

Cerebral venous thrombosis associated with homozygous factor V Leiden mutation in a 15-year-old girl of Tunisian origin

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Cerebral venous thrombosis (CVT) is a rare disease. It has numerous and complex etiologies. Inherited or acquired prothrombotic states play a key role in the development of this disease, such as factor V G1691A mutation (FV Leiden). A 15-year-old girl presented to the Department of Neurology with a complaint of severe headache with visual blurring. The diagnosis of CVT was not initially suspected because of the patient's condition on presentation. An MRI showed thrombosis in the superior sagittal sinus, confirming venous stroke. Anticardiolipin and antiphospholipid antibodies were assessed. In addition, inherited prothrombotic defects, such as protein C, protein S, and antithrombin deficiencies, and genetic mutations for FV Leiden, prothrombin gene G20210A (FII G20210A), and methyltetrahydrofolate reductase C677T (MTHFR C677T) were studied. All results were unremarkable except for the unique homozygous FV Leiden mutation, which likely contributed to this prothrombotic situation. This study highlights the fact that FV Leiden may play a significant role in the onset of CVT in young patients.

Cerebral venous thrombosis (CVT) is often misdiagnosed and is rare compared with stroke that has an arterial cause. It is often encountered in young patients and may occur in children and neonates. Despite the continuous description of new conditions predisposing for CVT, no apparent cause is found in about 12.5% of cases.¹ CVT is usually associated with predisposing factors such as hematologic disorders, gynecologic and obstetric infectious diseases, as well as other medical causes.¹⁻⁴ Recently, thrombophilic defects have been identified as risk factors, including factor V G1691A (FV Leiden [FVL]), the prothrombin G20210A mutation (FII G20210A), and hyperhomocysteinemia caused by gene mutation methyltetrahydrofolate reductase (MTHFR).^{1,5} In the current study, we discuss the case of a young Tunisian female with confirmed CVT caused by a homozygous FVL mutation.

CASE

We investigated the case of a 15-year-old girl from a consanguineous family of south Tunisian origin. She

was admitted to the hospital with a 4-month history of increasing chronic holocranial headache with neither nausea nor vomiting. Headache was nonfrequent and it became nocturnal and continuous for 45 days. This situation was aggravated, leading to visual blurring. After consulting a private ophthalmologist, she was treated with dexamethasone sodium phosphate (ingredient of Unidex in Tunisia) for 3 days without any resolution of her symptoms.

The patient had a previous medical history of paroxysmal hallucinations. She was then treated with haloperidol and venlafaxine (Haldol, Effexor). She was not taking medications such as oral contraceptives and had no previous severe illnesses or surgeries. No pulmonary, urinary, gastrointestinal, or inflammatory disease was present. She did not smoke or travel. In addition, the patient was not aware of any history of cancer, bleeding problems, or thrombotic disease in her family.

On admission, she was conscious, and her blood pressure and temperature were normal. Examination revealed an alert patient with bilateral papilledema. Her visual acuity was reduced, and she was not able

to count fingers. The other cranial nerves and her gag reflex were intact. Her sensory testing was unremarkable. Furthermore, examination of the lungs, heart, and abdomen revealed no significant abnormalities. Blood count, biochemical tests, and simple coagulation tests were done. The following results were obtained: hematocrit, 32.2%; hemoglobin, 13.1 g/dL; white blood cell count, 6500/mm³; platelet count at the time of the diagnosis of this venous thrombosis, 544 000/mm³; prothrombin time, 14.7 s (normal range, 12-15); activated partial thromboplastin time, 38 s (normal range, 26-39); fibrinogen, 260 mg/dL (normal range, 200-400); and random blood sugar, 57 mg/dL (normal, <200). She was not pregnant, and liver function tests, and tests for serum calcium, electrolytes, and urea were unremarkable.

At the last lumbar puncture, the opening pressure was normal. Infectious central nervous system disease and subarachnoid hemorrhage were excluded by cerebrospinal fluid analysis. A computed tomography (CT) scan and magnetic resonance angiography were obtained in the initial hours. In the cranial CT scan, the brain parenchyma was unremarkable, but magnetic resonance imaging with gadolinium revealed a linear filling defect in the superior sagittal sinus (**Figure 1**).

Because of the existence of these cerebral complications, we carried out tests for acquired and inherited thrombophilia. Anticardiolipin and antiphospholipid antibodies were assessed by enzyme-linked immunosorbent assay. The plasma homocysteine level was

measured also by an automated immunoassay method. Analyses of protein S (PS), protein C (PC), antithrombin (AT), and activated protein C resistance (APCr) were carried out. The patient was then immediately treated with heparin at 25×10³ IU. Results from the workup for hypercoagulability for homocysteine, and antiphospholipid and anticardiolipin antibodies were unremarkable except D-dimers of 1227 ng/mL (normal, <500). APCr activity was negative. Her PC, PS, and AT levels were 97%, 84%, and 82%, respectively (normal, 80%-120%). Also, we investigated the association between this idiopathic cerebral vein thrombosis and the three mutations: FVL, FII G20210A, and MTHFR C677T variant using ViennaLab assay (FV-PTH-MTHFR StripAssay; ViennaLab Labordiagnostika GmbH, Vienna, Austria). The polymerase chain reaction products underwent electrophoresis on 3% agar minigels containing ethidium bromide at 120 V for 1 hour. After hybridization, genotyping results for prothrombin G20210A and MTHFR C677T were negative, but the patient was homozygous for the FVL mutation. After treatment with intravenous heparin and a 6-month course of coumarin, CVT resolved completely. At the 3-year follow-up at the Department of Neurology, the patient had no complaints, her neurological examination was unremarkable, and her visual acuity was intact.

DISCUSSION

At admission, the patient presented with four major clinical syndromes: isolated intracranial hypertension, progressive and intensive headaches, papilledema, and loss of visual acuity. Venous thrombosis is a rare and potentially fatal disease, presenting with a wide range of symptoms. The most frequently observed symptoms are headache (74%-89%) and impaired vision caused by papilledema (45%-80%).^{6,7} Because of the rarity of CVT, much of the knowledge about this neurologic disorder has been obtained through case reports, retrospective studies, and a few small prospective studies. Since research on CVT in children and adolescents is limited, extrapolation from adult data was difficult because of age-related differences in hemostatic, vascular, and neurologic systems.⁸

The pathogenesis of CVT in this case is explained by the effects of occlusion of superior sagittal sinus. This conforms with the findings of many studies that have shown that the most frequently thrombosed sinuses involve the lateral, cavernous, and superior sagittal sinuses, unlike the vein of Galen and straight sinus.⁹

The measurement of the D-dimer level has been proven to be useful in the evaluation of suspected ve-



Figure 1. Nuclear magnetic resonance imaging with white arrow showing less blood flow in the superior sagittal sinus indicating thrombosis.

nous thrombosis and pulmonary embolism. Our patient presented with a positive D-dimer level (1227 ng/mL) associated with isolated intracranial hypertension. A recent study concluded that the D-dimer test is helpful in the diagnosis of acute CVT.¹⁰ A value below 500 ng/mL makes acute thrombosis unlikely. The D-dimer level was found to be raised in cases with particular clinical signs such as epilepsy, focal deficits, isolated intracranial hypertension, and encephalopathy. Quantitative D-dimer measurement is useful for diagnosis of deep venous thrombosis, but its utility during CVT remains to be determined.⁶

FVL is the most abundant blood coagulation factor found in plasma, and the normal function of activated FV occurs in the common pathway of coagulation. The single-nucleotide polymorphism resulting in a change of guanine to adenine at 1691 of the factor V gene makes it resistant to activated protein C.¹¹ The frequency of this mutation varies according to ethnicity. In the overall healthy Tunisian population, the prevalence of FVL is only 6%, and in homozygote counts, only 0.5%.¹² To our knowledge, this is the first Tunisian case of homozygous FVL mutation presenting as CVT. The FVL mutation is the most relevant hereditary risk factor for CVT.^{13,14} In addition, patients with the FVL mutation are at an increased risk for recurrent venous thrombosis.¹⁴ Coexisting risk factors are usually involved in the initiation of CVT. A synergistic effect

between homozygous FVL and OC use was found in a 24-year-old white woman.¹⁵ In a Spanish report, a female patient of Syrian origin, CVT was described associated with homozygous FVL and other circumstantial factors: pregnancy and miscarriage.¹⁶ Another case of concomitant mutations of heterozygous FVL and homozygous FII G20210A in a woman with CVT was also presented, in which her status was complicated by additive OC administration.¹⁷ A recent meta-analysis concluded that OC users and in patients with FVL, the FII G20 120A mutation, and hyperhomocysteinemia are at a significantly increased risk of CVT.¹⁸ Our patient's CVT likely resulted only from the homozygous FVL. As a result, this unique risk factor seems to be a sufficient condition to increase the likelihood of this thrombotic event.

In conclusion, we investigated a case of a young female with good recovery of venous stroke who was a carrier of a unique homozygous mutation, FVL. To our knowledge, in the Tunisian population, such a case has never been described before. Such a prothrombotic condition seems to play a significant role in the onset of CVT in young female patients even without predisposing factors such as hematologic disorder, gynecologic and obstetric infectious diseases, as well as other medical causes. The investigation of FVL should be indicated in the diagnosis panel of CVT to maximize a successful outcome.

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