Cerebral Venous Sinus Thrombosis Associated With Iron Deficiency

—Two Case Reports—

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Abstract

Two patients presented with cerebral venous sinus thrombosis (CVST) associated with iron deficiency. A 14-year-old man had thrombosis extending from the end of the superior sagittal sinus to the left transverse sinus. Severe dehydration after competitive sport had induced CVST. The laboratory findings showed severe iron deficiency anemia which persisted for 1 year. A 47-year-old man had thrombosis in the entire superior sagittal sinus. Dehydration caused by poor nutrition had induced CVST. The laboratory findings showed transient iron deficiency in the acute phase. Both patients received conservative treatment for dehydration and iron supplementation. These two cases indicate that iron deficiency is a risk factor for CVST.

Key words: cerebral venous sinus thrombosis, iron deficiency, dehydration

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease, and the diagnosis is often delayed because the symptoms and signs are not specific.⁹⁾ The symptoms are not focal, consisting of headache, vomiting, drowsiness, lethargy, and confusion. Some patients complain of hemiparesis, cranial nerve disturbance, and ataxia.^{9,12,14)} Approximately 80% of patients with CVST improve completely, but a minority have severe outcomes such as intracerebral hemorrhage and deep venous infarction resulting from intracranial hypertension. The mortality of patients with CVST is about 10%.

The diagnosis of CVST is based on magnetic resonance angiography, three-dimensional computed tomography (3D CT) angiography, or angiography.¹⁴⁾ The most frequently affected locations are the superior sagittal sinus and the transverse sinus, followed by venous infarctions.¹⁴⁾ The main treatments for CVST are treatment for the symptom and antithrombotic therapy.³⁾

CVST may be caused by various conditions, including dehydration, infection, oral contraceptive use, trauma, cancer, and hematological disorder. In

particular, abnormality in the activity of protein C, protein S, coagulating factors, and antithrombin III have been proposed.^{6,10,14)} Iron deficiency anemia has been reported as the cause of several pediatric cases of CVST,¹²⁾ but not in adult patients.

We treated two adult patients with CVST apparently caused by iron deficiency.

Case Reports

Case 1: A 14-year-old man complained of sudden onset of headache and nausea persisting for 3 days, after playing a competition game of table tennis in midsummer 2004. He had an unbalanced eating habit. On admission to our clinic, he had no neurological deficits other than severe headache. CT of the head demonstrated a high density area in the left transverse sinus (Fig. 1), and 3D CT venography revealed absence of flow from the confluence of sinuses to the left transverse sinus. On the 2nd hospital day, the venous phase of left carotid angiography showed occlusion extending from the end of the superior sagittal sinus to the entire left transverse and sigmoid sinuses (Fig. 2). Treatment for dehydration and hemodilution with low-molecular-weight dextran were begun under a diagnosis of CVST.

Fig. 1 Case 1. Head computed tomography scan on admission showing an abnormal high density area in the left transverse sinus.

Fig. 2 Case 1. Left internal carotid angiogram on the 2nd hospital day showing absence of the confluence of sinuses and the left transverse sinus.

The laboratory findings on admission were red blood cells $502 \times 10^4/\mu\text{l}$, hemoglobin 7.4 g/dl, hematocrit 28.5%, mean corpuscular volume 56.8 fl, and platelet count 289,000/ μl . The findings 3 days later were serum iron 9 $\mu\text{g}/\text{dl}$ and total iron binding capacity 380 $\mu\text{g}/\text{dl}$. However, protein C activity, anticardiolipin antibody (immunoglobulin G), and antithrombin III were within the normal ranges. One month later, the findings were red blood cells $629 \times 10^4/\mu\text{l}$, hemoglobin 14.6 g/dl, hematocrit 49.6%, mean corpuscular volume 79.4 fl, and platelet count 303,000/ μl . Although the data revealed progressive concentration of the blood, the serum iron level was still low at 34.6 $\mu\text{g}/\text{dl}$.

3D CT venography on the 40th hospital day showed that the confluence of sinuses was recanal-

Fig. 3 Case 1. Left internal carotid angiogram demonstrating recanalization of the confluence of sinuses and the vein of Labbé draining into the left transverse sinus (arrow), as well as the hypoplastic left sigmoid sinus.

ized but the left transverse sinus was still occluded. He was discharged with no neurological deficit but continued to take oral medicine for iron supplementation and anticoagulation (warfarin 1.0 mg/day).

Left internal carotid angiography at 8 months after the onset showed that the confluence of sinuses was recanalized but the left sigmoid sinus remained occluded, and the vein of Labbé drained into the left transverse sinus (Fig. 3). The laboratory findings showed improvement of iron deficiency anemia and compensated erythroid proliferation with serum iron 60 $\mu\text{g}/\text{dl}$, red blood cells $624 \times 10^4/\mu\text{l}$, hemoglobin 15.3 g/dl, hematocrit 49.4%, mean corpuscular volume 78.6 fl, and platelet count 310,000/ μl . He continued to take iron supplementation for 1 year, when the findings were red blood cells $561 \times 10^4/\mu\text{l}$, hemoglobin 14.8 g/dl, and serum iron 92 $\mu\text{g}/\text{dl}$ (Fig. 4).

Case 2: A 47-year-old man presented with progressively worsening symptoms, including left hemiparesis and tonic-clonic seizures in midsummer 2005. He was alcoholic and usually took only two meals a day at that time.

CT of the head showed intracerebral hemorrhage in the right temporal lobe and the left parietal lobe, and infarction in the right frontal lobe (Fig. 5). On the 2nd hospital day, the venous phase of right internal carotid angiography showed absence of flow in the superior sagittal sinus and congestion of the superior superficial cerebral vein (Fig. 6). The laboratory findings demonstrated early concentration of his blood: red blood cells $659 \times 10^4/\mu\text{l}$,

Fig. 4 Case 1. Time course showing iron deficiency anemia (hemoglobin [Hb, $\blacktriangle$] was 7.4 g/dl and serum iron [Fe, $\blacklozenge$] was 7 $\mu\text{g/dl}$) persisting for 1 month, then improving (hemoglobin was 14.8 g/dl and serum iron was 92 $\mu\text{g/dl}$ 1 year after the onset). Red blood cell count (RBC, $\blacksquare$) reactively increased from $502 \times 10^4/\mu\text{l}$ to $629 \times 10^4/\mu\text{l}$ 1 month after the onset, and then gradually improved.

Fig. 5 Case 2. Head computed tomography scans on admission showing right temporal hemorrhagic infarction, left parietal hemorrhage, and right motor area infarction (arrow).

hemoglobin 15.7 g/dl, hematocrit 51.5%, mean corpuscular volume 78.1 fl, and platelet count 276,000/ μl . The level of serum iron was 44 $\mu\text{g/dl}$.

Conservative treatment with hemodilution therapy was begun under a diagnosis of CVST with dehydration. One month later, his left hemiparesis was gradually improved and 3D CT venography showed partial recanalization of the superior sagittal sinus. On the 43rd hospital day, right internal carotid angiography revealed partial recanalization of the superior sagittal sinus and improvement of congestion of the superficial veins (Fig. 7).

The laboratory findings on the 40th hospital day were red blood cells $476 \times 10^4/\mu\text{l}$, hemoglobin 12.0

Fig. 6 Case 2. Right internal carotid angiogram on the 2nd hospital day showing absence of the superior sagittal sinus and congestion of the superior superficial cerebral vein.

Fig. 7 Case 2. Right internal carotid angiogram revealing partial recanalization of the superior sagittal sinus and improvement of congestion of the superficial veins.

g/dl, hematocrit 37.6%, mean corpuscular volume 79.0 fl, and platelet count 230,000/ μl . The level of serum iron was 117 $\mu\text{g/dl}$. Protein C activity, and anticardiolipin antibody (immunoglobulin G) and antithrombin III levels were within the normal ranges.

Two months after the onset, he was discharged with mild paresis in the left upper limb. He continued to take anticonvulsants. Four months after the onset, the findings were red blood cells $473 \times 10^4/\mu\text{l}$, hemoglobin 14.1 g/dl, hematocrit 42.6%, mean corpuscular volume 90.0 fl, and platelet count 329,000/ μl . The level of serum iron had decreased to 37 $\mu\text{g/dl}$. He was given oral iron supplementation.

Discussion

Both of the present patients with CVST had no hematological disorder, collagen disease, or cardiomyopathy. Iron deficiency was the only abnormal laboratory finding in these patients. Both patients were treated for dehydration and hemodilution with low-molecular-weight dextran, but no antithrombotic or anticoagulant therapy was performed.

The association of iron deficiency with CVST has been reported only in pediatric patients.^{2,5,8)} Thrombosis of the pulmonary vein and lower limb vein are known during pregnancy.⁴⁾ Half of a series of 42 pediatric CVST patients had anemia.¹²⁾ Iron deficiency anemia is more common than protein S or C deficiency, or cardiomyopathy. The status of iron deficiency anemia should be comprehensively treated, because anemia is commonly observed as relative hemoconcentration in the acute phase of CVST.¹²⁾

The mechanism of iron deficiency anemia causing CVST can be described as follows. Serum iron acts as a regulator of thrombopoiesis⁷⁾ by helping to maintain steady platelet levels.²⁾ Therefore, iron deficiency allows the level of megakaryocytes to rise followed by increased production of platelets and consequent hypercoagulation state. Moreover, the production of platelets is stimulated by the high levels of erythropoietin associated with iron deficiency.¹⁾ On the other hand, blood flow patterns can depend on the deformity of the red blood cells and the capacity for binding with oxygen.⁸⁾ Under conditions such as dehydration and infection, metabolic stress is increased and hypoxia secondary to anemia can worsen.⁸⁾ Multiple factors are associated with CVST, but iron deficiency may be one of the most important.

Although thrombocytosis is present in most cases of CVST with iron deficiency anemia, reactive thrombocytosis has not usually been regarded. Transient thrombocytopenia at diagnosis could be the result of consumption by the acute thrombosis, that is why the platelet counts of both our cases were only slightly elevated.²⁾

Previous patients in the acute phase of CVST received intravenous heparin which doubled the activated partial thromboplastin time within 2 or 3 weeks, followed by oral anticoagulants.³⁾ Anticoagulation therapy for CVST in a patient with hemorrhagic infarction is controversial.¹³⁾ Anticoagulant therapy may not increase hemorrhagic infarction, so the location and unchanged volume on follow-up CT may be important factors.¹⁵⁾ On the other hand, there was a statistical trend for intracerebral hemorrhage to occur more frequently in cases with fatal out-

come.¹¹⁾ Recently, local infusion therapy by recombinant human tissue-type plasminogen activator was delivered by catheterizing the superior sagittal sinus through the transfemoral route, resulting in complete recovery of the CVST.¹⁶⁾

These two cases of CVST associated with iron deficiency suggest that iron deficiency status should be considered in both adult and pediatric patients as an underlying cause of CVST. Supplementation therapy for iron deficiency may be an important strategy to prevent CVST.

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