Case report

Cerebral vein thrombosis associated with MTHFR A1289C mutation gene in a young postpartum woman

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Abstract

Cerebral venous thrombosis is a rare cerebrovascular disease that accounts for approximately 1% of strokes, with an incidence of 3-4 cases / million inhabitants per year, with a significant mortality rate of 10-13%. Pregnancy and puerperal period are physiological states that predispose to thrombosis through hypercoagulability due to hormonal change. These alterations occur in blood flow, vascular wall and clotting factors and while superimposed on a genetically predisposing field, create the optimal conditions for the occurrence of embolic phenomena. Here we present the case of a young, secondipara woman with recurrent thrombotic events, even under optimal anticoagulation therapy, where the extensive laboratory investigations identified the predisposing terrain: the heterozygous mutation of the MTHFR A1289C gene.

Keywords: *cerebral venous thrombosis; pregnancy; thrombophilia; MTHFR A1289C*

Introduction

First described in 1825 by French physician Ribes, cerebral venous thrombosis (CVT) is a rare condition, frequently underdiagnosed, with a low incidence of 3-4 cases/million inhabitants/year, but an important mortality rate (10-13%), affecting especially young women, between ages of 20-40 years [1]. Many causative conditions have been described, idiopathic CVT being responsible for approximately 20% of cases [2].

Unfavorable genetic background increases the risk of CVT: antithrombin III deficiency, protein C, protein S, factor V or II mutation, activated protein C resistance, mutations in the methylenetetrahydrofolate reductase (MTHFR) gene. CVT can also occur secondary to conditions or therapies which create a prothrombotic state: inflammatory bowel diseases (Crohn's disease and ulcerative colitis), infections (sinusitis), trauma, nephrotic syndrome, liver cirrhosis, neoplasms, autoimmune diseases (systemic lupus erythematosus, granulomatosis with polyangiitis, Behcet's disease), sarcoidosis, anemia, pregnancy and puerperal period, high altitudes, use of drugs: oral contraceptives, erythropoietin, tamoxifen, corticosteroids, thalidomide, asparaginase [3].

The clinical setting of CVT is polymorphic, most often nonspecific, leading to the delay of diagnosis. The most common symptom is represented by constant or postural headache (70-88%) [4]. Also, they can experience focal neurological deficits (50%), epileptic seizures

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(40%), and behavioral symptoms such as delirium and amnesia [2].

After a detailed history and physical examination, the most useful diagnostic method is imaging. The initial scan can be a non-contrast CT of the head, but in absence of hemorrhage or infarction, signs of CVT on a non-contrast CT are very indiscernible [5]. Also helpful in the evaluation and confirming CVT is MRI. Edema without hemorrhage is often easier detected on MRI than on CT brain (25% versus 8%) [6].

Case report

We present the case of a 29 year-old female patient, who developed during the 17th week of her second pregnancy an episode of superficial thrombophlebitis in the right external saphenous vein and the right popliteal vein, complicated in the 24th week with right ilio-femoral thrombosis, for which treatment with low molecular weight heparin (LMWH) was initiated.

On the 3rd day of postpartum confinement, after the cesarean section on a scarred uterus, and while on LMWH treatment, she developed a sudden motor deficit in the upper left limb, predominantly brachial, left-sided numbness, dizziness and equilibrium disturbance, occipital headache, and transient vision disturbances, so she was transferred to the neurology department. On admission, the patient was anxious, with hemodynamic parameters within normal range. The neurological examination revealed: left hemiparesis, diminished osteotendinous reflexes in left upper limb and slightly exaggerated in the left lower limb, hypoesthesia on left side of body accompanied by mild paresthesia involving the left side of her face and her left arm and leg, gait disturbances. Laboratory findings revealed: RBC = 5x106/mm3, Hemoglobin = 11g/dl, Hematocrit = 32.5%, WBC = 5000/mm3, platelets = 229,000/mm3. Renal and hepatic functions were within normal limits. The electroencephalogram (EEG) and thoracic radiography were normal. Echocardiography showed mitral valve prolapse with mild mitral regurgitation.

The cranial CT scan did not reveal signs of ischemic or hemorrhagic stroke. Cranio-cerebral MRI angiography were ordered, detecting the presence of thrombosis in the right sigmoid sinus and the confluence between the transverse sinus and the superior sagittal sinus without intraparenchymal ischemic signs (Figures 1 and 2).

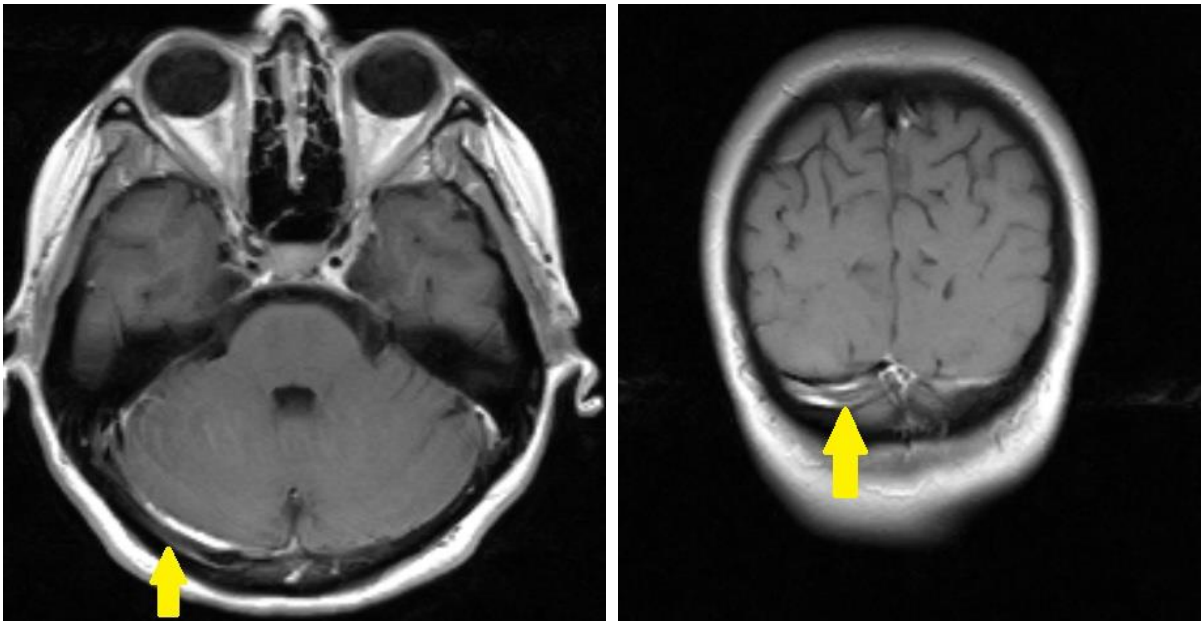

Fig. 1. T1 + Gd sequence (gadolinium), axial section. Yellow arrows demonstrate hyposignal area on the right transverse sinus topography - suggestive of thrombosis

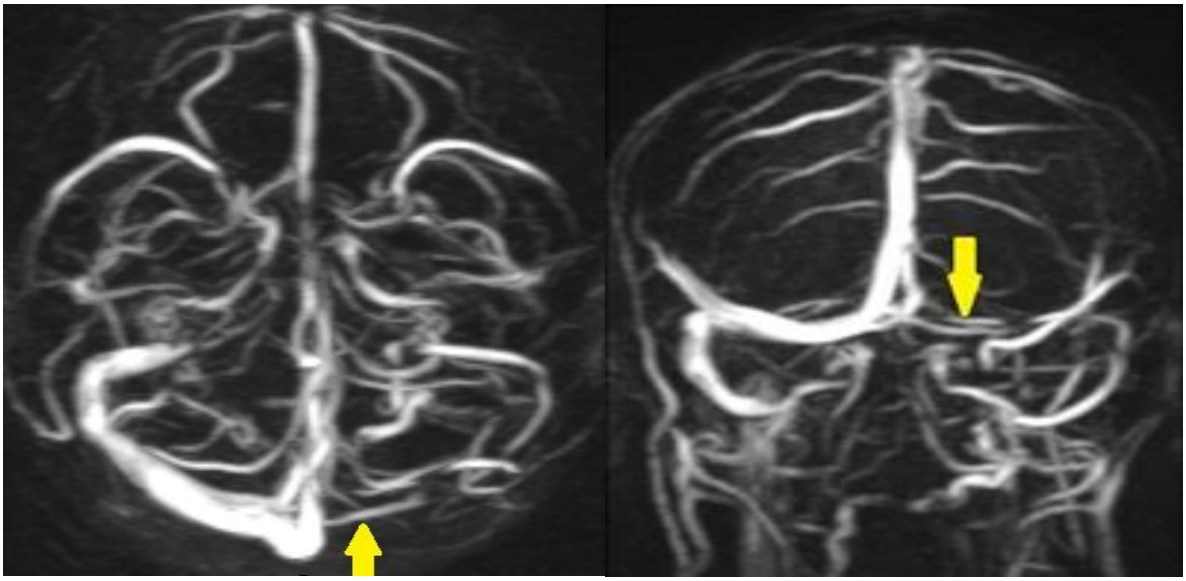

Fig. 2. 3D TOF sequence (RM venography) –Arrows demonstrate the absence of flow at the level of transverse sinus on a distance of 30 mm in the middle third portion, close to the sinus confluence

After administration of anticoagulant, anti-inflammatory and antiedematous therapy, the evolution of the patient was favorable, with improvement of motor deficits in the left limbs and recovery of walking, but with residual paresthesia involving the left upper limb.

An extensive workup was performed after the acute episode in order to determine the etiology of the thrombotic episodes.

Anti-cardiolipin antibodies (IgM/IgG), antithrombin III, as well as the protein C activity were within normal range. No mutations of FII, FV Leiden were identified. The polymorphism of the MTHFR gene was also tested, which revealed the heterozygous mutation of the MTHFR A1289C gene. The MTHFR C677T gene mutation was absent. To evaluate these mutations of MTHFR we performed Real-time PCR (LightCycler), which assumes polymerase chain reaction with real-time detection of the accumulated PCR product by measuring the emitted fluorescence. Oral anticoagulant therapy with vitamin K antagonist (VKA) was the treatment of choice.

Seven months later, under optimal anticoagulant treatment with VKAs (INR= 2.21), the patient's clinical evolution was marked by the sudden onset of a partial limb motor deficit on the left side accompanied by facial asymmetry. This time, the cranial CT scan detected the presence of thrombosis in left lateral sinus and left sigmoid sinus. Under anticoagulant treatment and cerebral trophic agents, the evolution was favorable with full remittance of the motor deficit. After a five month period, the patient was admitted with dyspnea and chest pain, installed 3 days prior to admission, raising the suspicion of pulmonary thromboembolism. At the time of admission, the patient was hemodynamically stable. D-dimers were slightly increased. Thoracic CT scan revealed a parietal thrombus, at approximately 2 mm before the origin of upright lobar artery. Due to the recurrence of the thrombotic events, it was decided to maintain the target INR close to 3. On subsequent follow-ups, under this anticoagulation strategy no recurrent thrombotic events were noted.

Discussions

CVT is a rare neurological condition, frequently affecting women during pregnancy in the peripartum period, with a reported incidence in developed countries of 11.6/100,000 births/year, representing approximately 6-64% of pregnancy related stroke [7,8]. Previous studies cited the hypercoagulability state during pregnancy and

puerperium as the main pathophysiological explanation for pregnancy-related CVT. Additional risk factors are represented by: traumatic delivery, caesarean section, anemia, dehydration, increased homocysteine concentrations, and decreased cerebrospinal fluid pressure due to subdural anesthesia [9].

MTHFR is essential for vitamin B12 metabolism and the polymorphism of its enzyme-encoding gene causes hiperhomocisteinemia, favoring a prothrombotic state. Currently, two types of mutations are described leading to decreased enzyme efficacy in different proportions: C677T and A1298C. Although both mutations are associated with increased homocystein levels, the heterozygous A1298C mutation reduces the enzyme activity to a lesser extent than the C677T mutation. Because of this, most studies were performed on the C677T mutation, and there is clear evidence of its association with cerebral venous thrombotic events. Few data are available for the A1298C mutation [10].

Our case is particular through the etiology of cerebral venous thrombosis represented by the A1298C heterozygous mutation. Due to its rare incidence and clinical polymorphism (sudden onset headache, visual disturbances, focal neurologic deficit, consciousness disorder, and seizures), CVT diagnosis is often delayed. When predisposing conditions and suggestive symptomatology are present, a high index of suspicion is recommended, which can be confirmed via MRI.

CVT treatment is mainly supportive. Endovascular thrombolysis or surgical thrombectomy are reserved for patients with persistent or aggravated symptomatology, despite optimal anticoagulant therapy [11]. There are two phases for the anticoagulant treatment strategy: immediate treatment to prevent subsequent thrombotic events (a risk that may be prolonged for 3 months after the initial event), and secondary prophylaxis [12].

In our patient, the anticoagulant treatment was initiated with LMWH, and continued with VKA (acenocoumarol). In the presence of an important risk factor (MTHFR A1289C mutation) and the recurrence of the CVT, the anticoagulant therapy is recommended for indefinite period of time. There are no clear data or guideline recommendations for new oral anticoagulants for the treatment of acquired thrombophilia [13]. Rivaroxaban, a direct factor Xa inhibitor already approved for acute and long-term treatment of deep vein thrombosis and pulmonary embolism, showed controversial data about the efficacy in patients with inherited thrombophilia [14]. Anticoagulant treatment in cerebral vein thrombosis that occurs during pregnancy consists of administering LMWH during pregnancy, continuing after birth with VKAs [15].

Patients with CVT have low mortality rates, 5.6% in the acute phase and 9.4% after 12 months) [16, 17]. A review of 13 studies comparing CVT patients to the general population highlighted the increased risk of pregnancy-related recurrent thrombosis, while the risk spontaneous miscarriage remained low [18].

A recent meta-analysis showed that long-term predictors of an adverse prognosis for CVT include: central nervous system infections, all types of neoplasms, deep vein thrombosis, intracranial hemorrhage, mental status disorder, age over 37 years and male gender [19].

Conclusion

CVT is a rare clinical entity, encompassing a both polymorphic and often nonspecific symptomatology. Therefore, the diagnosis and proper treatment are often delayed. Even though little is known about the specific role of the MTHFR A1289C mutation in generating a prothrombotic state, our case highlights its contribution in the genesis of thrombotic events. The particularity of the presented case consists in the occurrence of thrombotic events, despite optimal anticoagulant treatment, which led us to upscale the optimal INR values, thus achieving a better outcome. Nevertheless, despite numerous and recurrent episodes of venous thromboembolism, the patient has fully recovered.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Coutinho JM. Cerebral venous thrombosis. *J Thromb Haemost* 2015; 13(Suppl 1):S238-S244.
2. Ferro J, Canhão P, Stam J, Bousser G, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004; 35(3):664-670.
3. McBane D, Tafur A, Wysokinski WE. Acquired and congenital risk factors associated with cerebral venous sinus thrombosis. *Thromb Res* 2010; 126(2):81-87.
4. Thammishetti V, Dharanipragada S, Basu D, AnanthakrisHnan R, Surendiran D. A prospective study of the clinical profile, outcome and evaluation of D-dimer in cerebral venous thrombosis. *J Clin Diagn Res* 2016; 10(6):7-10.
5. Narra R, Kamaraju SK, Pasupaleti B, Juluri N. Case of cerebral venous thrombosis with unusual venous infarcts. *J Clin Diagn Res* 2015; 9(4):TD08-TD10.
6. Leach JL, Fortuna RB, Jones BV, Gaskill-Shipley MF. Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls. *Radiographics* 2006; 26(Suppl 1):S19-S41.
7. Liang ZW, Gao WL, Feng LM. Clinical characteristics and prognosis of cerebral venous thrombosis in Chinese women during pregnancy and puerperium. *Sci Rep* 2017; 7:43866.
8. Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* 2000; 31:1274–1282.
9. Daif A, Awada A, Al-Rajeh S, Abduljabbar M, Al TahanAR, Obeid T. Cerebral venous thrombosis in adults: a study of 40 cases from Saudi Arabia. *Stroke* 1995; 26(7):1193-1195.
10. Friedman G, Goldschmidt N, Friedlander Y, Ben-Yehuda A, Selhub J, et al. Common mutation A1298C in human methylenetetrahydrofolate reductase gene: association with plasma total homocysteine and folate concentrations. *J Nutr* 1999; 129(9):1656-1661.
11. Mathukumalli NL, Susarla RM, Kandadai MR, et al. Intrasinus thrombolysis in cerebral venous sinus thrombosis: Experience from a university hospital, India. *Ann Indian Acad Neurol* 2016; 19:307-311.
12. Key NS, Kasthuri RS. Current treatment of venous thromboembolism. *Arterioscler Thromb Vasc Biol* 2010; 30(3):372-375.
13. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women a statement for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke* 2014; 45:1545-1588.
14. Skelley JW, White CW, Thomason AR: The use of direct oral anticoagulants in inherited thrombophilia. *J Thromb Thrombolysis* 2017; 43(1):24–30.
15. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141(2):e419S-e496S.
16. Gupta R, Aggarwal M, Patil S, Vyas V. Cerebral venous thrombosis associated with pregnancy: a case report. *IOSR JDMS* 2015; 14(5):43-45.
17. Giofrè MC, Napoli F, La Rosa D, et al. Recurrent thrombosis: a case of hereditary thromboembolism. *Am J Case Rep* 2017; 18:1157-1159.
18. Aguiar de Sousa D, Canhao P, Ferro JM. Safety of pregnancy after cerebral venous thrombosis. *Stroke* 2016; 47:713–718.
19. Gala NB, Agarwal N, Barrese J, Gandhi CD, Prestigiacomo CJ. Current endovascular treatment options of dural venous sinus thrombosis: a review of the literature. *J Neurointerv Surg* 2013; 5(1):28-34.