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Original Research

Hereditary thrombophilia in the puerperium: a retrospective review of 11 cases complicated by cerebral venous thrombosis

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Summary

Purpose of Investigation: The purpose of this study was to conduct a multidisciplinary analysis of a 11 cases of cerebral venous thrombosis in the puerperium associated with hereditary thrombophilia. *Materials and Methods:* The medical records of patients with ereditary thrombophilia and cerebral venous thrombosis in the puerperium were reviewed retrospectively. Clinical suspicion of cerebral venous thrombosis had been confirmed by CT or MRI. *Results:* Only in 11 cases the authors found the association between hereditary thrombophilia and cerebral thrombosis. The evaluation of the thrombophilic profile revealed that MTHFR C677T in combination with Factor V Leiden G1691A and Prothrombin G20210A were the commonest gene defects among cases studied. *Conclusion:* Hereditary thrombophilia may increase the risk of cerebral venous thrombosis in the puerperium.

Key words: Thrombophilia; Pregnancy; Cerebral thrombosis; CT; MRI.

Introduction

Thrombophilia, a multigenetic disorder due to either acquired, inherited or to the metabolic coagulation abnormalities, was defined originally as a predisposition to thrombosis, increasing the risk of pregnancy-associated venous thromboembolism [1]. Besides that, the absolute incidence of venous thromboembolism in pregnancy is relatively low (0.49 to 2 cases per 1,000 pregnancies), multiple risk factors often associated with hereditary thrombophilia (deficiencies of protein S, protein C, and antithrombin III, factor V Leiden mutation, mutation in the gene encoding prothrombin, and methylene tetrahydrofolate reductase mutations C677T and A1298) may further increase this risk, and is one of the leading causes of maternal morbidity and mortality [2, 3]. It seems that the relative risk increases further in the puerperium and persists until 12 weeks after delivery, based on endothelial dysfunction, venous stasis and hemostatic changes induced by delivery [4, 5]. In some cases, the manifestation of venous thromboembolism in postpartum period may represent the first sign of an associated thrombophilia [6]. Although cerebral venous thrombosis is a rare complication in pregnancy or in the puerperium (0.5% of all acute strokes) [7], it represents at the same time a severe thrombotic manifestation with a high mortality rate (between 5.5% and 30%, if the patient was not diagnosed and treated in time) [8]. This important thromboembolic complications has the potential to cause severe neurological sequelae, with severe socio-economic impact, and the tendency to recur (between 2.8 % and 11.7 %) [9]. Because clinical presentation of cerebral venous thrombosis in the puerperium is non-specific and variable, with atypical or mild symptoms presentation, it is relatively simple to misdiagnose this acute disease, which frequently delays the real diagnosis in time even when we use plain MRI or CT scan [10, 11]. In this context, the purpose of this study was to conduct a multidisciplinary analysis of a 11 cases of cerebral venous thrombosis in the puerperium associated with hereditary thrombophilia in a tertiary referral maternal and fetal care centre, from clinical presentations, diagnosis, and treatment of this important complication.

Materials and Methods

This study was conducted at the "Cuza Vodă" University Hospital of Iași, Romania, Department of Obstetrics and Gynecology, from January 2012 to December 2017. This important medical unit is a tertiary referral center in obstetrics and gynecology, with approximately 5,400 babies delivered each year, including 1,500 caesarean sections. The medical records of this pregnant women admitted for regular monitoring of pregnancy and delivery were reviewed retrospectively. In this study period, the authors identified pregnant women with known ereditary thrombophilia or later diagnosed during hospitalization in this centre and cerebral venous thrombosis in the puerperium, some of them being sent from other medical centres and hospitalized in this clinic for specialized care of their ongoing high-risk pregnancy. Eligible women were

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Table 1. — *Clinical characteristics and adverse pregnancy outcomes of the study group.*

Patient	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Parity	Smoker	Gross varicose veins	Adverse pregnancy outcomes
1	29	79	167	28.3	2	Yes	Yes	Preterm live birth (33 WG) Fetal loss (2)
2	32	82	158	32.8	1	Yes	No	Embryonic loss (2)
3	36	92	177	29.3	3	No	Yes	HELLP syndrome Eclampsia, fetal loss (3)
4	37	79	162	30.1	1	Yes	No	Fetal loss (2), miscarriage (1)
5	34	69	158	27.6	1	No	No	Fetal loss (1) Embryonic loss (1)
6	27	102	176	32.9	2	No	No	Severe SGA, fetal death (29 WG) Miscarriage (2)
7	35	82	163	30.8	1	No	No	Miscarriage (2)
8	35	71	166	25.7	3	No	Yes	Preterm live birth (32 WG)/PE Fetal loss (2)
9	34	79	156	32.4	1	No	No	Embryonic loss (3)
10	29	92	172	31.1	2	Yes	Yes	Placental abruption (37 WG)/PE Embryonic loss (3)
11	34	90	174	29.7	1	No	No	Fetal loss (1), miscarriage (2)

BMI - body mass index; WG - week of gestation; SGA - small for gestational age; PE - preeclampsia.

identified by the research coordinator and/or the medical staff involved in project. The data on the clinical evolution of the patients and their lab tests were taken from the hospital computerized database of all the deliveries, as well as their observation charts from the present archive. The following general data were collected: age, gravidity, parity and body mass index, duration of pregnancy, history of previous deep vein thrombosis/venous thromboembolism or adverse pregnancy outcome. In the study group, all the women were investigated for the presence of inherited thrombophilia (factor V Leiden mutation, methylene tetrahydrofolate reductase C677T mutation, prothrombin 20210A mutation, homocystein level, protein S and C deficiency, antithrombin III deficiency, and plasminogen activator inhibitor-1 mutation) in two accredited laboratories, according to the standard protocols. These specific tests were performed in the period of time between six months and one year after the end of previous pregnancy or later during hospitalization, and all women included in the study were treated with low-molecular-weight heparins (LMWHs) after being diagnosed with inherited thrombophilia. The LMWH prophylaxis was initiated in the first trimester, after first pregnancy positive test, or from five to 12 weeks of gestation after proven fetal viability. Clinical suspicion of cerebral venous thrombosis in the puerperium after c-section was based on the presence of intracranial hypertension syndrome, focal neurological deficits, seizures, and impaired consciousness. Diagnosis was confirmed after a complete neurologic examination by CT/CT venography or MRI magnetic resonance venography (MRV), at University Emergency Hospital "Prof. Dr. Nicolae Oblu" Iaşi. In this context, the authors recorded the following information: onset of symptoms after birth, the types of symptoms, and aspects of diagnostic imaging such as location of the thrombus and parenchymal lesions (presence of ischemia, hemorrhagic foci). The exclusion criteria were pregnancies with acquired thrombophilias (lupus anticoagulant (LA), anticardiolipin antibodies (aCL), chromosomal abnormalities, severe heart failure, valvular heart disease, or pre-existing cardiac diseases, autoimmune disease, systemic infection, nephrotic syndrome, diabetes, prepregnancy convulsive disease (epilepsy), a history of coma, traumatic brain injury and brain surgery in the past, alcohol or substance abuse, a known cerebrovascular accident and other neurological disorders, or patients with incomplete data. The study was approved by the local ethical committee and conducted in accordance with the Helsinki Declaration. Statistical analysis was performed using SPSS version 17.0 software, and data and were analyzed for frequency by descriptive analysis and expressed as mean ± SD. Categorical variables were expressed as number and percentage (%) of patients.

Results

Between January 2012 and December 2016 in "Cuza Vodă" University Hospital of Iaşi, 30,268 births were assisted. In this births group we identified 862 (2.84 %) patients who had associated inherited thrombophilia and 147 (0.48 %) patients who developed different neurological complications in the puerperium. Among cases with neurological complications after birth, 16 (0.05 %) patients were diagnosed with cerebral thrombosis. Of all these patient, only in 11 (0.03 %) cases the authors found the association between hereditary thrombophilia and cerebral thrombosis and were able to recover the full data for a complete statistical processing. The relevant clinical characteristics and risk profiles of the patients included in the study are shown in Table 1. The average biometrical age in the study group was of 34.2 weeks of gestation (between 32 and 39). Nine mothers gives birth by caesarean at ≥ 32 weeks of gestation for specific pregnancy complications (the most prevalent indication being acute fetal distress) and two had vaginal delivery. Mean age of the patients was 32.9 years and mean body mass index was 30.06 kg/m^2. Also four women had six previous pregnancies, five women had four previous pregnancies, and two women had three previous pregnancies. Regarding pregnancy outcomes in the study group, most common were highlighted fetal loss (after ten weeks' gestation), embryonic loss (between five and ten weeks of gestation) and miscarriage (before 20 weeks of gestation). The evaluation of the

Table 2. — *Distribution of thrombophilic mutations, personal and family history for venous thrombotic events and types of therapy in the study group.*

Patient	Type of thrombophilia	Thrombotic history ST/DVT/VTE*	Family history of thrombosis	Types of anticoagulant (pregnancy)	Therapy (pregnancy)
1	MTHFR C677T/AT III heterozygous	ST	Absent	LMWH Enoxaparin	40 mg/12 h
2	FVL G1691A heterozygous	None	Absent	Low-dose aspirin	75 mg/24 h
3	FVL G1691A heterozygous MTHFR C677T	DVT	Absent	LMWH Enoxaparin	40 mg/12 h
4	Protein C/ MTHFR C677T	ST	Present	LMWH enoxaparin	40 mg/12 h
5	FVL G1691A homozygous MTHFR C677T	None	Absent	LMWH Enoxaparin	40 mg/12 h
6	FVL G1691A homozygous	ST	Present	LMWH enoxaparin	40 mg/day
7	PT G20210A heterozygous PAI-1	DVT	Present	LMWH enoxaparin	40 mg/12 h
8	PT G20210A heterozygous	VTE	Present	None	None
9	Protein S	None	Present	None	None
10	FVL G1691A heterozygous	None	Absent	Low-dose aspirin	75 mg/day
11	Protein S/ MTHFR C6 77T	None	Absent	LMWH enoxaparin	40 mg/12 h

MTHFR - methylenetetrahydrofolate reductase; AT III - antithrombin III; FVL - factor V Leiden; PT – prothrombin; PAI-1 - plasminogen activator inhibitor-1; LMWH - low-molecular-weight heparin; ST - superficial thrombophlebitis; DVT - deep vein thrombosis; VTE - venous thromboembolism.

thrombophilic profile revealed that MTHFR C677T in combination with factor V Leiden G1691A and prothrombin G20210A were the commonest gene defects among cases studied (Table 2). Six patients had previous episodes of superficial or deep venous thrombosis before the current pregnancy and five patients had a family history of thrombosis. In the study group the authors had seven LMWH-treated pregnancies and two with low-dose aspirin. Two patients included in the study were diagnosed with hereditary thrombophilia later after the occurrence of cerebral thrombosis. Cerebral thrombosis in the study group were diagnosed and confirmed within 48 hours after birth. Regarding clinical manifestations associated with cerebral venous thrombosis, the most common symptoms were headache (6/11), papilloedema (4/11), vomiting (3/11), meningeal signs (3/11), hemiparesis (2/11), visual defects (2/11), aphasia (2/11) (Table 3). Thrombosis was more frequent in the area of the transverse sinus/superior sagittal sinus and most common type of parenchymal injury was represented by haemorrhagic infarct (Figure 1).

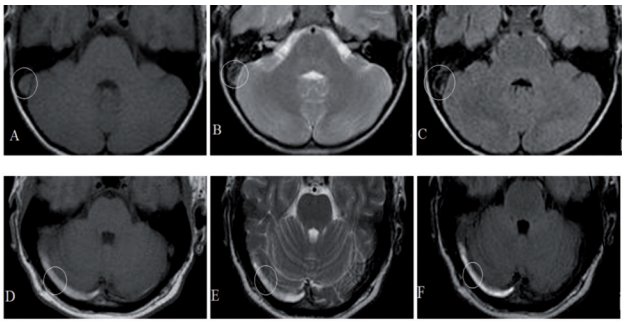

Figure 1. — Axial T1-weighted (A-isointense), axial T2-weighted (B-hypointense) and axial-flare (C) MRI show acute thrombus of transverse sinus. Axial T1-weighted (D-isointense), axial T2-weighted (E-hypointense), and axial-flare (F) MRI show subacute thrombus of transverse sinus at the same patient (no. 7 for Tables 1, 2, and 3).

Discussion

It is well known that hemostasis adaptive changes during pregnancy, attributed mainly to increased levels of estrogen, affects all the elements which it competes: vascular capacity, vascular walls, plasma levels of coagulation factors and fibrinolysis, platelet function, and plasma proteins [12]. The absolute incidence of venous thromboembolism in pregnancy is one or two cases per 1,000 pregnancies, the risk increasing further in the puerperium (from six to 12 weeks after delivery), due to endothelial damage to the pelvic vessels that occurs during delivery. It is important to note at the same time, approximately 80% of postpartum thromboembolic events occur in the first three weeks after delivery [13, 14]. There is a four- to ten-fold increased thrombotic risk throughout gestation and the postpartum period, being also amplified by changes of specific coagulation factors (factors VII, X, VIII, fibrinogen, von Willebrand factor - an increase in prothrombin fragment 1+2 and thrombin-antithrombin complexes, protein S, and tissue plasminogen activator are reduced), the existence of risk factors characteristics to pregnancy (endothelial damage by stasis, vasodilation by increasing nitric oxide, and prostacyclin production, and timing and way of birth), to which may be added at times congenital thrombophilic status. Pregnant women with inherited thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or in the postpartum period [15, 16]. In

Table 3. — *Distribution of types and site of lesions with clinical features in the study group.*

Patient	Clinical features	Confirmed diagnosis	Types of lesions	Site of lesion
1	Headache, vomiting	Within 48 hours	Infarct without haemorrhage	Sigmoid sinus
2	Headache, vomiting	Within 48 hours	Infarct without haemorrhage	Superior sagittal sinus
3	Hemiparesis, headache	Within 24 hours	Haemorrhagic infarct	Transverse sinus
4	Aphasia, visual defects	Within 24 hours	Haemorrhagic infarct	Transverse sinus
5	Headache, papilloedema	Within 48 hours	Infarct without haemorrhage	Superior sagittal sinus
6	Meningeal signs, papilloedema	Within 24 hours	Haemorrhagic infarct	Transverse sinus
7	Headache, papilloedema	Within 48 hours	Infarct without haemorrhage	Transverse sinus
8	Meningeal signs, aphasia	Within 24 hours	Haemorrhagic infarct	Transverse sinus
9	Headache, vomiting	Within 48 hours	Infarct without haemorrhage	Superior sagittal sinus
10	Hemiparesis, visual defects	Within 24 hours	Haemorrhagic infarct	Transverse sinus
11	Meningeal signs, papilloedema	Within 24 hours	Haemorrhagic infarct	Transverse sinus

general cerebral venous thrombosis is more prevalent in women, and is a uncommon neurologic disorder with uncharacteristic symptoms in puerperium, which frequently leads to underdiagnosis or misdiagnosis that can increase the risk of severe complications, including hemorrhagic stroke or death [17]. True frequency of occurrence of cerebral venous thrombosis is unknown, but it is responsible for 0.5% of all strokes and its annual incidence is estimated to be three to four cases per one million population [18]. The issue of cerebral thrombosis is controversial, because there is no systematic studies to show the frequency of the disease in the puerperium. In the present case, all over the five-year study period, the authors identified 16 cases of cerebral venous thrombosis (0.05 %). In the pathogenesis of the disease, risk factors incriminated are represented by pregnancy, postpartum period, oral hormonal contraceptives, hormone replacement therapy, dehydration, trauma, essential thrombocytosis, thrombophilia, or other hypercoagulability syndromes (antithrombin III, protein S and protein C deficiency, factor V Leiden, polycythemia), collagenoses, paraneoplastic syndromes and neoplasms, as well as systemic and local inflammatory states [18, 19]. In the present study the authors had multiple risk factors that have coexisted in women in whom venous thromboembolism develops in postpartum period, from 16 patients with cerebral thrombosis, 11 patients being diagnosed with hereditary thrombophilia. Hereditary thrombophilias, a genetic deletion or alteration of a functional protein in the coagulation cascade is associated with an increased risk of venous thromboembolism in pregnancy and postpartum period, inducing a hypercoagulable state via direct or indirect augmentation of prothrombin to thrombin and its active clot-inducing form [19]. The prevalence of hereditary thrombophilia in general population varies from 0.2%-0.4% for protein C deficiency, 0.2% for protein S deficiency, 0.02% for AT III deficiency, and 4-5% for FVL [20, 21]. There is a large variability in published studies regarding the association between inherited thrombophilia and adverse pregnancy outcomes. All 11 patients with hereditary thrombophilia and cerebral thrombosis had a history of pregnancy outcomes, such as pregnancy loss and placenta-mediated complications: pre-eclampsia/eclampsia, HELLP syndrome, intrauterine fetal death, small-for-gestational-age, and placental abruption. Also, most of these patients (6/11) had a history of venous thromboembolism. Nine patients from the present study received thromboprophylaxis during pregnancy (seven with enoxaparin and two with aspirin), according to different protocols, considering also the classification of hereditary thrombophilia in: low-risk thrombophilia (FV Leiden heterozygous, prothrombin G20210A heterozygous, protein C or protein S) and high-risk thrombophilia (AT deficiency, double heterozygous for prothrombin G20210A and FV Leiden, FV Leiden homozygous or prothrombin G20210A homozygous). In the case of patients who gave birth by C-section, heparin doses were adjusted due to the additional risk of thrombosis due to surgery. In general the need for prophylaxis is based on the risk of thrombosis associated with the thrombophilia, the personal or family history of VTE, and if the previous VTE was due to a transient risk factor or an idiopathic event. LMWH is the recommended drug for antithrombotic prophylaxis in pregnancy, but the most important problem is represented by the fact that the most suitable scheme of dosing has not been established, including the duration of treatment, and the possibility of dose reduction after initial treatment. Also the value of monitoring LMWH activity (anti–factor Xa activity) it was not well-determined [22, 23]. In the present study, in the case of 11 patients with thrombophilia, thromboprophylaxis could not prevent thromboembolism, which reinforces the idea that cerebral venous thrombosis in pregnancy has a multifactorial etiology and partially unknown. In this situation resistance to heparin could be also considered, caused by antithrombin deficiency, increased heparin clearance, heparin binding proteins or levels of factor VIII / fibrinogen. Patients with heparin resistance have a reduction in the formation of heparin-antithrombin complexes and require higher heparin doses to reach a therapeutic aPTT, but these situations are difficult to diagnose and manage [24]. In the case of aspirin, also use in the present study, the role in the management of thrombophilia, remains controversial compare to heparin in thromboprophylaxis. The present authors could not es-

tablish a correlation between cerebral injuries and a specific mutation associated with hereditary thrombophilia, although few studies have shown some correlation between CVT and Protein C (APC) resistance (caused by the F V Leiden mutation), prothrombin G20210A gene mutation, deficiency of Protein S (PS), or heparin cofactor II [22, 24). Another risk factor associated with thromboembolism in postpartum period, besides smoking, is a high BMI. BMI over 30 kg/m^2, which was highlighted in the present study, increases the risk for VTE 1.5−5.3-fold [25, 26]. Obesity is associated with alteration of local/systemic vascular and endothelial functions, and with a prothrombotic state with plasma concentrations of prothrombotic factors including von Willebrand factor, fibrinogen, and factor VII [27]. It is also important to consider as a risk factor for cerebral venous thrombosis, cesarean delivery, which is associated with an increased risk of thromboembolism (the prevalence of clinically significant VTE is 0.9%), especially if it was performed urgently during labor or was associated with other factors such as postpartum hemorrhage, preeclampsia with fetal growth restriction, thrombophilia, and postpartum infection [28]. Clinical presentation of CVT depends on several factors, including location of the thrombosis, the presence of venous infarction or hemorrhage, patient's age, and duration of CVT (acute *vs.* chronic) [29].

The most common symptom initially identified in the patients from our group with cerebral venous thrombosis was headache, which is consistent with current studies. This symptom found in over 90% of cases, is highly unspecific and very often causes delay in diagnosis or diagnostic errors. However it must be mentioned that headache in combination with isolated intracranial hypertension (diplopia, visual impairment/papilloedema, decreased level of consciousness or sixth-nerve palsy), focal neurologic deficit (motor weakness, sensory deficit, aphasia), encephalopathy, and seizures (accompanied or not by a focal neurologic deficit) may suggest the presence of a venous cerebral infarction [30, 31]. The present authors could not establish a correlation between imaging lesion and some specific symptoms. Neuroimaging should not be omitted in the management algorithm of patients with headache complaint postpartum [32]. MRI/MRV is the best method for the diagnosis and follow-up of CVT, although in some cases MRI may still be normal [33]. When the authors suspected CVT, confirming the diagnosis was made by non-contrast or contrast CT (intracerebral hemorrhages/ hemorrhagic infarction/ delta sign thrombosis of the posterior portion of the superior sagittal sinus or transverse sinus) or with MRI (T2 hypointensity suggestive of a thrombus, a central isodense lesion in a venous sinus with surrounding enhancement/visualization of the thrombus in T1-weighted images or loss of signal in the venous system - MRV). In general the most commonly affected venous sinus in CVT is the superior sagittal (62%), followed by the transverse sinus (41% to 45%) [34, 35], which is consistent with lesions highlighted in the present study. It is important to note that a decreased chance of parenchymal damage could occur with a slower rate of occlusion, caused by the increased time available for collaterals to form, therefore although a plain CT or MRI is useful in the initial evaluation of patients with suspected CVT, a negative plain CT or MRI does not rule out CVT, and a venographic study should be performed later [36, 37].

Conclusion

Cerebral venous thrombosis although rare in pregnancy disease, is one of the major and increasing causes of materal morbidity and mortality in postpartum period, this condition necessitated a proper diagnosis and multidisciplinary management. Therefore, it is important to understanding the transient and chronic favoring factors, including hereditary thrombophilia, which may increase the risk of cerebral venous thrombosis and other pregnancy-related VTE events. In this context, neuroimaging examinations should be performed timely to ensure an correct diagnosis and to initiate appropriate treatment.

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