Mokri B: Spontaneous cerebrospinal fluid leaks: from intracranial hypotension to cerebrospinal fluid hypovolemia—evolution of a concept. **Mayo Clin Proc** 74:1113–1123, 1999
29. Mokri B: Spontaneous low pressure, low CSF volume headaches: spontaneous CSF leaks. **Headache** 53:1034–1053, 2013
30. Nardone R, Caleri F, Golaszewski S, Ladurner G, Tezzon F, Bailey A, et al: Subdural hematoma in a patient with spontaneous intracranial hypotension and cerebral venous thrombosis. **Neurol Sci** 31:669–672, 2010
31. Rai A, Rosen C, Carpenter J, Miele V: Epidural blood patch at C2: diagnosis and treatment of spontaneous intracranial hypotension. **AJNR Am J Neuroradiol** 26:2663–2666, 2005
32. Rice CM, Renowden SA, Sandeman DR, Cottrell DA: Spontaneous intracranial hypotension and venous sinus thrombosis. **Pract Neurol** 13:120–124, 2013
33. Richard S, Kremer S, Lacour JC, Vespignani H, Boyer P, Ducrocq X: Cerebral venous thrombosis caused by spontaneous intracranial hypotension: two cases. **Eur J Neurol** 14:1296–1298, 2007
34. Rozen TD: Pachymeningeal enhancement on MRI: a venous phenomena not always related to intracranial hypotension (resolving pachymeningeal enhancement and cerebral vein thrombosis). **Headache** 53:673–675, 2013
35. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al: Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. **Stroke** 42:1158–1192, 2011
36. Savoirdo M, Armenise S, Spagnolo P, De Simone T, Mandelli ML, Marcone A, et al: Dural sinus thrombosis in spontaneous intracranial hypotension: Hypotheses on possible mechanisms. **J Neurol** 253:1197–1202, 2006
37. Sawarkar DP, Verma SK, Singh PK, Doddamani R, Kumar A, Sharma BS: Fatal superior sagittal sinus and torcular thrombosis after vestibular schwannoma surgery: report of a rare complication and review of the literature. **World Neurosurg** 96:607.e19–607.e24, 2016
38. Schievink WI: Misdiagnosis of spontaneous intracranial hypotension. **Arch Neurol** 60:1713–1718, 2003
39. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks. **Cephalalgia** 28:1345–1356, 2008
40. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. **JAMA** 295:2286–2296, 2006
41. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks: a review. **Neurosurg Focus** 9(1):e8, 2000
42. Schievink WI, Maya MM: Cerebral venous thrombosis in spontaneous intracranial hypotension. **Headache** 48:1511–1519, 2008
43. Schievink WI, Maya MM, Nuño M: Chronic cerebellar hemorrhage in spontaneous intracranial hypotension: association with ventral spinal cerebrospinal fluid leaks: clinical article. **J Neurosurg Spine** 15:433–440, 2011
44. Schievink WI, Morreale VM, Atkinson JL, Meyer FB, Piepgras DG, Ebersold MJ: Surgical treatment of spontaneous spinal cerebrospinal fluid leaks. **J Neurosurg** 88:243–246, 1998

45. Schulman S, Bijsterveld NR: Anticoagulants and their reversal. **Transfus Med Rev** 21:37–48, 2007
46. Sencakova D, Mokri B, McClelland RL: The efficacy of epidural blood patch in spontaneous CSF leaks. **Neurology** 57:1921–1923, 2001
47. Sopelana D, Marcos A, Arroyo R, Gutiérrez E, Cuenca R, Vázquez AV, et al: May intracranial hypotension be a cause of venous sinus thrombosis? **Eur Neurol** 51:113–115, 2004
48. Stam J: Cerebral venous and sinus thrombosis: incidence and causes. **Adv Neurol** 92:225–232, 2003
49. Stephen CD, Rojas R, Lioutas VA, Papavassiliou E, Simon DK: Complicated spontaneous intracranial hypotension treated with intrathecal saline infusion. **Pract Neurol** 16:146–149, 2016
50. Takeuchi S, Takasoto Y, Masaoka H, Hayakawa T, Otani N, Yoshino Y, et al: Spontaneous intracranial hypotension associated with dural sinus thrombosis. **Neurol Med Chir (Tokyo)** 47:555–558, 2007
51. Tan K, Venketasubramanian N, Hwang CY, Lim CC: My headache does not get better when I lie down: spontaneous intracranial hypotension complicated by venous thrombosis. **Headache** 48:149–152, 2008
52. Theofanis B, El-Chalouhi M, Tjoumakaris M: Cerebrospinal fluid leakage and cerebral venous sinus thrombosis: a case report. **JHN J** 8:2, 2013
53. Tian CL, Pu CQ: Dural enhancement detected by magnetic resonance imaging reflecting the underlying causes of cerebral venous sinus thrombosis. **Chin Med J (Engl)** 125:1513–1516, 2012
54. Wang YF, Fuh JL, Lirng JF, Chang FC, Wang SJ: Spontaneous intracranial hypotension with isolated cortical vein thrombosis and subarachnoid haemorrhage. **Cephalalgia** 27:1413–1417, 2007
55. Yoon KW, Cho MK, Kim YJ, Lee SK: Sinus thrombosis in a patient with intracranial hypotension: a suggested hypothesis of venous stasis. A case report. **Interv Neuroradiol** 17:248–251, 2011

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Link, Perry, Rabinstein. Acquisition of data: all authors. Analysis and interpretation of data: Link, Perry, Brinjikji, Copeland. Drafting the article: Perry, Brinjikji. Critically revising the article: all authors. Reviewed submitted version of manuscript: Link, Perry. Administrative/technical/material support: Perry. Study supervision: Link.

Correspondence

Michael J. Link: Mayo Clinic, Rochester, MN. link.michael@mayo.edu.