Isolated inferior sagittal sinus thrombosis caused by a rare combination of elevated lipoprotein (a) and iron deficiency anemia

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ABSTRACT

تم إدخال مريضة تبلغ من العمر 21 عاماً المستشفى مصابة بشلل نصفي، ووذمة حليمة العصب البصري للجانبين، ورمع عضلي سلبي. أظهر التصوير الطبقي عدم وجود أي تدفق وريدي في الجيب السهمي السفلي. ظهر ارتفاع البروتين الشحمي والانيميا الناتجة عن نقص الحديد. إن وجود ارتفاع البروتين الشحمي وانيميا نقص الحديد في المرضى المصابين بالتجلط الوريدي بالدماغ يعد حالة نادرة جداً في المرضى البالغين. يجب التحقق من عوامل الخطر في المرضى المصابين بالتجلط الوريدي بالدماغ.

A 21-year-old woman was admitted with right hemiparesis, bilateral papilledema, negative myoclonus of right upper extremity, and bilateral pyramidal findings. An MRI showed no venous flow in the inferior sagittal sinus. Lipoprotein a (Lp [a]) level was high and iron deficiency anemia (IDA) was found. The coexistence of IDA and Lp (a) in patients with cerebral venous thrombosis is a very rare condition in adult patients. These risk factors should be investigated in patients with cerebral venous thrombosis.

Neurosciences 2012; Vol. 17 (4): 374-377

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Received 23rd June 2012. Accepted 25th August 2012.

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Dural sinus and cerebral venous thrombosis (CVT) are an uncommon form of stroke, generally affecting young persons. The CVT represents 0.5-1% of all strokes.[1] Despite advances in the recognition of CVT in recent years, diagnosis and management can be difficult because of the diversity of underlying risk factors. The predisposing factors of CVT are multiple. The risk factors for venous thrombosis in general are linked to the Virschow triad. The features of this triad are as follows: stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.[2,3] The risk factors reported for CVT by the American Heart Association/American Stroke Association are as follows: prothrombotic conditions such as antithrombin III, protein C, protein S deficiency, antiphospholipid and anticardiolipin antibodies, resistance to activated protein C and factor V Leiden, mutation G202101 of factor II, and hyperhomocysteinemia. Pregnancy, puerperium, oral contraceptives, cancer related conditions, or parameningeal infections may also be the cause of CVT.[2] There is anecdotal reports of other risk factors such as paroxysmal nocturnal hemoglobinuria, iron deficiency anemia (IDA), thrombocythemia, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, nephrotic syndrome, inflammatory bowel disease, systemic lupus erythematosus, Behçet disease, mechanical precipitants such as epidural blood patch, spontaneous intracranial hypotension, and lumbar puncture.[2] The CVT is most frequently located in the superior sagittal sinus, but has also been reported in the transverse and sigmoid sinus and the deep cortical veins. Thrombosis of the inferior sagittal sinus (ISS) was rarely reported.[4,5] Lipoprotein a (Lp [a]) particles are similar to low-density lipoproteins (LDL), consisting of a cholesterol-rich core with an apolipoprotein B-100 protein attached. Lipoprotein (a) has known prothrombotic potential. This effect is related to plasminogen like functions of Lp (a). It is also known that Lp (a) is a risk factor for ischemic arterial

cerebral stroke and thrombosis. The American Heart and Stroke Association do not consider Lp (a) as a risk factor for CVT.[1] Although there are a few reports on the isolated high level of Lp (a) and CVT in adult patients, Lp (a) is a well known etiological factor for CVT in children and neonates.[6,7]

Another rare risk factor for CVT is IDA. Iron deficiency anemia is a common anemia caused by insufficient dietary intake or absorption of iron, and iron loss from intestinal bleeding, parasitic infection, menstruation, and so forth. The IDA is usually related to menorrhagia in young women. It has been known as a risk factor for CVT in pediatric cases. However, there are anecdotal case reports of CVT associated with IDA in adults.[8,9] We report the case of 21-year-old woman with ISS thrombosis accompanied with elevated Lp (a) and IDA. Our objective in reporting this particular case is to highlight these rare coexisting conditions in patients with CVT.

Case Report. A 21-year-old woman was referred to our hospital for headache, abnormal movements, and weakness of the right arm and leg, and visual blurring. She had no medical history before these complaints. She had no history of oral contraceptives use, or hormone supplements, and no previous craniofacial trauma or lumbar puncture. She denied any family history of stroke, hypertension, diabetes mellitus, valvular heart disease, blood disorders, or malignancies. Her blood pressure was 110/70 mm Hg, and her pulse was 90/min. Neurological examination revealed bilateral papilledema, right hemiparesis (grade 4/5), negative myoclonus of the right upper extremity, bilateral Babinski sign, and brisk deep tendon reflexes of the right side. A brain MRI and magnetic resonance venography (MRV) were performed. The T2 and FLAIR-weighted sequences showed increased signal in the splenium of the corpus callosum. There were similar lesions in the frontal and parietal subcortical regions bilaterally. There was no diffusion restriction. Contrast enhanced T1-weighted MR image showed thickening and diffuse enhancement of the dura mater over the falx cerebri (**Figures 1A-D**). The MRV revealed patent superior sagittal, rectus, transverse, and sigmoid sinuses. There were irregular appearance and poor detection of the ISS (**Figures 2A & B**). Laboratory findings revealed that the erythrocyte sedimentation rate, C-reactive protein, glucose, urea, creatinine, sodium, potassium, liver function tests, thyroid function tests, and vitamin B12, folic acid, and homocysteine levels were normal. Coagulation tests (antithrombin III, prothrombin time, protein C, protein S, activated partial thromboplastin time,

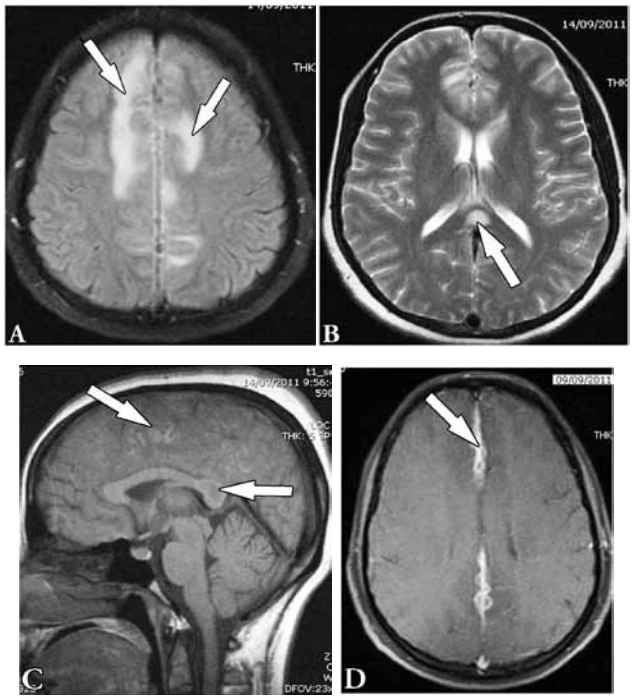

Figure 1 - Axial fluid attenuated inversion recovery (FLAIR) **A**) and T2 weighted **B**) images showing increased signal in bifrontal/biparietal areas of the splenium of the corpus callosum. Sagittal **C**) and axial **D**) fat saturated enhanced T1-weighted images revealed increased signal in paramedian localization and enhancement in thickening and diffuse enhancement of the dura mater over the falx cerebri.

fibrinogen) were normal. The results of the peripheral blood analysis were as follows: erythrocytes: 3.7 x 10^6/mm^3, hemoglobin: 8 g/dL, mean corpuscular volume: 75 fL, platelet counts: 324 × 10^6/mm^3. Peripheral blood smear revealed hypochromatic microcytic red blood cells. The serum iron (14 µg/dL), and iron saturation index (5%) was low. Direct and indirect Coombs tests were negative. A hematologist evaluated iron deficiency anemia. Genetic thrombophilia tests; factor V Leiden (1691 G>A), MTHFR C677T, and factor II (prothrombin 20210G>A) were normal. Antinuclear antibody was studied to investigate connective tissue disease, and the results were negative. Anticardiolipin antibody and lupus anticoagulant tests, and complement tests (C3, C4) were normal. Total cholesterol, high-density lipoprotein, LDL, very low-density lipoprotein and triglyceride levels were normal. The Lp (a) level was 100 mg/dL (normal range: 0-20 mg/dL).

She was examined by a dermatologist for Behçet's syndrome; she had no history of oral/genital aphthae ulcers, and the Pathergy test was negative. She was examined for uveitis by an ophthalmologist, and the

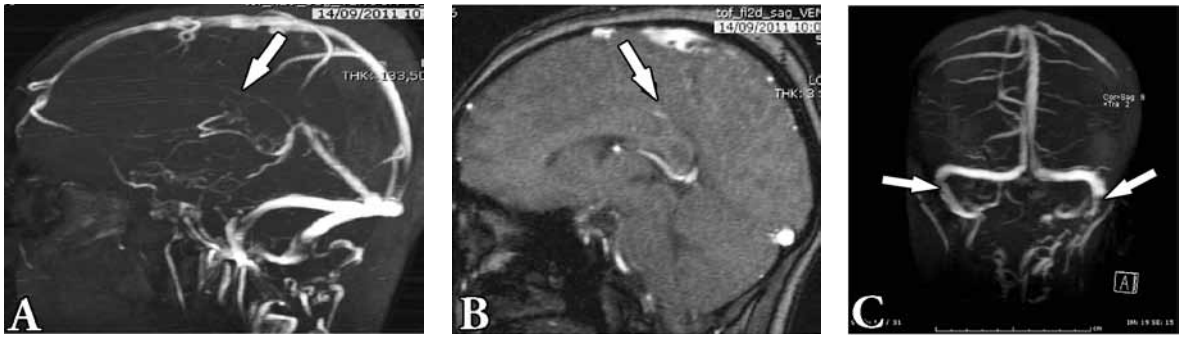

Figure 2 - Magnetic resonance venography (MRV) demonstrated **A & B)** irregular appearance and poor detection of the inferior sagittal sinus. **C)** Bilateral narrowing at the transverse sigmoid junctions was seen on 3D reconstruction of the MRV. The rest of the deep sinuses and veins were patent.

results were normal. She was given heparin, continued with warfarin (Coumadin 5 mg, Zentiva, Luleburgaz, Turkey) treatment for cerebral sinus thrombosis. Intravenous heparin (Nevparin, Mustafa Nevzat, Istanbul, Turkey) was given as a 5000 units bolus, followed by an infusion of 1000 units per hour. The activated partial thromboplastin time value was kept between 60 and 80 seconds. Warfarin was added to the heparin therapy. The international normalized ratio was regulated between 2.5 and 3 during the warfarin treatment. She had visual field deficiency, headache, and papilledema. These findings suggested intracranial hypertension. In addition to clinical findings 3D reconstruction of the MR venography showed bilateral narrowing at the transverse sigmoid junctions (**Figures 2A & C**). Thus, acetazolamide (Diazomid 250 mg, Sanofi-Aventis, Istanbul, Turkey) one mg/day was started for intracranial hypertension. In addition, oral iron treatment was given. One week later, her headache ameliorated, right hemiparesis gradually improved, and negative myoclonus on the right upper extremity was resolved. One month after these treatments her visual field defect improved significantly, and there was no papilledema in her ophthalmologic examination. Two months later, the cranial MRI showed regression of the dural thickening and contrast enhancement improved. The MR venography showed bilateral narrowing at the transverse sigmoid junctions (**Figures 3A, B, & C**).

Discussion. Our patient presented with headache and right hemiparesis and was diagnosed with CVT based on the cranial MRI and MRV examinations. The conventional risk factors for CVT were investigated, and Lp (a) elevation and IDA were determined to be risk factors for CVT.

The association of isolated IDA with CVT has been reported in case reports of adult patients.[8,9] Three mechanisms have been proposed to explain the association between IDA and thrombosis. First, thrombocytosis secondary to IDA causes thrombosis

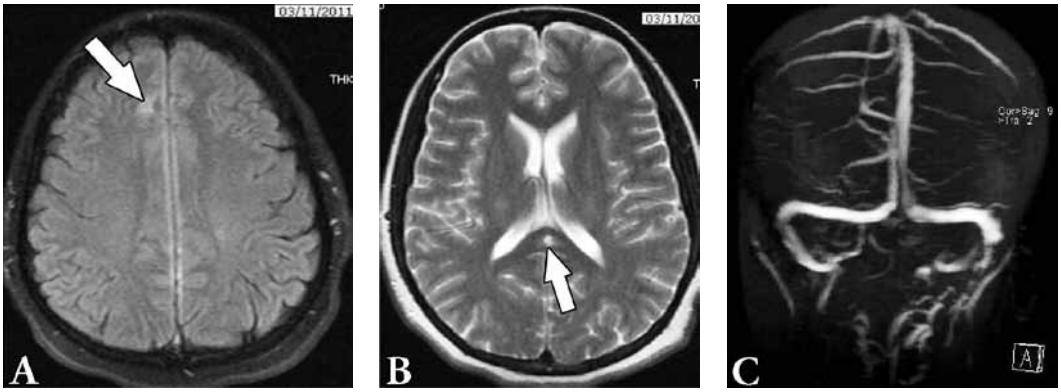

Figure 3 - One month later, the control MRI showed regression of the dural thickening and contrast enhancement and hyperintense lesion axial fluid attenuated inversion recovery (FLAIR) **A)**, and axial T2 **B)**, weighted images **A & B)**. Bilateral narrowing at the transverse sigmoid junctions seen on 3D reconstruction of the MRV resolved after treatment **C)**.

because iron is considered to be a regulator of thrombopoiesis, and normal iron levels are required in order to prevent thrombocytosis by inhibiting thrombopoiesis. Second, iron deficiency results in a hyper-coagulable state. The microcytosis resulting from iron deficiency causes reduced red cell deformability and increased viscosity, which contributes to thrombosis in a negative-pressure environment as found in the veins. Third, anemic hypoxia causes ischemic damage in the area of the brain supplied by the terminal arteries.[8,9] Although the number of platelets in our patient was not increased, microcytic poorly deformable red blood cells increase the viscosity, and may contribute to reduced flow velocity in the veins, and enhance the risk of CVT. Our patient had both IDA and elevated Lp (a). These factors may have synergistic effects in the formation of CVT. Two different risk factors caused CVT, probably due to hyper-coagulable state. In the follow up, the patients' symptoms fully recovered after 3 months. Two months later, a control MRI showed that regression of the dural thickening and contrast enhancement were improved.

The systematic review identified 19 studies on CVT in 2006. The mortality rate during the peri-hospitalization period was 5.6-9.4% at the end of the follow up period. Eighty-eight percent of surviving patients fully recovered or had only mild deficit.[10] The good prognosis of our patient correlated with the literature findings.

Non-visualization of the ISS is said to occur in up to 10% of cases. The distribution of the presumed venous infarct is certainly consistent with the territory drained by the ISS, supporting the interpretation of thrombosis. The brain infarct resolved after anticoagulation. This also suggests that the venous infarct may be due to ISS thrombosis. In addition, the pattern of signal abnormalities was only detected in the ISS and not the rest of the deep sinuses and veins. This resulted in sparing of involvement of the basal ganglia. After Elsherbiny et al[4] reported isolated ISS thrombosis in 1997; Erbas et al[5] reported corpus callosum hematoma secondary to ISS thrombosis in 2006. Literature review revealed no other reports on ISS thrombosis.

In conclusion, there are a few published case reports on adult patients with IDA with sinus thrombosis.[8,9] The association between Lp (a) and CVT in adult patients is a rare occurrence.+ Co-existing IDA and Lp (a) is a risk factor for CVT, and a very rare condition. Our case of CVT associated with IDA and elevated Lp (a) suggests that these abnormalities should be considered as an underlying cause of CVT in adult patients. We were unable to find previous reports on coexisting IDA and Lp (a) in patients with CVT.

Acknowledgments. *We extend our thanks to Dr. Meliha Tan, MD, PhD, from the Department of Neurology, Baskent University Medical School, Adana Teaching and Medical Research Center for advice and support.*

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