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Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura

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ABSTRACT

Introduction: Survivors of thrombotic thrombocytopenic purpura (TTP) have high rates of chronic morbidities including neurocognitive complications and depression. There is limited information regarding the psychological consequences of TTP. We conducted this cross sectional study to estimate the prevalence of symptoms of PTSD and depression in survivors of TTP.

Methods: An online survey tool comprising demographic and clinical information and two validated self-administered questionnaires, the PTSD checklist for DSM-5 (PCL-5) and Beck Depression Inventory-II (BDI-II), was distributed to individuals with TTP. Multivariable regression was used to identify clinical and demographic associations of depression and PTSD.

Results: A total of 236 individuals completed either the BDI II or PCL-5 and were included in the analysis. Median age was 44 years and 87.3% were female. Median time from diagnosis was 80 months. BDI-II scores >13 indicating at least mild depressive symptoms were present in 80.8% individuals (15.8%, 28.2%, and 36.8% with mild, moderate and severe symptoms, respectively) and 35.1% had a positive screen for PTSD (PCL-5 score ≥ 38). A previous diagnosis of depression [OR 3.65 (95% CI 1.26–10.57); $p = 0.017$] and unemployment attributed to TTP [OR 5.86 (95% CI 1.26–27.09); $p = 0.024$] were associated with depression. Younger age ($p = 0.017$), a pre-existing anxiety disorder [OR 3.57 (95% CI 1.76–7.25), $p < 0.001$], and unemployment attributable to TTP [OR 6.42 (95% CI 2.75–415.00), $p < 0.001$] were associated with PTSD.

Conclusion: We report a high prevalence of PTSD and depression in TTP survivors. These results are concerning and indicate a need for further investigation to better define this association and its consequences.

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life threatening disorder characterized by acute episodes of widespread microvascular thrombosis and multiorgan impairment [1]. The advent of plasma exchange dramatically changed the natural history of TTP and mortality rates improved from over 90% without treatment to approximately 20% [2,3]. Recovery from TTP has been generally felt to be complete except for a 30–40% risk of relapse, highest in the first year after diagnosis [4,5]. However, recent studies have demonstrated that survivors of TTP have higher rates of hypertension, depression, stroke and overall mortality than the general population [6–8]. Others have reported a high incidence of persistent cognitive deficits [9–11], depression [6,7,10], and poor quality of life [12]. The majority of studies regarding TTP survivorship have focused on neurocognitive deficits and health related quality of life; however, there is limited published data on the mental health impact of TTP [13], particularly the presence of psychiatric morbidities such as depression and post-traumatic stress disorder (PTSD). Based on published reports suggesting problems with endurance, memory, and concentration after recovery from TTP [14], and our clinical experience with TTP patients who report difficulties in coping with the stress of the illness and returning to their previous level of functioning, we hypothesized that as an acute life-threatening illness associated with intensive care admission and invasive procedures, TTP conceivably represents an emotionally traumatic episode with a risk of post-traumatic stress disorder (PTSD) and depression. We conducted this exploratory, survey-based and cross-sectional study to estimate the prevalence as well as clinical and social determinants of PTSD and depression in individuals with TTP.

Abbreviations: TTP, thrombotic thrombocytopenic purpura; PTSD, post-traumatic stress disorder; DSM-5, diagnostic and statistical manual of mental disorders; PCL-5, post-traumatic stress disorder checklist for DSM-5; BDI-II, Beck Depression Inventory II; OR, odds ratio; IQR, interquartile range.

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2. Materials and methods

2.1. Participants and recruitment

Individuals with an established diagnosis of TTP were included in this cross-sectional survey. Participants were recruited via email using the contact list of Answering TTP Foundation, an international non-profit organization dedicated to supporting patients and families affected by TTP, educating medical professionals, and supporting research. The survey was administered from February 1, 2016 to February 29, 2016. A single email was sent on the first day, followed by a reminder email the day prior to study closure. This study involved minimal risk; however, participants were instructed to stop taking the survey at any point if they experienced emotional distress and were also directed to a 24-hour mental health helpline. The survey was available only in English, and is therefore limited to English speaking participants. Online consent was obtained prior to administering the survey. Only individuals ≥18 years of age were included. Survey responses were collected and managed in REDCap, a secure, web-based application for building and managing online research surveys and databases hosted at Vanderbilt University [15]. The institutional review board at Vanderbilt University approved this study.

2.2. Survey instrument

The survey instrument for this study (provided in the supplemental file) had three components: (i) **Baseline participant characteristics**: age, sex, educational level, current employment status, details of TTP diagnosis (including whether low ADAMTS13 activity was documented), and an existing diagnosis of depression, PTSD, anxiety disorder or other mental health disorder made by a healthcare professional. (ii) **PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 (PCL-5)**: the PCL-5 is a validated 20-item self-administered tool that assesses the updated DSM-5 symptom of PTSD [16]. Each item is scored on a 5-point Likert scale (0 to 4; 'not at all' to 'extremely') and total symptom severity is obtained by summing the scores from all 20 questions (range 0 to 80). The PCL-5 may be used as a screening tool or to make a provisional diagnosis of PTSD. A total symptom severity score cutoff of 38 is recommended as the cutoff for a positive screening test. A provisional diagnosis of PTSD is made based on the DSM-5 rule of at least one cluster B symptom (intrusion; questions 1–5), one cluster C symptom (avoidance, questions 6 and 7), two cluster D symptoms (changes in mood and cognition, questions 8–14), and 2 cluster E symptoms (arousal and hyper-reactivity, questions 15–20). A score of 2 (moderately) or higher is considered as a positive symptom endorsed (Table 1). We selected this instrument because it is an easily self-administered tool that is congruent with the DSM-5 criteria for PTSD and can be used to make a provisional diagnosis of PTSD. (iii) **Beck Depression Inventory II (BDI-II)**: the BDI-II is an extensively validated self-administered screening tool for depression [17]. It contains 21 items, each with a 4-point scale ranging from 0 to 3; total scores range from 0 to 63. In accordance with suggested guidelines, we interpreted the BDI-II as follows: minimal range = 0–13, mild depression = 14–19, moderate depression = 20–28, and severe depression = 29–63. We characterized depressive symptoms as either cognitive or somatic, following the approach of Beck and Steer [17]. Scores on BDI-II items 1–14 (sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal ideation, crying, agitation, loss of interest, indecisiveness, and worthlessness) were summed to calculate cognitive/affective scores. Items 15–21 (loss of energy, sleep problems, irritability, appetite problems, concentration, fatigue, loss of interest in sex) were summed to calculate somatic symptom scores. We selected this instrument because there has been extensive documentation of the internal consistency of the scale, its test-retest reliability, and its extensive validation against other measures of depression and independent criteria for depression over the past several decades.

Table 1
Scoring and interpreting the PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders-5 (PCL-5) and Beck Depression Inventory II (BDI-II).

PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM) 5

- Each of 20 items is scored on a five-point scale of 0–4 ("not at all" to 'extremely').
  - A total symptom severity score (range - 0–80) can be obtained by summing the scores for each of the 20 items. A total symptom severity score cutoff of 38 was used as a positive screening test for PTSD.
  - A provisional PTSD diagnosis can be made by treating each item rated as 2 = "Moderately" or higher as a symptom endorsed, then following the DSM-5-diagnostic rule which requires at least: one B item (intrusion; questions 1–5), one C item (avoidance; questions 6–7), two D items (changes in mood and cognition; questions 8–14), and two E items (arousal and hyperreactivity; questions 15–20).

Beck Depression Inventory II

- Each of the 21 items is scored on a four-point scale from 0 to 3. Items 1–4 indicate cognitive/affective symptoms and items 15–21 indicate somatic symptoms.
  - The following criteria are used to interpret scores: minimal range = 0–13, mild depression = 14–19, moderate depression = 20–28, and severe depression = 29–63.

Moreover, compared with another commonly used tool, the 9-item patient health questionnaire (PHQ-9), the BDI-II also allows us to distinguish between somatic and cognitive symptoms, which is an important consideration in a medically ill population with a potential burden of somatic symptoms [18].

2.3. Statistical analysis

Only data from patients who completed either the PCL-5 or BDI-II were included in the analysis. Continuous data are presented as medians and interquartile ranges (IQR); categorical variables are presented as frequencies and proportions. Outcome variables were: BDI-II and PCL-5 scores that were computed and interpreted as described. We used multivariable logistic regression to identify factors independently associated with positive screens for depression and PTSD on the BDI-II and PCL-5, respectively. Variables included in the model were selected a priori based on known or suspected relationships with the independent or outcome variables (depression and PTSD). Covariates included age, sex, education level, employment status, relapses of TTP, and history of depression and other mental health conditions. We used SPSS version 23 (IBM Corp, USA) statistical software for all analyses. All p-values are two sided, and we considered values <0.05 to indicate statistical significance.

3. Results

A total of 1150 individuals were contacted between February 1, 2016 and February 29, 2016. Three hundred and sixteen patients responded to the survey, a response rate of 27.5%. Of these, 290 completed a consent form to participate in the study. Fifty-four individuals completed only the demographics and clinical section, or did not confirm that they had diagnosis of TTP, and therefore were excluded. The remaining 236 respondents who completed either the PCL-5 (n = 231) or BDI-II (209) were included in the analysis (Fig. 1). Median age was 44 years (IQR 36 to 54 years) and 206 (87.3%) were female. Participants were a median period of 80 (IQR 37, 132) months from their initial diagnosis of TTP. All patients received plasma exchange treatment and a majority also received corticosteroids (86.0%). Over half (57.2%) reported having relapses of TTP and 59.7% had received Rituximab therapy. A preexisting diagnosis of depression, anxiety disorder and PTSD was present in 97 (41.1%), 81 (34.3%) and 37 (15.7%) respondents, respectively. Of the 97 patients with depression, 64 (66.0%) were on antidepressant therapy. A total of 82 (34.8%) respondents were unemployed. Of these, 53 (22.5% of entire sample) attributed their unemployment to