Iron Deficiency Anemia -
A Rare Etiology of Sinus Thrombosis in Adults

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Abstract-

\textbf{Purpose:} Cerebral venous thrombosis (CVT) has a wide spectrum of symptoms and is therefore difficult to diagnose. CVT has been reported to be associated with various etiologies. There are, however, very few reported cases of CVT associated with iron deficiency anemia (IDA), especially in adults.

\textbf{Case Report:} We reported the case of a female patient with seizure and hemorrhagic infarction due to sagittal sinus thrombosis. She had severe hypochromic microcytic anemia due to iron deficiency, and had a good prognosis after iron supplementation and oral anticoagulation therapy.

\textbf{Conclusion:} The present case indicates that iron deficiency is a risk factor for CVT.

\textbf{Key Words:} cerebral venous thrombosis, irondeficiency anemia, stroke, uterine myoma

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INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare condition with a wide spectrum of symptoms, which makes it difficult to diagnose. The initial symptoms of CVT may be due to increased intracranial pressure and include headache, vomiting, transient or persistent visual obscuration, focal or generalized seizures, lethargy, and even coma, although sometimes CVT is without obvious focal signs\textsuperscript{1,2}. Hemiparesis and cranial nerve disturbances might also be present, depending on the location of the venous structure involved. The clinical syndromes of CVT mimic neurological diseases such as brain tumor, stroke, and encephalopathy. CVT has been classified into three groups according to the initial symptoms and signs: (1) isolated intracranial hypertension, (2) focal neurological deficits, and (3) subacute diffuse encephalopathy.\textsuperscript{1,2} Approximately 80\% of patients with cerebral venous sinus thrombosis improve later, but there are poor outcomes in cases of intracerebral hemorrhage and deep venous infarction resulting from intracranial hypertension. The mortality of patients with CVT is approximately 10\%, and altered consciousness has been associated with a poor prognosis.\textsuperscript{1,2}

The diagnosis of CVT is based on magnetic resonance imaging (MRI) with MR angiography/venography, three-dimensional computed tomography (3D CT) angiography, or angiography\textsuperscript{3,4}. The most frequently affected locations are the superior sagittal sinus and the transverse sinus, and venous infarctions are noted in...
approximately 70% of CVT patients.(3) Thrombosis of the deep cerebral veins occurs very rarely and, like CVT in other locations, is difficult to diagnose because of its non-specific clinical and neuroradiological features. The main treatments for CVT include antithrombotic therapy and symptomatic treatments, especially for increased intracranial pressure and seizure.

CVT may be associated with dehydration, a hypercoagulable state, mastoiditis, tumor invasion of a venous sinus, head trauma, vasculitis, intracranial or systemic infections, pregnancy, puerperium, and oral contraceptive use. Iron deficiency anemia (IDA) has been reported as the cause of several pediatric cases of CVT.(4) However, CVT associated with IDA in adults has rarely been reported. Herein, we present the case of a patient with left posterior frontal hemorrhagic infarction due to superior sagittal sinus thrombosis who had hypochromic microcytic anemia due to iron deficiency.

CASE REPORT

A 39-year-old woman noticed weakness in her right limbs when she woke up early in the morning. She could not lift her right arm up to brush her teeth, comb her hair, or use chopsticks to eat. She could still walk but would deviate to the right side. She also noticed that she spoke non-fluently with some difficulty in naming objects. She had no headache, diplopia, sensory complaints, dysarthria, or dysphagia, and there was no progression in her weakness. There was no fever or any symptoms of respiratory tract infection.

Sixteen hours later, she had an episode of generalized tonic-clonic seizure lasting for 1 minute with initial presentation of right facial spasm and shouting. The post-ictal period lasted for approximately 10 minutes. She was sent to a local hospital, where two additional episodes of seizure occurred. Subsequently, she completely lost movement of her right limbs. Brain MRI was performed, and a corticosteroid was prescribed under the suspicion of vasculitis, but she did not regain her muscle power after the treatment. She was transferred to our hospital for help 5 days later.

The patient had suffered from menorrhagia for 4 years, and uterine myoma was diagnosed 1 year before admission. Because of the large size (10 cm) of the myoma and anemia (her hemoglobin level was 9.4 g/dL (normal range: 13.3+2 g/dL) with a hematocrit at 31.9% (normal range: 41+5%); she recalled that her hemoglobin had dropped to 4-5 g/dL and that she had received a blood transfusion earlier), immediate surgical intervention for the myoma was not suggested. She had not previously taken any supplements for anemia. She had been involved in a traffic accident 20 years before, with the sequelae of myopia and elevated intraocular pressure. She had had no previous craniofacial trauma. She had no history of spontaneous abortion and did not use oral contraceptives or hormone supplements. She was in her menstruation phase (menstruation had ended one day after the symptoms began to develop). Although she was a nurse at a local hospital, no recent infection or flu symptoms were present. She had no history of overseas travel or mountain climbing.

Neurological examination showed that the patient had a clear consciousness. Her blood pressure was 119/68 mmHg, heart rate 81 beats per minute, respiratory rate 19 breaths per minute. During physical examination, her skin turgor was normal, and there was no sign of dehydration. However, pale conjunctivas were noted. Cranial nerve examination showed mild, right-central-type facial palsy and left eye strabismus. Muscle power in the right upper and lower limbs was grade 0/0 of 5 and full on the left side. Relative hyperreflexia with an extensor plantar response was also noted in the right limbs.

Brain MRI and MR venography performed at our hospital showed left posterior frontal cortical veins and superior sagittal sinus thrombosis, with venous hemorrhagic infarction in the corresponding region (Fig. 1). The patient was sent to our intensive care unit, and heparin therapy was initiated at the time of admission. Angiography was performed 12 days after the initial symptoms and showed a focal filling defect in the middle portion of the superior sagittal sinus on the left side, with some dilated venous collaterals in the left frontal lobe during left carotid injection and minimal irregular contours of the superior sagittal sinus during right carotid injection (Fig. 2). Etiology factors for sinus thrombosis were investigated, and coagulation profiles
Figure 1. T2-weighted MRI shows venous infarction and hemorrhage in the left posterior frontal region. (A, C). MRV shows superior sagittal sinus thrombosis (arrows) and left posterior frontal cortical vein thrombosis with engorged cortical veins (B, D).

Figure 2. Angiography shows a focal filling defect at the middle portion of the superior sagittal sinus at the left side with some dilated venous collaterals at the left frontal lobe during left cortical injection. (A-C). The venous drainage on the right side during right cortical injection is acceptable (D).
(PT INR: 0.92; PTT: 24.4; platelet count: 262k/µL (normal range 120-320 k/µL); protein C 104% (normal range: >=79%), autoimmune profiles, anticardiolipin antibody, lupus anticoagulant (dRVVT), homocysteine, and tumor markers were unremarkable, except for increased D-dimer (3.8 µg/mL; normal range: <2.09 µg/mL) and relatively low levels of the protein S (44%; normal range: 59-118%) and anti-thrombin III antibody (75%; normal range: >= 82%). The patient was kept on phenytoin at 300mg/day orally, and anticoagulation therapy with heparin was given for 7 days followed by oral warfarin. IDA was suspected because of low hemoglobin levels (9.4 g/dL) and mean corpuscular volume (65.2 fL; normal range: 89+10 fL), and was confirmed when iron profiles showed low levels of iron (ferritin: 23.0 ng/mL; iron: 14 µg/dL; TIBC: 285 µg/dL) (normal range: 3.0 - 151 ng/mL, 66-155 µg/dL, 275-332 µg/dL). A gynecologist was consulted and gonadotropin-releasing hormone (GnRH) agonist was prescribed to stop the patient's menstruation and prevent further menorrhagia.

Under rehabilitation, the patient’s muscle power improved, except for weakness in the dorsi-flexion and plantar-flexion of the right foot. Follow-up brain MRI 3 months later showed focal encephalomalacia in the left posterior frontal lobe with a mild heterogeneous signal, which suggested a prior hemorrhage without new vascular insult. MR venography showed an irregular lumen at the superior sagittal sinus of the posterior frontal segment, suggesting chronic thrombosis. The patient regained her muscle power completely and has subsequently not experienced any more seizures. Under oral iron supplementation, the patient’s hemoglobin, MCV, and iron profiles improved (Hb: 9.4->15.3 g/dL; MCV: 65.2 -> 81.3 fL; ferritin: 23.0 -> 46.2 ng/mL; iron: 14-> 85 µg/dL; TIBC: 285->318 µg/dL). Follow-up D-dimer levels also returned to a normal range (3.8 -> 1.18 µg/mL), as did the value of anti-thrombin III (75% -> 133%).

**DISCUSSION**

Thrombosis of the cerebral veins and sinuses is a distinct cerebrovascular disorder that, unlike arterial stroke, more often affects young adults and children. It is known to be uncommon in adults, accounting for only 6% of all cases of CVT. A prothrombotic risk factor or a direct cause is identified in approximately 85% of patients with sinus thrombosis. It is known that CVT can be associated with various risk factors, but CVT in association with IDA is extremely rare.

Iron deficiency occurs with insufficient dietary intake or absorption\(^{14}\), and is more common in children than in adults\(^{3}\). Most commonly, iron deficiency causes anemia, although many other neurological sequelae can also result, such as irritability, headaches, developmental delays and, infrequently, papilledema, pseudotumor cerebri, and cranial nerve abnormalities. Iron deficiency is rarely recognized as a significant cause of stroke in the adult or pediatric populations\(^{5}\). The association of IDA with sinus thrombosis has been previously reported in children. There have been only a few reports of adult CVT patients with IDA\(^{9-13}\). However, unlike our patient, some of these cases were accompanied by other recognized risk factors of CVT, such as cryoglobulinemia, a hypercoagulable state (acquired protein C and protein S deficiency)\(^{10}\), and dehydration\(^{11}\). These factors may have synergistic effects in addition to IDA and contribute to the formation of CVT.

Some mechanisms have been proposed to explain the association between IDA and thrombosis. First, iron is considered to be a regulator of thrombopoiesis, and normal iron levels are required in order to prevent thrombocytosis by inhibiting thrombopoiesis\(^{7}\). Thrombocytosis occurs secondarily to iron deficiency and is thought to be associated with a hypercoagulable state. Thrombosis in some individuals may be explained by the decreased inhibition of thrombopoiesis due to insufficient iron stores. Second, iron deficiency may contribute to a hypercoagulable state by affecting flow patterns within the vessels\(^{5}\). The microcytosis resulting from iron deficiency causes reduced red cell deformability and increased viscosity, which contributes to thrombosis in a negative-pressure environment, as is found in veins. Third, anemic hypoxia secondary to iron deficiency may occur in situations with increased metabolic demands (i.e., infection) in the brain, which cannot be
met because of low hemoglobin levels causing poor oxygenation\(^{(5,13)}\). In addition, according to Virchow’s triad, hypercoagulability, hemodynamic changes (either stasis or turbulence), and endothelial injury may contribute to the formation of thrombosis. Anemia causes increased arterial blood flow velocity\(^{(15-16)}\). However, IDA causes markedly reduced deformability in red blood cells, resulting in increased viscosity despite the smaller size of the cells, and may contribute to reduced flow velocity in the veins\(^{(17)}\).

In a case-control study, data on whole blood counts and screening for thrombophilic coagulation abnormalities of 121 prospectively identified adult patients with CVT and 120 healthy adult controls were compared. Severe anemia, defined as Hb <9 g/dL, was significantly and independently associated with CVT\(^{(8)}\). However, thrombocytosis was not significantly associated with CVT. This may explain the role of anemia itself in accounting for CVT rather than thrombocytosis secondary to anemia. Although this study did not include a systematic analysis of iron metabolism and did not specify the type of anemia, 63% of the patients with severe anemia in this study had microcytic anemia, and there was a female preponderance in the group. Thus, in most cases in this case-control study, IDA can be assumed.

There are several published case reports of adult patients with IDA who had sinus thrombosis\(^{(9-13)}\). Unlike children, in which the major cause of IDA is insufficient dietary iron intake, blood loss is the most common cause of IDA in adults and may result from menstruation in premenopausal women, chronic gastrointestinal loss (ulcer, malignancy, parasites), urine loss (hemoglobinuria, hemosiderinuria), and hemoptysis. One study reported two women with hemorrhagic infarction due to thrombosis of the superior sagittal and transverse sinus \(^{9}\). The severe IDA secondary to myoma uteri seen in those two patients was suggested to play a significant role in the development of CVT. Our patient also had uterine myoma and severe IDA. In middle-aged women with IDA, myoma uteri deserve special attention as a possible etiological contributor to CVT\(^{(9)}\).

Treatments have included thrombectomy, corticosteroids, mannitol, heparin, low-molecular-weight heparin, warfarin, aspirin, blood transfusion, and iron supplementation, but there is no consensus regarding therapy, other than to correct the anemia and treat the iron deficiency\(^{(10)}\). In recent studies, anticoagulation therapy has been used for the treatment of CVT\(^{(2)}\). Our patient received heparin and mannitol in addition to iron and erythrocyte supplementation, and was then treated with oral warfarin. IDA should be comprehensively treated, because anemia is commonly observed as a relatively low hemoglobin concentration in the acute phase of CVT\(^{(17)}\).

The case of our patient with sagittal sinus thrombosis associated with IDA suggests that iron deficiency status should be considered as an underlying cause of CVT in both adult and pediatric patients. Supplementation therapy for iron deficiency may be an important strategy to prevent CVT.

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