Case Report

Cerebral Venous Thrombosis in Two Patients with Spontaneous Intracranial Hypotension

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Although few patients with spontaneous intracranial hypotension develop cerebral venous thrombosis, the association between these two entities seems too common to be simply a coincidental finding. We describe two cases of spontaneous intracranial hypotension associated with cerebral venous thrombosis. In one case, extensive cerebral venous thrombosis involved the superior sagittal sinus and multiple cortical cerebral veins. In the other case, only a right frontoparietal cortical vein was involved. Several mechanisms could contribute to the development of cerebral venous thrombosis in spontaneous intracranial hypotension. When spontaneous intracranial hypotension and cerebral venous thrombosis occur together, it raises difficult practical questions about the treatment of these two conditions. In most reported cases, spontaneous intracranial hypotension was treated conservatively and cerebral venous thrombosis was treated with anticoagulation. However, we advocate aggressive treatment of the underlying cerebrospinal fluid leak.

1. Introduction

Spontaneous intracranial hypotension (SIH) indicates cerebrospinal fluid (CSF) leakage in the absence of a known dural puncture or tear. SIH is defined as CSF pressure ≤ 6 cm and/or imaging evidence of CSF leakage in patients with no history of lumbar puncture. SIH is characterized by the appearance of headaches or worsening of preexisting headaches within minutes of change in body posture from recumbent to standing position with improvement or even disappearance of pain on reclining [1].

Typical imaging features include subdural fluid collections that may mimic primary subdural hematomas, diffuse pachymeningeal gadolinium enhancement, engorgement of venous structures, pituitary hyperemia, sagging or downward displacement of the brain, and sometimes dilation of the vertebral venous plexuses with extradural fluid collections [2, 3].

Numerous cases of cerebral venous thrombosis (CVT) in patients with SIH have been reported since 2004 (see Table 1) [4–28]. We report two cases of patients with clinical signs of SIH who developed CVT.

2. Case Presentation

2.1. Case Report 1. A 29-year-old woman with history of migraine and no other known health problems presented with a 3-week history of headache. She was taking no medication other than oral contraceptives and did not smoke.

Head computed tomography (CT) ordered by her primary care physician was normal. With a presumptive diagnosis of sinusitis, she underwent 7 days’ treatment with amoxicillin/clavulanic acid. General analgesics, nonsteroidal anti-inflammatory drugs, and benzodiazepines brought no relief.

She presented at our emergency department for persistent headaches. From the onset, her symptoms were orthostatic and disappeared on lying down. During this period, the headache was frontal and orbital, nonpulsating, with photophobia and phonophobia. No rhinorrhea, lacrimation, or
| Authors, year          | Age-sex | MRI SIH | MRI CVT | CVT location | OP | Location of CSF leak | AC | EBP | Complications                        |
|-----------------------|---------|---------|---------|--------------|----|----------------------|----|-----|--------------------------------------|
| Berroir et al., 2004 [4] | 46 F    | Yes     | Yes     | SSS, RLS     | 5  | ?                    | Yes| No |                                      |
|                       | 32 F    | Yes     | Yes     | SSS, RLS     | 17 | ?                    | Yes| No |                                      |
| Sopelana et al., 2004 [5] | 56 M    | Yes     | Yes     | Right TS, SS, JV, and SSS | ? | ?                    | Yes| No |                                      |
| Flemming and Link, 2005 [6] | 31 F    | Yes     | Yes     | SSS and Right TS | 3 | ?                    | Yes| No | Dural AV fistula                      |
|                       | 31 M    | Yes     | Yes     | SSS, left TS, and SS | ? | Cerv/Thor            | Yes| No |                                      |
| Savoiardo et al., 2006 [7] | 40 M    | Yes     | Yes     | SSS, StS, and the initial segment of both TS | ? | ?                    | Yes| No | Venous infarct                       |
| Lai et al., 2007 [8]  | 45 F    | Yes     | Yes     | Left frontal CV | 1 | ?                    | Yes| Yes| Venous infarct, seizure              |
| Kataoka et al., 2007 [9] | 36 M    | Yes     | Yes     | SSS          | 4 | Cerv/Thor            | Yes| Yes| Subdural hemorrhage                  |
| Albayram et al., 2007 [10] | 45 M    | Yes     | Yes     | SSS          | ? | Thoracic            | Yes| Yes| Seizure, intracerebral hemorrhage, Dural AV fistula, subdural hemotoma |
| Lan et al., 2007 [11]  | 36 M    | Yes     | Yes     | CV (right vein of Trolard) | ? | ?                    | No | No |                                      |
| Richard et al., 2007 [12] | 38 M    | Yes     | Yes     | SSS, both TS and bilateral parietal CV | ? | ?                    | Yes| No |                                      |
| Wang et al., 2007 [13] | 33 F    | Yes     | Yes     | CV (left vein of Trolard, vein of Labbé) | 8 | Cervical             | No | Yes| Seizure                              |
| Takeuchi et al., 2007 [14] | 32 M    | Yes     | Yes     | SSS and CV (vein of Labbé) | 5 | ?                    | No | Yes|                                      |
| Tan et al., 2008 [15]  | 46 F    | Yes     | Yes     | Left TS and SS | ? | ?                    | Yes| No |                                      |
|                       | 40 M    | Yes     | Yes     | SSS and left hemispheric CV | ? | ?                    | Yes| No |                                      |
|                       | 26 F    | Yes     | Yes     | Left TS and SS | 5 | Thoracic            | Yes| Yes|                                      |
| Schievink and Maya, 2008 [16] | 32 M    | Yes     | Yes     | SSS, TS, and cortical veins | 0 | Thoracic            | Yes| Yes| Venous infarct, seizure, transient diplopia |
|                       | 43 M    | Yes     | Yes     | SSS, right TS, and SS | 4 | Thoracic            | Yes| Yes| Seizure, intracerebral hemorrhage    |
| Haritanti et al., 2009 [17] | 42 M    | Yes     | Yes     | SSS and right TS | 2 | ?                    | Yes| No |                                      |
| Seiler and Hamann, 2009 [18] | 48 F    | Yes     | Yes     | SSS          | ? | ?                    | Yes| No | Epileptic seizure                    |
| Ivanidze et al., 2010 [19] | 33 F    | Yes     | Yes     | SSS          | 3 | ?                    | Yes| No |                                      |
| Nardone et al., 2010 [20] | 44 M    | Yes     | Yes     | SSS and CV on the right side | 4 | ?                    | Yes| No | Subdural hemorrhage                  |
| Yoon et al., 2011 [21]  | 26 M    | Yes     | No      | SSS          | 5 | Cervical            | No | Yes|                                      |
| Dangra et al., 2011 [22] | 35 M    | Yes     | Yes     | SSS and SS  | ? | Cervical            | Yes| No | Subdural hemorrhage                  |
| Mao et al., 2011 [23]  | 34 M    | Yes     | Yes     | SSS, ISS, and StS | 0 | ?                    | Yes| No | Subdural hemorrhage                  |
| Ferrante et al., 2012 [24] | 59 M    | Yes     | Yes     | SSS and frontal CV | 32 | ?                    | Yes| No | Subdural hemorrhage                  |
| Tian and Pu, 2012 [25]  | 41 F    | Yes     | Yes     | SSS, both sides of the TS and SS | 3 | ?                    | Yes| No |                                      |
| Costa et al., 2012 [26] | 48 F    | Yes     | Yes     | Left TS      | ? | ?                    | Yes| No | Transient diplopia, blurred vision  |
| Rozen, 2013 [27]       | ?       | Yes     | Yes     | SSS, TS, SS, and proximal JV | ? | ?                    | Yes| No | Probable seizure                     |
| Rice et al., 2013 [28] | 75 M    | Yes     | Yes     | SSS          | ? | ?                    | Yes| No | Status epileptics, intracerebral hemorrhage |
| Present study          | 29 F    | No      | Yes     | SSS and multiple CV | 3 | Thoracic            | Yes| Yes| Subarachnoid hemorrhage, right parietal hematoma |
|                       | 54 M    | Yes     | No      | CV (right vein of Trolard) | 2 | Thoracic            | Yes| Yes|                                      |

SIH = spontaneous intracranial hypotension, MRI = magnetic resonance imaging, CVT = cerebral venous thrombosis, OP = opening pressure (cm H2O), CSF = cerebrospinal fluid, AC = anticoagulation, EBP = epidural blood patch, and AV = arteriovenous.

Location: SSS = superior sagittal sinus, RLS = right lateral sinus, ISS = inferior sagittal sinus, TS = transverse sinus, SS = sigmoid sinus, StS = straight sinus, CV = cortical veins, JV = jugular vein.
conjunctival injection was present. The patient reported no prior dural puncture, surgical intervention, or trauma.

Findings at physical and neurological examinations, routine blood tests, and immunology were unremarkable.

Magnetic resonance imaging (MRI) (Figure 1) showed thrombosis of the superior sagittal sinus and of multiple cortical cerebral veins. There was no parenchymal damage. Treatment with intravenous heparin followed by oral anticoagulation did not improve the headaches.

Radionuclide cisternography revealed both direct and indirect signs of intracranial hypotension (delayed radiotracer ascent, with retained activity in the basal cisterns and no uptake in the cerebral convexity, together with early concentration of radiotracer in the bladder). Radionuclide cisternography also detected a slight left dorsal parameningeal uptake at the T4-T5 level that could correspond to a CSF leak. The CSF opening pressure was 3 cm H$_2$O. The composition of the CSF was normal.

A dorsal epidural blood patch provided good but temporary relief from symptoms. Three weeks later, a second blood patch achieved complete resolution of symptoms within two weeks.

Two months after onset, with the patient asymptomatic and still on oral anticoagulants, MRI showed extensive but incomplete recanalization of the superior sagittal sinus; no signs of SIH were present.

Extensive investigation for thrombophilia was negative except for hyperhomocysteinemia. Oral contraceptives were not discontinued.

2.2. Case Report 2. A 54-year-old previously healthy man was admitted from another hospital for subarachnoid hemorrhage with left hemiparesis and hemihypesthesia.

During the previous two weeks, he had complained of a progressive headache and neck pain associated with dizziness. The headache was oppressive and holocranial, but particularly intense in the occipital region. It had strong postural variation, appearing only in the upright position and disappearing within seconds after lying down. He had no history of trauma. He developed numbness of the left limbs and fell, resulting in head injury and admission to the other hospital.

Physical examination detected a contused wound in the left temporal area. Neurological examination showed left hemiparesis with hemihypesthesia and left hemianopsia.

CT scan revealed right frontoparietal subarachnoid hemorrhage and a right parietal hematoma measuring 8 mm in diameter (reported as a probable venous malformation) (Figure 2). The patient was treated with nimodipine and transferred to our hospital for further tests.

Cranial CT angiography showed hypoplasia of the A1 segment of the right anterior cerebral artery. The carotid artery, vertebral artery, and other branches of the circle of Willis were of normal size and patency.

Digital subtraction angiography to investigate the cause of intracerebral hemorrhage (Figure 3) found no aneurysms or arteriovenous malformations but revealed a tubular filling defect within the right frontoparietal superficial cortical vein (vein of Trolard) and signs of congestion of the other deep and superficial veins of the brain. Contrast material was slow to empty from the left transverse sinus, suggesting moderate intracranial hypertension.

After treatment with subcutaneous heparin and subsequently with oral anticoagulants, the patient's neurological deficits resolved but his headaches persisted. The headache worsened when standing and improved shortly after lying down.

Brain MRI (Figure 4) to investigate this headache showed diffuse pachymeningeal enhancement after gadolinium administration, suggestive of liquorhial hypotension, and a small right parietal hematoma in the acute phase (correlating with the CT findings).

Radionuclide cisternography showed delayed ascent of radiotracer, with no uptake in the cerebral convexity, and retained activity in the basal cisterns, together with intense renal and bladder activity (indirect signs of intracranial hypotension). It was impossible to locate the level of the CSF leak with certainty, although it was thought that some parameningeal punctiform images immediately to the left of T3-T4 might correspond to a leak.

CSF opening pressure was 2 cm H$_2$O; the composition of the CSF was normal.

The patient was diagnosed with intracranial hypotension associated with intraparenchymal hematoma secondary to cortical venous thrombosis. Treatment with oral anticoagulants and blood patch brought about complete resolution of symptoms.

3. Discussion

The diagnosis of SIH is based on a purely orthostatic headache (increased intensity when upright and decreased intensity when lying down) occurring in the absence of recent dural puncture or trauma. SIH can lead to nausea and vomiting. SIH may also produce traction on the cranial nerves, causing diplopia, hearing loss, tinnitus, dysgeusia, dizziness, visual deficits, and neck pain. SIH is confirmed by a CSF opening pressure of <6 cm H$_2$O and/or evidence of CSF leakage on imaging [1]. Findings at cytochemical analysis of CSF can be normal or reveal increased protein and pleocytosis. The orthostatic headache remits after normalization of CSF pressure [29].

Brain MRI may show subdural fluid collections, descent of the midbrain and cerebellar tonsils, a reduction in the size of the prepontine cistern, dilation of the dural sinuses and spinal epidural plexus, and enlargement of the pituitary gland. However, the most characteristic finding is diffuse pachymeningeal enhancement. Downward displacement of the brain due to low CSF pressure may produce tears in bridging veins in the dural border cell layer, causing them to rupture and leading to subdural hematoma. Downward sagging of the brain produces headache by applying traction to pain-sensitive structures, in particular the VI cranial nerve [2, 3]. The MRI findings in SIH reflect an increase in venous volume throughout the brain. The increased venous volume can be explained by the Monro-Kellie hypothesis in which total intracranial volume is constant and volume equilibrium among its constituents (brain tissue, CSF, and blood) means...
Figure 1: Brain MRI. (a) Sagittal T2-weighted image, (b) coronal T1-weighted image, and (c) axial gradient-echo image show superior sagittal sinus thrombosis (arrow) and thrombosis of multiple cortical cerebral veins (arrowheads).

Figure 2: CT. ((a), (b)) Right frontoparietal subarachnoid hemorrhage. (c) Right parietal hematoma measuring 8 mm in diameter.

Figure 3: Cerebral angiography. Venous phase image of the right internal carotid artery shows a tubular filling defect within the superficial cortical vein of Trolard (arrow) and engorgement of the surrounding venules, suggestive of thrombosis of the vein of Trolard.
that a decrease in the volume of one constituent must be compensated by an increase in another constituent [30]. Nevertheless, any or even all of these imaging features may be absent in patients with SIH.

CVT has occasionally been observed in patients with SIH. The number of observations, although limited, seems to indicate that the association between these two entities cannot be simply interpreted as a coincidental finding. We found 26 reports totaling 35 patients with both CVT and SIH [4–28], to which we add two cases. Although an association between SIH and CVT was not reported until 2004 [4], the development of CVT following an iatrogenic spinal CSF leak had been noted since the 1980s [30,31].

A review published in 2008 [17] noted that SIH is a risk factor for CVT, but CVT is found in only 2% of patients with SIH. As we have seen in our cases, the presence or development of CVT in SIH may be associated with little or no change in the characteristics of the headache [17].

Several mechanisms can explain how SIH can lead to CVT. First, as dictated by the Monro-Kelly Doctrine, in a closed compartment such as the intracranial and spinal dural space, any loss of one component must be compensated by an increase in another one. Therefore, the CSF volume that is lost must be replaced by an increase in the most easily expansible component, which is venous blood [32]. Venous engorgement causes both the appearance of a thickened dura and a relative accumulation of contrast material. The dilation of cerebral veins and sinuses results in a decrease in blood flow velocity. Transcranial Doppler ultrasound has demonstrated that blood flow velocities in the straight sinus decrease by about 47% after lumbar puncture. As patients with SIH probably lose more CSF volume than those undergoing lumbar puncture, it is reasonable to suppose that their decrease in blood flow velocity is even more marked [33].

Second, SIH is associated with rostrocaudal sagging of the brain due to the loss of CSF buoyancy [3], resulting in a negative intracranial pressure gradient that may damage the venous endothelial lining by stretching the cerebral vessels [17]. Third, the loss of CSF reduces absorption of CSF into the cerebral venous sinuses, resulting in increased blood viscosity in the venous compartment [34], which could contribute to dural sinus thrombosis in patients with risk factors for thrombosis, such as hereditary thrombophilia (mainly the factor V Leiden mutation (15%–17% of cases) and the prothrombin-gene-mutation 20210GA (10%–12% of cases); by contrast, antithrombin III-, protein C-, and protein S-deficiency are found in only 2%–6% of cases), anti-cardiolipin antibodies, hyperhomocysteinemia, cesarean delivery, pregnancy-related hypertension, and the use of oral contraceptives.

The occurrence of intracranial hypotension in patients with CVT raises difficult practical questions about the treatment of the two conditions. The first-line treatment for intracranial hypotension is an epidural blood patch, but it is unknown whether early blood patch treatment would avoid the occurrence of venous thrombosis. On the other hand, there is now a consensus that the treatment for CVT should be heparin since a meta-analysis of the only two randomized studies concluded heparin treatment is safe and associated with a clinically relevant (though not statistically significant) reduction in the risk of death and dependency. Nevertheless, the potential benefit of anticoagulation must be weighed against the risk of subdural hematoma, especially when subdural fluid collections are present [20,35].

In most reported patients, SIH was treated conservatively and CVT was treated with anticoagulation (Table 1). However, we advocate aggressive treatment of the underlying spinal CSF leak, particularly when symptoms of SIH persist.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.
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