CASE REPORT

Spontaneous intracranial hypotension complicated with cerebral venous thrombosis and intracerebral hemorrhage in a patient with protein S deficiency: a case report

Chun-Hsiang Lin¹, Yen-Yu Chen¹, Yi-Zhe Hsieh², Man-Chi Lo¹

¹Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan
²Department of Anesthesia, Changhua Christian Hospital, Changhua, Taiwan

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Abstract

Cerebral venous thrombosis (CVT) has been reported as an uncommon complication of spontaneous intracranial hypotension (SIH). Since this is a rare presentation, we report a patient with SIH complicated by CVT and intracerebral hemorrhage (ICH).

A 43-year-old woman presented with a 2-day history of orthostatic headache and neck stiffness. Magnetic resonance imaging (MRI) of the brain demonstrated typical findings of SIH with pituitary hyperemia and engorgement of the venous structures, as well as flattening of the pre-pontine space. Lumbar puncture confirmed low opening cerebrospinal pressure (10 mm H2O). Neurological examination on admission was normal, except for left optic nerve atrophy with associated blindness that was due to an old central retinal artery occlusion. However, on day 3 of admission, the patient developed acute left-sided hypesthesia and hemiparesis. Computed tomography (CT) scan of the brain revealed CVT related ICH. The headache failed to respond to conservative treatment, but resolved within an hour of applying an epidural blood patch to the lower cervical region. Thrombophilia screening was performed and showed protein S dysfunction (<10 %). Warfarin was initiated as maintenance therapy and the patient did not experience any recurrent CVT event or orthostatic headache during the 1.5-year follow-up period.

This report highlights that CVT with ICH is a potential complication of SIH. Any change of neurological status in a patient with SIH should raise the index of suspicion for CVT. A thorough investigation of the underlying cause is warranted and should include a thrombophilia screen.

KEYWORDS

Spontaneous intracranial hypotension; Cerebral venous thrombosis; Intracranial hemorrhage; Orthostatic headache; Epidural blood patch
Introduction

Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache, low cerebrospinal fluid (CSF) pressure, and non-interrupting diffuse pachymeningeal enhancement in magnetic resonance imaging (MRI) of the brain. SIH is caused by spontaneous CSF leaks leading to low cerebral fluid volume or decreased CSF pressure [1]. Cerebral venous thrombosis (CVT) has rarely been observed and is found in only about 2% of patients with SIH [2]. We report a very rare case of a patient with SIH complicated by CVT and intracerebral hemorrhage (ICH).

Case report

A 43-year-old woman was admitted to the neurology ward with a 2-day history of orthostatic headache and neck stiffness. Her past medical history included an episode of left central retinal artery occlusion that had occurred 8 years previously. She had no history of hypertension, diabetes mellitus, heart disease, hyperlipidemia, or use of oral contraceptives. There was no recent history of pregnancy, dehydration, trauma, strenuous exercise, or lumbar puncture. She had no family history of vascular events, or other predisposing factors for stroke. Neurological examination on admission was normal, apart from the left optic nerve atrophy and blindness that caused by prior central retinal artery occlusion. Blood tests including complete blood count, prothrombin time, activated partial thromboplastin time, glucose, creatinine, and liver function were all normal. Brain MRI with contrast revealed typical findings of SIH, including pituitary hyperemia, engorgement of the venous structures, and flattening of the pre-pontine space (Fig. 1). MR venography showed a normal venous flow pattern (Fig. 2). Lumbar puncture confirmed low opening pressure (10 mm H₂O). The patient was treated with analgesics, bed rest, and hydration.

On day 3 of her hospital admission, the patient developed acute onset left-sided hypesthesia with mild left-sided hemiparesis. A non-contrast brain CT scan revealed a 1.41cm intraparenchymal hematoma in the right high parietal subcortical region, with a non-arterial vascular territory distribution, suggesting cortical venous thrombosis-related hemorrhage (Fig. 3). On day 6, a whole spine MRI with contrast and heavily T2-weighted MR myelography demonstrated suspicious CSF collections along the lower cervical nerve roots (Fig. 4). An epidural blood patch was then applied to the lower cervical region on day 7 and the orthostatic headache was relieved within an hour after the procedure.

Figure 1. Sagittal T1-weighted image shows hyperemia and enlargement of the pituitary gland, measured up to 9.4mm (yellow arrowheads), engorgement of superior sagittal sinus (arrow) and flattening of the pons with obliteration of the pre-pontine cistern (black arrowheads).

Figure 2. MR venography shows normal venous flow pattern.
Further screening for thrombophilia showed protein S dysfunction (<10% ; normal range :74-157%), while protein C, antithrombin III, and homocysteine were normal. The results of lupus anticoagulant, antinuclear antibody, and cardiolipin antibody IgG were also negative. The protein S dysfunction was followed up after the initial acute phase, at 4, 6, and 9 months, with warfarin being withheld for 3 weeks prior to each protein S examination. All results were consistent with protein S deficiency (<10%).

The patient was admitted for 10 days and she achieved full recovery on discharge without any sequelae of weakness or sensory impairment. She has been maintained on warfarin therapy without suffering from recurrence of either the CVT or orthostatic headache during a 1.5-year follow-up period.

Discussion

SIH is an uncommon disorder with an estimated annual incidence of 5 per 100,000 [3, 4]. SIH has occasionally been reported to be complicated by subdural hemorrhage, and more rarely, by CVT and subarachnoid hemorrhage [5, 6]. The present case report of ICH associated with CVT is also a very rare complication of SIH.

SIH often results from a spontaneous leak of spinal CSF due to an underlying fragility of the spinal meninges. Most of these leaks occur at the thoracic and cervicothoracic levels. The etiology and pathogenesis of these spinal CSF leaks is multifactorial and there is often a history of trauma preceding the onset of symptoms [3]. According to the revised International Classification of Headache Disorders criteria, orthostatic headache is the hallmark of SIH that may occur or worsen anywhere from a few seconds to 15 minutes after maintaining an upright position (Table 1)[1].
Table 1. Diagnostic criteria for headache due to spontaneous spinal CSF leak and intracranial hypotension according to the international classification of headache disorders, 2nd edition

7.2.3 Headache attributed to spontaneous (or idiopathic) low CSF pressure

A. Diffuse and/or dull headache that worsens within 15 minutes after sitting or standing, fulfilling criterion D and with 1 of the following:
   1. Neck stiffness
   2. Tinnitus
   3. Hypacusia
   4. Photophobia
   5. Nausea

B. At least 1 of the following:
   1. Evidence of low CSF pressure on MRI (eg, pachymeningeal enhancement)
   2. Evidence of CSF leakage on conventional myelography, CT myelography, or cisternography
   3. CSF opening pressure 60 mm H\textsubscript{2}O in sitting position

C. No history of dural puncture or other cause of CSF fistula

D. Headache resolves within 72 hours after epidural blood patching

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

Our case had the typical presentation with orthostatic headache that developed shortly after sitting upright and subsided promptly after lying down. In many cases, SIH-related headaches resolve with conservative treatment, such as strict bed rest and hydration [1]. However, in our case, conservative treatment failed to relieve the patient’s headache. Therefore, she received an epidural blood patch of 20 ml of autologous blood to the lower cervical region, which resulted in prompt resolution of her symptoms within an hour. Based on the above findings, this case fulfilled the criteria for SIH.

CVT is uncommon, with an overall annual incidence less than 1 per 100,000 [7]. The predisposing factors for CVT include hematologic conditions (thrombophilia disorders, polycythemia, and anemia), oral contraceptives, pregnancy, infection, malignancy, head injury, dehydration, chronic inflammatory disorders (systemic lupus erythematosus, inflammatory bowel disease), lumbar puncture, and SIH[8]. The Monro-Kellie doctrine may explain the mechanism of CVT in SIH patients. This doctrine states that the total volume of intracranial blood, brain tissue, and CSF intracranial compartments remains constant. Therefore, a volume increase in one compartment would cause a volume shift in one or both of the other compartments[9]. When CVT occurs in SIH, the brain volume remains nearly constant, so the CSF leakage may reduce the intracranial volume and cause compensatory venous engorgement and distortion of venous walls. This in turn may contribute to stagnancy and turbulence of blood flow in the cerebral veins, leading to thrombosis.

CVT is characterized by a wide variety of clinical presentations, such as isolated intracranial hypertension, focal neurologic disorders (seizures or focal deficits), or encephalopathy (multifocal signs, mental or consciousness changes)[10]. Neuroimaging in CVT may reveal focal areas of edema or venous infarction, or ICH due to venous infarction. ICH is common in CVT, being reported in approximately one-third of CVT patients, although it is usually associated with a more severe clinical presentation and a worse outcome than non-hemorrhagic cases [8]. Hemorrhagic infarction is attributed to blockage of the venous sinuses, causing an increase in venous and capillary pressure with RBC diapedesis and subsequent rupture of small vessels [11].

The predictors of poor long-term prognosis in CVT are as follows: central nervous system infection, malignancy, thrombosis of the deep venous system, ICH, Glasgow Coma Scale Score <9 on admission, mental status abnormality, age >37 years, and male gender [8]. Our patient, apart from having a small ICH, had none of these risk factors. She recovered well after the attack, without any sequelae of weakness or numbness in her left limbs.

Our patient was discovered to have an underlying prothrombotic state due to protein S deficiency, which placed her at increased risk for CVT. Protein S deficiency can be acquired or congenital. Acquired protein S deficiency occurs in the acute phase of thrombosis, in patients receiving warfarin therapy for thrombosis and in those with nephrotic syndrome or severe liver disease [12]. Our patient had normal renal and liver functions. Additionally, protein S function was monitored several times after the acute stage and warfarin was withheld for 3 weeks prior to each blood test. The results were consistent with protein S deficiency (<10%).

Congenital protein S deficiency is inherited as an autosomal dominant trait and can cause recurrent thrombotic events, with or without a precipitating condition. Protein S is a vitamin K-dependent plasma
protein. It serves as a cofactor in facilitating deactivation of factor Va and factor VIIIa by protein C. Protein S deficiency causes a hypercoagulative state that can result in multiple episodes of venous thrombosis and pulmonary emboli. However, CVT is a rare complication among patients with hereditary thrombophilia, and is even rarer in congenital protein S deficiency [13]. Engesser and colleagues [14] have found similar results. Their report revealed that of 71 patients who were heterozygous for protein S deficiency, 39 (55%) had venous thrombotic events. The common thrombotic manifestations were superficial thrombophlebitis, deep vein thrombosis, and pulmonary embolism; CVT was an uncommon presentation and had an unusual site of thrombosis [15]. Reports of arterial thrombosis are very rare [15].

Apart from the past history of central retinal arterial occlusion and the current presentation of CVT, our patient did not have any other history of thrombotic events. The CVT can probably be attributed to the presence of a prothrombotic condition, together with a precipitating factor such as SIH.

CVT is an uncommon complication affecting only 2% of patients with SIH [2]. The development of concurrent SIH, CVT and ICH in our patient is rarely reported in the literature. The proposed mechanism is that an underlying protein S deficiency led to a prothrombotic state and that the SIH, with compensatory cerebral venous engorgement and stagnant blood flow, ultimately resulted in the thrombosis; and that the increasing pressure eventually caused the venous hemorrhagic infarction.

The optimal duration of oral anticoagulation (AC) for patients with CVT after an acute event is uncertain. The 2012 European Federation of Neurological Societies (EFNS) Guidelines suggest that oral AC should be given for 6-12 months in patients with idiopathic CVT. Indefinite oral AC should be considered in patients with recurrent episodes of CVT and in those with one episode of CVT associated with a severe form of thrombophilia, including antithrombin, protein C or protein S deficiency, homozygous factor V Leiden or the prothrombin G20210A mutation, antiphospholipid antibodies, and combined abnormalities [15]. Our patient had both CVT and protein S deficiency. Therefore, she will almost certainly require life-long AC therapy.

Conclusion

This report highlights that CVT with ICH is a potential complication of SIH. Any change of neurological status in a patient with SIH should raise the index of suspicion for CVT. A thorough investigation of the underlying cause is warranted and should include a thrombophilia screen.

References
