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Thrombosis of sinus sagitalis during puerperium caused by thrombophilic gene mutation

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Abstract	Cerebral veno-sinus thrombosis (CVT) during puerperium may have fatal consequences. A nonspecific clinical picture must be complete with computed tomography of the brain and digital substract angiography of the brain blood vessels, and, once the clinical diagnosis is confirmed, coagulation tests and genetic analysis of the coagulation factor are to be made as well. Genetic polymorphisms associated with thrombophilia such as factor V Leiden, prothrombin G20210A, MTHFR C677T, ACE and PIA1/A2 may be the cause of the hypercoagulability that results in CVT.	
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Thrombosis of sinus sagitalis during puerperium caused by thrombophilic gene mutation

Marina Titlic · Sanda Pavelin · Ante Tonkic · Ivana Jukic · Ante Buca · Simun Andelinovic

Abstract Cerebral veno-sinus thrombosis (CVT) during puerperium may have fatal consequences. A nonspecific clinical picture must be complete with computed tomography of the brain and digital substract angiography of the brain blood vessels, and, once the clinical diagnosis is confirmed, coagulation tests and genetic analysis of the coagulation factor are to be made as well. Genetic polymorphisms associated with thrombophilia such as factor V Leiden, prothrombin G20210A, MTHFR C677T, ACE and PIA1/A2 may be the cause of the hypercoagulability that results in CVT.

Keywords Headache · Thrombosis · Sinus sagitalis superior · Gene · PCR

Background

Puerperal cerebral veno-sinus thrombosis (CVT) occurring during puerperium is a common form of stroke in young women associated with high mortality and morbidity. The etiology of this condition is unclear. The risk associated with the established thrombophilic risk factors is insignificant [1, 2]. Symptoms include headache, seizures, incresased intracranial pressure in the form of papilloedema, neurologic deficits, and atlered consciousness [3–5]. As the clinical findings were found to be nonspecific, computed tomography (CT), magnetic resonance imaging (MRI) and digital substract angiography (DSA) turns out to be valuable for the early diagnosis (CVT) [6, 7]. Enviromental risk factors of thrombosis are sex, age, hypertension, heart and vessel disease, diabetes mellitus, hyperlipidaemia, smoking, alcoholism, obesity and stress. Secondary hypercoagulabile (trauma, malignous diseases, puerperium, etc.) conditions may cause the thromboembolic disease. Thrombosis is a multifactorial disease in which genetic factors play an important role. Our aim was to study the role of the common genetic polymorphisms associated with thrombophilia such as factor V Leiden, prothrombin G20210A and methylene tetrahydrofolate reductase (MTHFR) C677T, angiotensin-converting enzyme (ACE), plasminogen activator inhibitor (PIA1/A2) gene in aseptic puerperal CVT [2, 8–11].

Case report

A 29-year old female gave birth without any special complications during the delivery or puerperium. The patient has no thrombotic history. Her uncle had a deep venous thrombosis in his right leg when he was 59. On the twenty-sixth day of the puerperium, that is, three days before hospitalization she complained about a headache, which gradually worsened. On admission the patient was soporific and optic nerve papillae had unsharp edges

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Journal : 11239 | Dispatch : 5-6-2007 | Pages : 3
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bilaterally, and computed tomography (CT) of the brain was indicated the presence of hypodensity lesions, intensity being 23 HU bilaterally in the thalamus region that would clinically correspond to embolic ischemic lesions. Compressive effect of the described changes on the surrounding structures was also noticed, followed with mild widening of the right temporal horn. After antiedemic therapy (20% mannitol solution) the patient's state only temporarily improved, but the patient still felt somnolent. Soon the state of mind progressively deteriorated until it reached deep coma (GCS was 3). Neurological deficit gradually advanced to a left-sided hemiplegia. Ten hours after the first CT of the brain, another one was obtained showing extensive hypodensity of the temporal region, more thalamic, with cerebral edema and consecutive sulcus 'deletion' of both cerebral hemispheres, Fig. 1.

Due to the billateral ishaemic changes in the thalamus and the brain tissue oedema, we assumed this was a case of thrombosis of the sagital sinus. A DSA was therefore made, which confirmed thrombosis of the sinus sagitalis. A low-molecular heparine therapy was introduced. We also introduced antioedematous therapy by hyperventilation (machine breadhing) and antioedemic therapy (20% mannitol solution). Gradually, over several days, the state of mind and the neurological deficit improved to somnolency and left-sided hemiparesis. Following further four weeks of improvements, there remained only a milder left-sided hemiparesis, 1/5, and the state of mind normalised. In the course of examinations, there were performed a comprehensive internist-neurological diagnostic testing; fibrinogen and d-dimers showed increased values. Additional gene analysis of the coagulation factor was made as well.

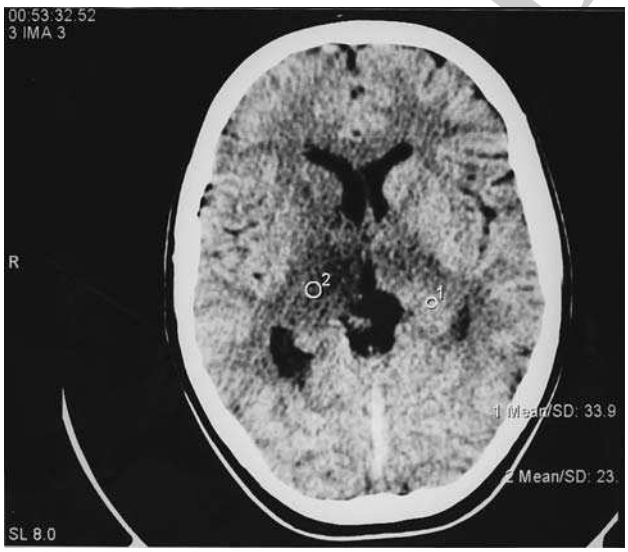

Fig. 1 CT of the brain-cerebral edema and sulcus 'deletion' of both cerebral hemispheres

Genetic polymorphisms associated with thrombophilia such as factor V Leiden, prothrombin G20210A, MTHFR C677T, ACE and PIA1/A2 were tested. Polymerase chain reaction (PCR)/restriction fragment length polymorphism analysis was used to identify her genotipes. There was established normal gene for the factor V Leiden, prothrombin G20210A i PIA1/A2 gene, but also mutation of the MTHFR gene and ACE gene I/D.

Permanent anticoagulation therapy with varfarine, with regular coagulation parameters control, was included. The patient recovered and three months later her neurological status is absolutely normal.

Comments

Puerperal CVT is less frequent than arterial thrombosis, present in an atypical fashion, and is an uncommon cause of stroke. Nonspecific symptoms of CVT include headache, seizures, neurologic deficits, and altered consciousness [4], as in our patient's case.

The diagnosis of CVT was strongly suggested by the CT scan, which showed spontaneous high density in the deep venous system associated with bilateral hypodensities in the thalamus, as described by other authors [12]. DSA finally confirms CVT with certainty. Authors state that a final diagnosis is also possible with MRI angiography [12]. Etiologies and risk factors included local causes, infection, cancer, postpartum state, coagulopathies, oral contraception and remained unknown [13]. CVT, like other thromboses, is caused by multiple factors. Standard clinical risk factors (hypertensia, diabetes mellitus, hypelipidaemia, smoking, alcoholism, obesity, stress) did not present in our patient. Secondary hypercoagulability, puerperium, makes an additional risk element for thrombosis, therefore for CVT as well. Coagulation tests had increased values. We wondered why a previously healty person had this dramatic and grave picture of CVT in puerperium, with a significant state of mind disorder, to coma and grave neurological deficite. Was there a genetic predisposition to developing the hyperkoagulability!? Researches of other authors contradict, and include researches of the gene polymorphism in patients with ischemic stroke, only a few researches assess influence of particular gene polymorphisms to CVT occurence [8–11, 14, 15]. In the large series of CVT patients, a positive association with established thrombophilic risk factor, factor V Leiden, and especially the prothrombin G20210A mutation was confirmed [8]. Persons with PIA1/A2, MTHFR C677T, and ACE ID/DD genotypes had an elevated incidence of ischemic stroke [14, 15]. Researches of gene polymorphism in CVT are insufficient. In the case of our patient,

Journal : 11239 | Dispatch : 5-6-2007 | Pages : 3
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gene analysis of the basic coagulation factors was made. Polymerase chain reaction (PCR)/restriction fragment length polymorphism analysis was used to identify her genotipes. There was established normal gene for the factor V Leiden, prothrombin G20210A and PIA1/A2 gene, but also mutation of the MTHFR gene and ACE gene I/D. Since there were no other thrombophilia risk factors, this indicates that the base for developing of hypercoagulability, and therefore of CVT, was a gene mutation. Therefore, the anticoagulation therapy was introduced.

With the general population the risk of recurrence of CVT is low, particularly after the first 12 months of the first episode but young women with a history of ischemic stroke have a increased risk for recurrence stroke in the postpartum period [16, 17]. The risk of recurrence for CVT during pregnancy seems to be low [18]. However, we do not know the risk of recurrence CVT in the course of puerperium in young women with thrombophilic gene mutation; factor V Leiden, prothrombin G20210A, PIA1/A2 gene, MTHFR and ACE gene I/D, which issue should make subject matter of future research.

Conclusions

Puerperal CVT is rare but may have fatal consequences. Nonspecific clinical signs demand further neuroradiological diagnostics. Deep cerebral internal venous thrombosis was suspected based on the CT scan showing bilateral hypodensity in the thalamus. DSA of the brain blood vessels confirmed the final diagnosis of CVT. Causes of this hypercoagulability should be additionally researched by genetic testing of the coagulation factors. Besides the factor V Leiden, protrombine G20210A mutation, attention should certainly be also paid to MTHFR C677D and ACE I/D gene mutations.

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