

Simultaneous Thrombosis of Cerebral Artery and Venous Sinus

Bo-Lin Ho, Poyin Huang, Gim-Thean Khor, and Ruey-Tay Lin

Abstract- Cerebral venous thrombosis (CVT) is infrequent among cerebrovascular diseases. The simultaneous thrombosis involving both cerebral artery and venous sinus is even extremely rare. We reported a 41-year-old woman who presented with acute headache and left hemiparesis due to concomitant arterial ischemic stroke and recurrent CVT. Extensive investigation disclosed acquired protein C and protein S deficiency, iron deficiency anemia (IDA) and cryoglobulinemia. She was treated with intravenous injection of heparin followed by oral anticoagulant therapy. The headache rapidly subsided; however, left hemiparesis persisted over five months. The rare condition of simultaneous thrombosis of cerebral artery and venous sinus may be caused by the synergistic effect of coagulation disorders, IDA and cryoglobulinemia.

Key Words: Cerebral venous thrombosis, Ischemic stroke, Protein C, protein S, Iron deficiency anemia, Cryoglobulinemia

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INTRODUCTION

Cerebral venous thrombosis (CVT) accounts for less than 1% of all strokes, and its clinical presentations are highly variable⁽¹⁾. In contrast to arterial ischemic stroke (AIS), the thrombotic process in cerebral venous thrombosis may continue over days to several weeks with thrombosis in one site and recanalization in another site. CVT occurs in all age groups with peak incidences in neonates and adults in their third decade with a female/male ratio of 1.5-5⁽²⁾. Multifactorial etiologies can lead to CVT, and therefore extensive investigations are often essential once the diagnosis is established. Atherosclerosis may also induce venous thrombosis, and these two conditions may share common risk factors⁽³⁾.

Simultaneous cerebral arterial and venous infarction has never been reported in previous literatures, and a complete survey of underlying disorders should be recommended for this unusual clinical condition.

CASE REPORT

A 41-year-old woman with a history of chronic headache was hospitalized due to acute onset of severe headache and left-sided weakness. The worst headache was more localized at left temporal region, and worsened with bending over or lying flat. She had no antecedent head injury, cigarette smoking, or oral contraceptives use. Her family history concerning coagulation disorders was negative.

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Two months before the admission, she developed a similar isolated headache, while cranial magnetic resonance imaging (MRI) with venography at another hospital demonstrated thrombosis of left transverse sinus (Fig. A). She received oral anticoagulant therapy, and the headache subsided gradually within five days.

Upon admission, she was afebrile and fully oriented. Neurological examination revealed mild dysarthria, left hemiparesis (muscle power was 2/5 according to the Medical Research Council grading) and hypoesthesia with extensor plantar response. Fundoscopic examination was normal. Post-contrast computed tomography (CT) of the brain demonstrated filling defects in the superior sagittal sinus (SSS) and bilateral transverse sinuses. A follow-up brain MRI disclosed new thrombus in the SSS, and an acute infarction involving the right

basal ganglion, corona radiata and insular lobe. Diffusion-weighted images showed the hypersignal lesion (Fig. B) with a corresponding marked decrease of apparent diffusion coefficient values (Fig. C). The lesion was faintly hyperintense on fluid attenuated inversion recovery (FLAIR) sequences (Fig. D). These findings were consistent with cytotoxic edema usually observed at the acute phase of AIS. Three-dimensional time-of-flight MR angiography confirmed CVT in the SSS (Fig. E) and the right middle cerebral artery could not be recognized (Fig. F).

The laboratory data revealed microcytic hypochromic anemia with hemoglobin value of 8.7 g/dL and a mean corpuscular volume of 56.4 fL. Routine biochemical profiles including liver and renal panels, thyroid function and urine analysis were all normal. Serum

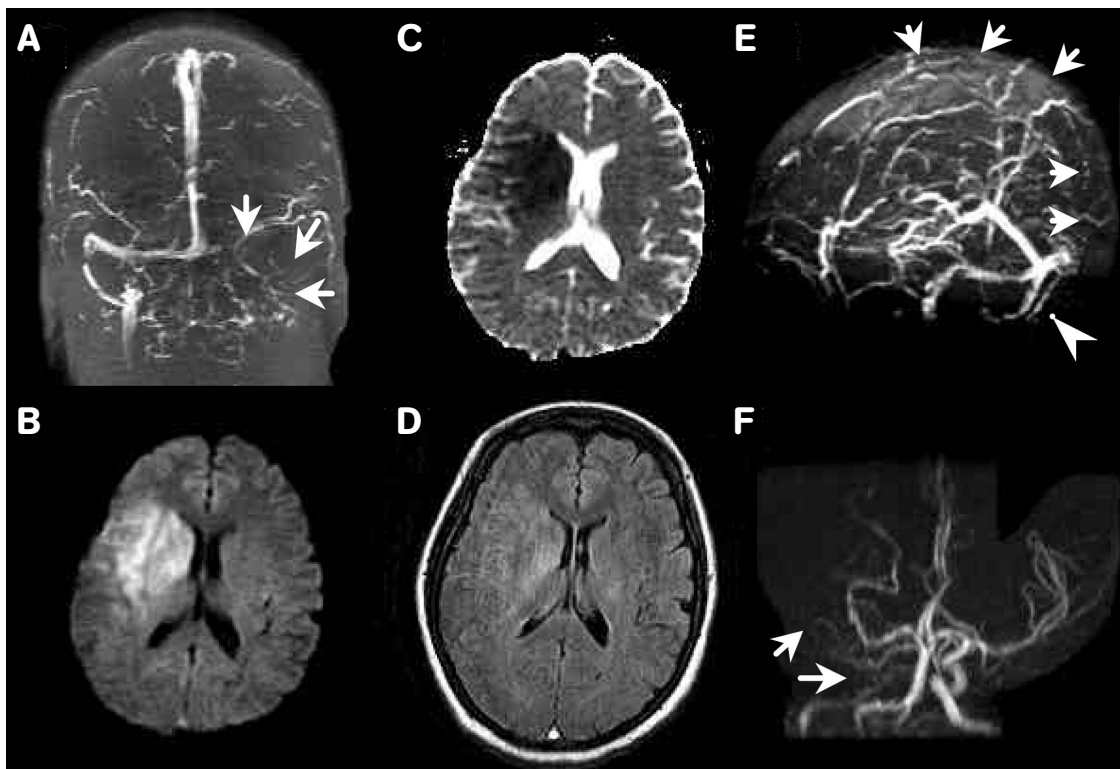


Figure 1. (A) Magnetic resonance venography two months before admission showed absence of flow in the left transverse sinus and the left jugular vein (arrows). (B, C, D) Diffusion-weighted images showed the hypersignal lesion (B) of the right basal ganglion, corona radiata and insular lobe, with a corresponding marked decrease in apparent diffusion coefficient values (C) and a faint hyperintensity on fluid attenuated inversion recovery sequences (D). (E) The follow-up magnetic resonance venography demonstrated recanalization of the left transverse sinus and jugular vein (arrowhead) but absence of the superior sagittal sinus (arrows) and congestion of the superior superficial cerebral veins. (F) The right middle cerebral artery (arrow) could not be visualized on magnetic resonance angiography.

iron concentration was 16 ug/dL (normal range: 50-170 ug/dL), and ferritin level was 11.8 ng/mL (normal range: 12-150 ng/mL). Screening investigations for coagulopathy showed decreased antigen level of protein C of 57% (normal: 70-150%) and protein S of 42% (normal: 65-135%). Antinuclear antibodies (titer 1:40) and cryoglobulin (IgG: 1790 mg/dL, IgM: 161 mg/dL, IgA: 157 mg/dL) were positive (normal: negative). Erythrocyte sedimentation rate was 78 mm/hour, and C-reactive protein was 0.77 ug/mL. Serum hepatitis B surface antigen and antibodies against hepatitis C virus were negative. Other tests including platelet count, prothrombin time, partial thromboplastin time, fibrinogen, antithrombin III, clotting factor VIII, rheumatoid factor, homocysteine, lipid profiles and tumor markers were normal. Lupus anticoagulant, anti β 2-glycoprotein 1, anticardiolipin and antiphospholipid antibodies were within normal limits. Protein immunofixation electrophoresis demonstrated no monoclonal or polyclonal gammopathy. Furthermore, the sugar water test and Ham's acid hemolysis test were negative. There was no clinical or laboratory evidence of dehydration.

24-hour Holter electrocardiogram revealed normal sinus rhythm without cardiac arrhythmia. Transthoracic cardiac echocardiography showed normal segmental wall motion with abnormal left ventricular relaxation. Carotid duplex and transcranial duplex showed small plaques over bilateral internal carotid arteries and bifurcations with normal blood flow pattern. Gynaecological examination as well as abdominal ultrasonography revealed a uterine myoma, which was thought to be the cause of occasional hypermenorrhea.

She was treated with intravenous heparin followed by daily oral warfarin to maintain the target international normalization ratio (INR) of 2.0 to 3.0. Oral iron supplement was concurrently administered. Her headache rapidly subsided; however, left hemiparesis persisted during hospitalization. Five months later, the follow-up exam disclosed recovering protein C of 83% and protein S of 72%, and absence of serum cryoglobulin. The left hemiparesis improved a little without further neurologic deficits.

DISCUSSION

As several etiologies have been identified for AIS, a multitude of conditions are attributed as risk factors for CVT. The more common conditions include hypercoagulable states, trauma, intracranial and local infections, pregnancy and purperium, and the use of oral contraceptives^(4,5). Frequently, the cause of CVT is multifactorial, and in up to 35% of patients no contributing factors can be identified⁽¹⁾. Virchow's triad encompasses three major categories which contribute to thrombosis: alternations of blood flow, injury to the vascular endothelium and disorders of coagulation. Unlike arterial events, damage to the vascular endothelium only accounts for 10% of CVT⁽⁴⁾. Extensive investigation in our patient disclosed acquired protein C and protein S deficiency, iron deficiency anemia (IDA) and cryoglobulinemia. Negative results of sugar water test and Ham's test exclude the possibility of paroxysmal nocturnal hemoglobinuria. The carotid duplex revealed only small plaques without stenotic blood flow. It is difficult to distinguish the clinical significance of each abnormality in our patient; however, we proposed that such combinations may enhance each other in the pathogenesis of simultaneous CVT and AIS.

Among the Virchow's triad of thrombosis, hypercoagulability and stagnant flow predominate in venous thrombosis. Hereditary thrombophilia should be suspected when a patient younger than 45 years of age has a family history of venous thrombosis, recurrent venous thromboembolism, or no apparent acquired risk factors⁽⁶⁾. Common inherited thrombophilic situations in the Western world such as the factor V Leiden mutation, G20210A mutation in the prothrombin gene and antithrombin deficiency, have relatively low prevalence in Asian people. Protein C and protein S deficiency is quite rare and detected in only 2-6% of cases⁽¹⁾. Being well-documented as causative factors of CVT, abnormalities in protein C and protein S have not been shown to be significantly associated with arterial infarction⁽⁷⁾. Acquired deficiency may occur with liver disease, infections and sepsis, disseminated intravascular coagulation, vitamin K malabsorption, and administration of L-

asparaginase or oral anticoagulants⁽⁸⁾. Under warfarin therapy, our patient had acquired quantitative deficiency of protein C and protein S during acute stage of the thrombotic episode. The relapsing thrombosis might be due to inadequate anticoagulant dose before. Furthermore, anticoagulation of heparin or warfarin is recommended only for clinical thrombosis, but not for those with asymptomatic subnormal levels⁽⁸⁾.

Serum iron acts as an essential regulator of thrombopoiesis, and insufficient iron stores may cause reactive thrombocytosis as hypercoagulable state. Reduced deformability and oxygen-carrying capacity of red blood cells secondary to IDA can worsen under the conditions such as infection or dehydration. Both mechanisms affect the flow pattern within vessels, and thus result in thrombotic events⁽⁹⁾. The association of IDA with CVT has been infrequently reported in pediatric patients and even rare in adults⁽¹⁰⁻¹²⁾. There were no other concurrent coagulation disorders found in previously reported patients, thus IDA could be the only contributor in thrombosis. In our patient, IDA was caused by chronic blood loss from uterine myoma. Without thrombocytosis, Aoki et al. and Stehle et al. have reported similar cases with chronic bleeding either from myoma uteri or rectal prolapse^(11,12). Iron supplementation, combined with anticoagulant therapy and blood transfusion mostly brings satisfactory outcomes⁽⁹⁾. As a potential risk factor for AIS or CVT, IDA is preventable and curable and deserves further considerations.

Cryoglobulins are serum immunoglobulins that precipitate with cold temperature, and become soluble when re-warming. They are found in small quantities in normal settings, but in variable concentrations associated with infections, malignancy, autoimmune and lymphoproliferative disorders⁽¹³⁾. The type I cryoglobulinemia has a single monoclonal immunoglobulin usually associated with hematological disorders. Types II cryoglobulinemia and III cryoglobulinemia have mixed cryoglobulins, with a mixture of monoclonal component in the type II cryoglobulinemia and only polyclonal immunoglobulin in the type III cryoglobulinemia. The mixed type cryoglobulinemia (i.e. type II or type III) with rheumatoid factor activities binding polyclonal

immunoglobulins, is usually characterized by the clinical triad of purpura, arthralgia and asthenia. The syndrome of mixed cryoglobulinemia represents the consequence of an immune-complex mediated vasculitis, and may often be a manifestation of underlying chronic active or persistent hepatitis. Chronic hepatitis C infection has been recognized as the main pathogenic factor responsible for the majority of patients with mixed cryoglobulinemia^(13,14). Peripheral neuropathy is the most frequent neurological manifestation; however, ischemic stroke has been scarcely reported in association with mixed cryoglobulinemia. As idiopathic in origin with absence of viral hepatitis, we suggested that cryoglobulinemia may be an indicator of acute ischemic stroke in our patient. Some case series have proposed cryoglobulinemia as a risk factor for ischemic stroke because it causes arterial thrombosis, and the level of cryoglobulins increases significantly over the course of entire acute period of ischemic stroke^(14,15).

Taken together, multiple etiologies contribute to the pathogenesis of young stroke, either with arterial or venous involvement. The combination of acquired coagulation disorders, IDA and cryoglobulinemia in our patient may enhance the individual effect for thrombosis. According to the best of our knowledge, simultaneous cerebral arterial and venous infarction has never been reported. Complete investigations of underlying disorders are required for this rare condition.

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