Original Article

Low levels of tissue factor pathway inhibitor increase the risk of cerebral venous thrombosis

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Abstract

Background: Decreased concentration of tissue factor pathway inhibitor (TFPI) is a risk factor for development of deep venous thrombosis and coronary heart disease, but there is no evidence for the relationship between TFPI and cerebral venous and sinus thrombosis (CVST). The aim of this study was to determine the level of TFPI in healthy population and in patients with CVST.

Materials and Methods: We determined the plasma level of TFPI in 20 patients with CVST (cases) and 31 healthy volunteer subjects (as control group) by enzyme linked immunoassay method. We also examined the association between TFPI and the risk of CVST. Continuous variables were compared between groups using Student's *t* test, and odds ratio was calculated by multiple logistic regression analysis.

Results: The mean TFPI was significantly lower in the CVST group compared with the control group (8.60 ± 4.05 ng/mL; 14.6 ± 8.6 ng/mL; $P = 0.005$), respectively. The odds ratio for CVST associated with low (<25th percentile) levels of TFPI was 5.429 (95% CI, 1.487-19.82, $P = 0.012$).

Conclusion: Our investigation demonstrates that reduced TFPI may be one of the risk factors of CVST and associated with increasing the risk of developing CVST.

Key Words: Cerebral venous, sinus thrombosis, tissue factor pathway inhibitor

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare and serious disorder in children and middle-aged adults recognized by clotting of blood in cerebral venous or dural sinuses.[1,2] Some coagulopathies have been reported with CVST.[3,4]

The risk factors for CVST are tumors, cerebral infections or trauma, oral contraceptive use, pregnancy and the peripartum period, and thrombophilia.[4]

Thrombophilia is an abnormality of blood coagulation as patients having a high risk for thrombosis, which can be either inherited or acquired.[5]

In our previous study in a CVST patient, we found that Factor VIII is associated with increased risk for

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developing CVST and this effect is independent of von Willebrand factor levels.[3]

However, in some patients of CVST, no underlying genetic or acquired risk factor can be found.[6] Indeed, the balance of procoagulant and anticoagulant factors is important for net thrombin generation and potentially for a prothrombotic phenotype.[6]

Recently, it has been shown that tissue factor pathway inhibitor (TFPI) is a critical inhibitor to modulate tissue factor-induced coagulation.[7] TFPI is a single-chain polypeptide, which inhibits Factor Xa and Thrombin (Factor IIa). After inhibiting Xa, the Xa-TFPI complex inhibits the Factor VIIa-tissue factor complex.[8]

The major part of plasma TFPI is bound to lipoproteins.[9] TFPI is produced by microvascular endothelial cells. Previous studies showed that the concentration of TFPI is elevated in inflammation and tissue injury such as disseminated intravascular coagulation and acute myocardial infarction, and it is considered as a marker for endothelial cell injuries.[10]

Decreased concentration of TFPI is a risk factor for the development of deep venous thrombosis and coronary heart disease.[11] But, there is no evidence for the relationship between TFPI and CVST. In this study, we aimed to investigate the role of TFPI as a risk factor for CVST in the patient without protein c and S deficiency. We hypothesized that low levels of TFPI may be a risk factor for CVST.

MATERIALS AND METHODS

The population consisted of 20 patients hospitalized in Alzahra Hospital, Isfahan, Iran, from 2007 to 2010 with diagnosis of CVST confirmed by magnetic resonance imaging (MRI) with and without contrast, MR venography, or plain and contrast computed tomography (CT) scan. All patients are older than 18 years and younger than 62 years. No patient had protein c and S deficiency. Thirty-one controls were matched with patients in gender, age, and ethnicity.

All demographic data including age, gender, smoking history, body mass index, drug history, family history of CVST, coagulation disorders, head trauma, neurosurgery operation, inflammatory disease, hyperthyroidism disease, rheumatoid disease, dehydration, past history of other disease, and traditional risk factor such as hypertension, ischemic heart disease, myocardial infarction, and hyperlipidemia were recorded. Sign, symptoms, and prognosis according to Modify Rankin Scale (MRS), sinus and venous involvement, and venous infarct in MRI and CT scan were recorded. In addition, all patients had thrombotic workup for protein S resistance and we excluded all patients with protein S deficiency.

We excluded all control groups with a history of coagulation disorders, sepsis, inflammatory diseases, hyperthyroidism disease, rheumatoid disease, ischemic heart disease, myocardial infarction.

Informed written consent was obtained from all patients and controls. The subjects were excluded from investigation by refusing from participating in the study.

TFPI were measured by FREE TFPI Asseracrom Enzyme Linked ImmunoAssay kit from Diagnostica STAGO, Paris, France, according to manufacturer's instruction.

In brief, full-length TFPI were measured by ELISA using a capturing antibody directed against the C-terminus and a horse-radish peroxidase (HRP)-conjugated detecting antibody directed against the second Kunitz domain of TFPI. Finally, TFPI levels were determined by measuring solution absorbances at 450 nm and comparing the values with those of standard curve.

The data were analyzed by SPSS for Windows version 14. Levels of TFPI were determined in patient and control groups and they were compared by using the Student's *t* test. In addition, we investigated whether a low level of TFPI is a risk factor for CVT by calculating the odds ratio (OR) by multiple logistic regression analysis. Low levels of TFPI were arbitrarily defined as levels at or below the 25th percentiles in the control group.

RESULTS

The study population consisted of 20 patients (15 women and 5 men) with a median age of 35.65 years (range 18-62) [Table 1].

The mean TFPI was significantly lower in the CVST group compare to control group respectively (8.60 ± 4.05 ng/mL; 14.6± 8.6 ng/mL; P = 0. 005).

Table 1: Basic characteristics of the studied and control subjects

Factors	Patients	Control	*P* value
Age	41.7	35.6	NS
Male/female	5M/15F	11M/20F	NS
TFPI (ng/mL)	8.60±4.05	14.6±8.6	0.005

NS: None significant; TFPI: Tissue factor pathway inhibitor

Headache was the more frequent first symptom: 16 patients (80%) presented with headache, 1 patient (5%) presented with seizure and 3 patients (15%) presented with paresis [Table 2].

In 2 patients lateral sinus (10%), in 6 patient sagittal sinus(30%), in 1 patients lateral and sagittal sinus (5%), in 2 patients lateral, sagittal and deep sinus (10%), in 1 patient transvers sinus (5%) and in 4 patients lateral, sagittal and transverse sinus (20%) were involved in their MRI and CT scan. There was 4 missing data (20%) [Table 2].

2 patient had migraine (10%) and 5 patient had history of trauma (car accident, falling, injury in war) more than 2 years before participating in this investigation.

No patient had sequel such as hemiparesis, weakness and coma.

The mean TFPI was significantly lower in the CVST group compare to control group respectively [Table 1].

The differences between the level of TFPI was not significant in male and female in both case and control group. There was no correlation between age and TFPI level.

The OR for CVST associated with low (<25th percentile) levels of TFPI was 5.429 (95% CI, 1.487-19.82, $P = 0.012$).

DISCUSSION

Previous case-control studies have shown that reduced concentration of TFPI is a risk factor for development of DVT[12,13] and heart disease,[14] but study with involvement in CVST is lacking. In our study, we focused on patients with CVST. Other studies have observed that the decreased plasma concentration of TFPI is related to deep venous thrombosis and heart disease.[11] In our study, we demonstrate that the plasma level of TPIF was significantly decreased in patients with cerebral sinus and venous thrombosis when compared with the healthy control group. None of our patient and controls using oral contraceptive pills (OCP) during blood collection, pervious study demonstrates the reduced plasma level of TFPI in women receiving OCP or hormone replacement therapy (HRT).[15] Many investigations found the relationship between HRT, estrogen, and progesterone and decreasing the level of TFPI in humans[16,17] and animal subjects[18]; on the other hand CVST is more common in women[19] and but we did not find the significant differences for TFPI between our male and female subjects. We could not find any correlation between age and TFPI level.

Protein S is sanitized in liver,[20] which acts as a cofactor for TFPI in the formation of FXa-TFPI[21,22] complex for inhibiting Factor VIIa-tissue factor complex.[6,23] The decreased level of TFPI is observed in patients with protein S deficiency because of circulating the protein S and TFPI complex in plasma.[24]

In our study, we tried to reduce the effect of protein S on the plasma level of TFPI by excluding the patients with protein S deficiency thereby our result is better stimulation of relationship between TFPI and CVST.

We acknowledge that the number of patients with CVST in our study is rather small because of rare condition of disease. However, we found decreased level of TFPI in CVST patients. For future research we suggest to perform this study in collaborating of multihospitals and multicities.

Furthermore, because pervious study showed differences between TFPI in acute and chronic phase of DVT,[25] we also suggest to determine the level of TFPI in acute and chronic phase of CVST.

Table 2: Frequencies of sign and symptoms in CVST patients

First symptom	Frequency (%)
Headache	16 Patients (80)
Seizure	1 Patient (5)
Paresis	3 Patients (15)
Sinus were involved in their MRI and CT scan	Lateral sinus: 2 patients (10), sagittal sinus: 6 patient (30), lateral and sagittal sinus: 1 patient (5), lateral, sagittal and deep sinus: 2 patients (10), transverse sinus: 1 patient (5), lateral, sagittal and transverse sinus: 4 patients (20), and 4 missing data (20)
Risk factors	
NO risk factor	14
Fat	1 (body mass index >25)
HLP and DM	1
HTN and DM	1
Smoking, HLP and DM	1

NS: None significant; HLP: Hyperlipidemia; DM: Diabetes mellitus; HTN: Hypertension.

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