Hypercoagulation in Chronic Post-Traumatic Stress Disorder

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ABSTRACT: **Background:** Whereas procoagulation abnormalities in acute stress are well established, little is known about the mechanism of hypercoagulation in chronic stress, such as post-traumatic stress disorder (PTSD). This is crucial, given the fact that chronic coagulation disturbances have been associated with increased morbidity and premature mortality due to thromboembolism and cardiovascular disorders, complications recently described in PTSD patients.

Objectives: To explore the mechanisms of hypercoagulation in chronic PTSD.

Methods: Thirty patients diagnosed with chronic PTSD were enrolled and compared with a control group matched for age, gender and ethnicity. Hypercoagulation state was evaluated by levels of fibrinogen, D-dimer, prothrombin fragment F 1+2, von Willebrand factor (vWF) antigen, factor VIII activity, activated protein C resistance, ProC Global assay, and tissue factor antigen. Psychiatric evaluation was performed using the Mini-International Neuropsychiatric Interview and Clinician Administered PTSD Scale (CAPS).

Results: vWF antigen levels were significantly higher in patients with chronic PTSD compared with the controls (121.3 ± 42 vs. 99.7 ± 23, respectively, $P = 0.034$). Higher levels of vWF antigen and factor VIII activity were found in patients with severe chronic PTSD (CAPS › 80), compared to controls and patients with chronic PTSD and less severe symptoms (CAPS ≤ 80). However, no differences were observed in any other studied coagulation parameters between patients and controls.

Conclusions: Increased levels of vWF antigen and factor VIII activity were documented in severe chronic PTSD. These findings suggest that the higher risk of arterial and venous thromboembolic events in PTSD patients could be related to endothelial damage or endothelial activation.

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KEY WORDS: chronic post-traumatic stress disorder (PTSD), hypercoagulation, von Willebrand factor, factor VIII, thromboembolic events

Acute stress has been extensively studied and is known to correlate with procoagulant changes such as increased levels of fibrinogen, clotting factors VII, VIII, XII and von Willebrand factor [1], especially in the elderly. However, the data on chronic psychological stress and coagulation are still contradictory. This information is particularly important, since chronic stress diseases, such as post-traumatic stress disorder, may affect 8% of the population [2] and persist for a lifetime in the vast majority of cases. PTSD was recently described as a concurrent psychiatric and somatic disorder [3], given the common cardiovascular complication, which could be partially explained by possible coagulation disturbances. PTSD may develop as a result of life-threatening traumatic events and is diagnosed by the presence of three clusters of symptoms: re-experiencing, avoidance, and hyperarousal for at least 1 month [2]. In acute PTSD the duration of symptoms is limited to 3 months; after this period it is considered to be chronic [2]. In a recent study, PTSD-like symptoms were found in approximately 10% of Israelis exposed to a long wave of terrorist attacks in 2002 [4]. Chronic PTSD has been associated with poor physical health [5] and premature mortality due to venous and arterial thromboembolism, even when depression is controlled [3,6]. In PTSD, biological factors such as lower cortisol levels, increased sympathetic activity [7] and resting mean blood pressure [8] have been shown to be related to a hypercoagulable state, reflected by an increased amount of procoagulant molecules, providing a plausible biopsychological link to coronary artery disease [9]. Patients with PTSD develop a low grade systemic inflammatory state [10], suggesting a mechanism that could contribute to coronary heart disease. The mediators of this mechanism could be stress hormones (norepinephrine) producing a cascade of inflammatory reactions (interleukin 6, IL-1, C-reactive protein, tumor necrosis factor-alpha, leptin, resistin and angiotensin II) [11], which may culminate with the metabolic syndrome, elevated blood pressure, obesity, dyslipidemia, diabetes, heavy smoking and low physical activity level that are associated with PTSD and are major risk factors for coronary artery disease [12].

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PTSD = post-traumatic stress disorder
IL = interleukin

Inflammation can induce local thrombosis which, in turn, can amplify inflammation and this cross-talk contributes to atherosclerosis progression [13]. A positive and partially independent correlation was revealed between the severity of acute PTSD and plasma levels of both factor VIII and fibrinogen [14]. In addition, markers of endothelial dysfunction, i.e., soluble tissue factor, and vWF were found to be associated with acute PTSD and partly affected by psychobiological distress [15]; however, the data concerning a possible link between chronic PTSD, its symptom severity and hypercoagulation are relatively limited.

The aim of the current study was to assess the levels of hypercoagulation parameters in patients with chronic PTSD compared to matched controls who were exposed to the same trauma.

PATIENTS AND METHODS

The study group included 30 civilians diagnosed as suffering from chronic PTSD after the Second Lebanon War in summer 2006. Study participants were recruited at the Center for Anxiety and Trauma Disorders of the Rambam Health Care Campus between October and December 2007 and were diagnosed by senior psychiatrists as suffering from chronic PTSD for more than a year. The study was approved by the Rambam Institutional Review Board and all patients signed an informed consent form.

Inclusion criteria were age 18–70, diagnosis of chronic PTSD, and the ability to give informed consent. Participants were excluded from the study if they had a history of psychiatric disorder, major cardiac or thromboembolic events, evidence of acute infectious disease, a diagnosis of cancer, or if they were pregnant, drug abusers, or receiving anticoagulant therapy. The control group included 30 healthy civilians matched for age, gender and ethnicity, exposed to the same war trauma, who had not developed PTSD or other psychiatric disorders.

PSYCHIATRIC ASSESSMENT

All study participants were invited for one clinic visit during which they underwent psychiatric assessment to confirm the diagnosis of chronic PTSD and its severity. Assessment instruments included the MINI and the CAPS. The MINI (Mini-International Neuropsychiatric Interview) is an abbreviated psychiatric structured interview evaluating major adult Axis I disorders using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and International Classification of Diseases-10 (ICD-10). MINI elicits all the symptoms listed in the symptom criteria for DSM-IV and for ICD-10 for 15 major Axis I diagnostic categories, one Axis II disorder and for suicidality. Its diagnostic algorithms are consistent with DSM-IV and ICD-10 diagnostic algorithms. The CAPS (Clinician Administered PTSD Scale) is a structured interview assessing PTSD diagnostic status, symptom severity, core and associated symptoms. It evaluates the frequency and intensity of each symptom using standard prompted questions and explicit, behaviorally anchored rating scales [16]. In the current study, a CAPS score > 80 corresponded to severe PTSD, and a CAPS score ≤ 80 corresponded to mild PTSD.

MINI = Mini-International Neuropsychiatric Interview

COAGULATION STUDIES

During the same visit, venous blood samples of patients and controls were collected by venipuncture into tubes with 3.2% sodium citrate for coagulation studies. Blood samples were centrifuged at 2000 g for 15 minutes. Prothrombin time, activated partial thromboplastin time, fibrinogen, ProC Global assay and activated protein C resistance tests were performed on fresh plasma samples. All other coagulation assays were performed on thawed frozen plasma samples. Plasma samples were frozen after a second centrifugation at 2000 g for 15 minutes in aliquots at -70 ± 5°C. Prior to testing, plasma aliquots were thawed in a 37 ± 0.5°C water bath for 15 min. PT, PTT, fibrinogen, ProC Global assay and APC-R were performed on the STA-R evolution analyzer (Diagnostica Stago, Gennevilliers, France). Recombinant human thromboplastin Dade Innovin® (Dade Behring Marburg GmbH, Germany) was used for PT assay. STA-PTT®, STA-FIBRINOGEN and STA-LIATEST® D-DI kits were employed for PTT, fibrinogen and D-dimer assays, respectively (Diagnostica Stago). The ProC Global assay kit (Dade Behring) and Coatest APC resistance kit (Chromogenix – Instrumentation Laboratory SpA Milan, Italy) were used for the relevant tests.

Levels of coagulation factor VIII activity were determined by one-stage assay using factor VIII deficiency plasma (Diagnostica Stago). Levels of vWF antigen were evaluated using the STA-LIATEST® vWF:ag kit (Diagnostica Stago). Prothrombin fragment F1+2 concentration, as a marker of prothrombin activation, was measured by an enzyme-linked immunosorbent assay using Enzygnost® F1+2 (monoclonal) (Dade Behring). Tissue factor antigen levels were determined with the IMUBIND® Tissue Factor ELISA kit (American Diagnostica Inc., Stamford, CT).

STATISTICAL ANALYSIS

Data were analyzed using the SPSS statistical software package. Differences between the two groups in coagulation parameter levels and other continuous variables (age, years of education) were estimated with the *t*-test. Differences

CAPS = Clinician Administered PTSD Scale
PT = prothrombin time
PTT = partial thromboplastin time
APCR = activated protein C resistance
vWF = von Willebrand factor
F1+2 = fragment F1+2

between the two groups in categorical demographic variables (gender, marital status, employment status and CAPS) were checked by Pearson chi-square or Fisher's exact test. Linear correlation between CAPS scores and the level of each of the coagulation factors as well as between CAPS scores and education duration was analyzed using Pearson correlation. $P < 0.05$ was considered significant.

RESULTS

Table 1 shows key demographic and ethnic characteristics of the two groups. The patients with chronic PTSD and the controls were matched in all criteria apart from education duration and employment status. Patients had higher PTSD symptom scores compared with controls; the mean CAPS score was 89 ± 25 for patients and 0.9 ± 1.4 for controls. In addition, PTSD patients had higher symptom levels of anxiety, suicidal thoughts and depression; almost 73% of PTSD patients had comorbid major depression and 26% had suicidal thoughts.

vWF antigen levels were found to be significantly higher in patients with chronic PTSD as compared with controls. No differences were documented in other studied coagulation factor levels between the two groups [Table 2]. Significantly higher levels of vWF antigen and factor VIII activity were observed in patients with severe chronic PTSD (CAPS > 80) compared with controls and 10 patients with mild chronic PTSD (CAPS ≤ 80) [Table 3].

Factor VIII levels correlated with those of vWF antigen in both patient and control groups ($r = 0.7$, $P < 0.0001$). However, factor VIII levels correlated with F1+2 only in the patient group ($r = 0.4$, $P = 0.04$), and with fibrinogen levels only in the control group ($r = 0.4$, $P = 0.02$). No correlation was found between the CAPS scores and the level of any of the coagulation factors, or education duration.

Among patients with chronic PTSD, no differences were found in any of the studied coagulation parameters between subjects with comorbid major depression or suicidal thoughts and those with PTSD only, or between employed and unemployed individuals. In the patient group, no correlation was observed between education duration and the CAPS score ($r = -0.005$, $P = 0.979$). In addition, no significant correlation was demonstrated between vWF and education duration or between factor VIII activity levels and education duration either in patients ($r = -0.12$, $P = 0.52$ or $r = -0.16$, $P = 0.38$, respectively) or in controls ($r = -0.04$, $P = 0.81$ or $r = -0.01$, $P = 0.95$, respectively).

Table 1. Demographic characterization of PTSD patients and controls

	Patients (n=30)	Controls (n=30)	*P* value
Gender (male/female)	11/19	11/19	NS
Age (yrs, mean ± SD)	39.63 ± 11	39.93 ± 10.9	NS
Marital status (married/not married)	15/15	14/16	NS
Ethnicity (Jewish/Arabs)	14/16	12/18	NS
Employment status (employed/unemployed)	18/12	30/0	< 0.001
Education (yrs, mean ± SD)	12 ± 1.6	16.43 ± 2.2	< 0.001

NS = not significant

Table 2. Plasma coagulation parameters in PTSD patients compared with controls

Plasma parameters (mean ± SD)	Patients (n=30)	Controls (n=30)	*P* value
PT (sec)	9.8 ± 1	9.9 ± 1	0.651
PTT (sec)	33.7 ± 3	34.8 ± 3	0.178
D-dimer (mg/L)	0.4 ± 0.4	0.35 ± 0.3	0.842
Fibrinogen (mg/dl)	322.8 ± 60	343.1 ± 66	0.324
Protein C global assay (PCAT-NR)	0.77 ± 0.13	0.78 ± 0.11	0.796
APC sensitivity ratio**	2.43 ± 0.23	2.42 ± 0.25	0.8
vWF antigen (u/ml)	121.3 ± 42	99.7 ± 23	0.034
Factor VIII activity (u/ml)	123.8 ± 31	111.3 ± 28	0.208
Tissue factor (pg/L)	36.4 ± 21	39.8 ± 20	0.279
Prothrombin F1+2 (pmol/L)	208.7 ± 109	191.3 ± 71	0.734

PCAT-NR = protein C activation time-normalized ratio, APC = activated protein C sensitivity ratio, vWF = von Willebrand factor

P < 0.05 considered significant

Table 3. Levels of FVIII activity and vWA antigen in severe PTSD compared with mild PTSD and controls

	CAPS > 80	CAPS ≤ 80	*P* value
Patients (n)	20	10	–
Controls (n)	0	30	–
vWF antigen (u/ml)	130.4 ± 32	111.1 ± 27	0.043
FVIII activity (u/ml)	128.5 ± 48	101.5 ± 21	0.022

CAPS = clinician administered PTSD scale

CAPS > 80 = severe PTSD, CAPS ≤ 80 = mild PTSD

DISCUSSION

The lifetime prevalence of PTSD is estimated to be about 8% in the general population, although an additional 5–15% may experience subclinical forms of the disorder [2]. The symptoms are chronic and often life-lasting, disabling people and causing a financial burden on society. PTSD patients are at increased risk of mortality, especially from cardiovascular disease and thromboembolic events that could be associated with hypercoagulation [2,5,17].

The aim of the current study was to assess the levels of hypercoagulation parameters in patients with chronic PTSD compared to matched controls who were exposed to the

same trauma. Among all the hypercoagulation parameters evaluated, including D-dimer, F1+2, tissue factor levels and protein C pathway activity, only levels of vWF antigen were found to be significantly higher in the patient group compared to the controls. These results suggest that the higher risk of arterial thrombosis in PTSD patients may be related to endothelial damage or endothelial activation and is not associated with coagulation activation or decreased activity of the protein C pathway. In patients with severe PTSD (CAPS > 80), elevated levels of vWF were accompanied by high FVIII activity levels.

vWF plays an important role in hemostasis and thrombosis, both as a cofactor in platelet adhesion and aggregation and as a circulating carrier protein for factor VIII [18]. Meta-analyses of prospective studies have suggested that increased circulating vWF levels are associated with a high risk of CAD [19,20], and elevated plasma levels of factor VIII are related to an increased risk of venous thrombosis [21,22].

Von Kanel et al. [14] found a positive and partially independent association between dimensional aspects of acute PTSD and plasma levels of both factor VIII and fibrinogen, suggesting a correlation between the severity of acute PTSD symptomatology and concentration of these procoagulant factors. Their data also suggest that traumatic stress could increase levels of factor VIII [14]. Factor VIII and fibrinogen are known to be acute-phase reactants [23-25]; however, in our study no differences were found in fibrinogen levels between patients and controls, but the high levels of factor VIII were associated with elevated levels of vWF. These findings may imply that fibrinogen levels return to normal in the chronic stress state and that higher levels of factor VIII and vWF are associated with chronic endothelial cell activation, but this should be further investigated.

In a later study, von Kanel and co-authors [15] revealed elevated levels of soluble tissue factor, which is another endothelial marker, in 14 patients with acute PTSD developed after an accident compared to 14 controls who did not have PTSD. In this study, no differences were documented in the levels of vWF antigen. In our study, the levels of soluble tissue factor, measured by the method used by von Kanel et al., did not differ between the study and control groups. Differences in the results of endothelial marker evaluation might stem from chronic versus acute state, variations in study populations and the type of trauma that patients were exposed to.

The aim of this study was to explore hypercoagulation parameters in a chronic stress disorder (PTSD). Our findings of elevated levels of vWF and FVIII activity support the hypothesis that hypercoagulation persists after an acute period in PTSD, which could contribute to the morbidity and mortality in these patients and should be addressed in the treatment program.

Compared to previous studies [14,15], the current trial included larger cohorts of patients with chronic PTSD (duration ≥ 1 year) and controls who were exposed to the same trauma. However, the limitation of our study is related to the small size of the group with severe chronic PTSD (CAPS > 80). Another limitation is associated with the higher education and employment levels found in the control group compared to the patient group.

Levels of vWF and factor VIII were not found to be affected by any concomitant psychiatric illness (e.g., depression, suicidal thoughts), education duration or employment status; however, they were associated with the incidence and severity of chronic PTSD.

CONCLUSIONS

Severe chronic PTSD is associated with high levels of vWF and factor VIII, which may explain the increased risk of developing arterial and venous thrombosis among patients with this disorder. These findings could contribute to the improvement of PTSD diagnosis and treatment. The results obtained in the current study may be considered preliminary. To assess their significance, prospective clinical trials larger cohorts of patients with severe chronic PTSD are warranted. It is also crucial that follow-up of arterial and venous thrombosis be incorporated in protocols of these studies.

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