Thrombosis Research 153 (2017) 14–18

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Depression and post-traumatic stress disorder in individuals with hereditary hemorrhagic telangiectasia: A cross-sectional survey

Shruti Chaturvedi [a], Marianne Clancy [b], Nicole Schaefer [b], Olalekan Oluwole [a], Keith R. McCrae [c,d,*]

[a] Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States
[b] CureHHT Foundation, Monkton, MD, United States
[c] Department of Cellular and Molecular Medicine, Cleveland Clinic, United States
[d] Hematologic Oncology and Blood Disorders, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, United States

ARTICLE INFO

Article history:
Received 5 October 2016
Received in revised form 1 March 2017
Accepted 6 March 2017
Available online 9 March 2017

Keywords:
Hereditary hemorrhagic telangiectasia
Post-traumatic stress disorder
Depression
Quality of life
Bleeding disorder other than hemophilia
Epistaxis

ABSTRACT

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is characterized by frequent severe bleeding, particularly epistaxis, and life-threatening complications including stroke, brain abscess and heart failure. The psychological impact of HHT is not known. We conducted this cross sectional study to determine the prevalence of depression and post-traumatic stress disorder (PTSD) related to HHT.

Methods: A 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 HHT. Associations with clinical and demographic variables with depression and PTSD were evaluated in a logistic regression model.

Results: A total of 222 individuals responded to the survey. Of these, 185 completed either the BDI II or PCL-5 and were included in the analysis. Median age was 54 years and 142 (76.8%) were female. An existing diagnosis of depression, anxiety disorder and PTSD was present in 81 (43.8%), 59 (31.9%) and 16(8.6%) respondents, respectively. BDI-II scores > 13 indicating at least mild depressive symptoms were present in 142 (88.7%) patients and 52 (28.1%) patients had a positive screen for PTSD (PCL-5 score ≥ 38). On multivariable analysis, depression [OR 2.17 (95% CI 1.045–4.489), $p = 0.038$], anxiety disorder [OR 2.232 (95% CI 1.066–4.676), $p = 0.033$], and being unemployed [OR 2.234 (95% CI 1.46–4.714), $p = 0.019$) were associated with PTSD.

Conclusion: We report a high prevalence of depressive and PTSD symptoms in individuals with HHT. While selection bias may lead to overestimation of prevalence in this study, our results are concerning and clinicians should remain vigilant for signs of psychological distress and consider screening for these disorders.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Osler Weber Rendu syndrome is a relatively common, frequently under-recognized, autosomal dominant disorder that affects 1 in 5000 to 1 in 10,000 persons worldwide, with an estimated 60,000 affected individuals in the United States [1]. Mutation in three genes account for the majority of HHT: the endoglin (*ENG*) gene on chromosome 9 (HHT type 1), the activin receptor–like kinase (*ACVRL1*) gene on chromosome 12 (HHT type 2), and the *SMAD4* gene on chromosome 18 (HHT with juvenile polyposis) [2]. These genes encode proteins that modulate transforming growth factor (TGF)-β superfamily signaling in vascular endothelial cells. HHT-causing gene mutations lead to vascular malformations ranging from capillary malformations to large arteriovenous malformations in the pulmonary, hepatic, cerebral and spinal circulations. The penetrance of symptoms approaches 100% by 40 years of age and clinical phenotype generally worsens with age; the type and severity of manifestations are variable with significant intra-familial and inter-familial variability [3]. Recurrent and severe epistaxis is the most common presentation and causes severe anemia requiring blood transfusions and iron infusions in a third of patients. Gastrointestinal bleeding increases with age. Approximately 50% of patients experience life-threatening or disabling complications such as stroke, cerebral abscess, or heart failure resulting from cerebral, pulmonary and hepatic arterio-venous malformations (AVMs), respectively [4].

Several studies have reported that HHT negatively impacts health-related quality of life [5–8]. Three independent studies have reported

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; 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.

* Corresponding author at: Taussig Cancer Institute, R4-018, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, United States.
E-mail address: mccraek@ccf.org (K.R. McCrae).

http://dx.doi.org/10.1016/j.thromres.2017.03.003
0049-3848/

that individuals with HHT had lower scores on the short form 36 (SF-36) in all domains except for pain compared to normative data [5–8]. Severe epistaxis is the most significant manifestation associated with poor health-related quality of life [9]. In another study that used a symptom-specific HHT questionnaire, 58% of participants with HHT reported that their condition affected their quality of life, with recurrent nosebleeds being the major factor that negatively impacted work, social activities and caused psychological strain [6]. These studies, however, focused on overall, health-related or symptom specific aspects of quality of life. Little published evidence has assessed the psychological impact of HHT, particularly the presence of psychiatric morbidities such as depression and post-traumatic stress disorder. We hypothesized that there is a high prevalence of depressive symptoms and post-traumatic stress disorder (PTSD) symptoms among individuals with HHT, that is likely associated with a stressful HHT-related event such as stroke, cerebral abscess or massive bleeding. We conducted this exploratory, survey-based and cross sectional study to estimate the prevalence and determinants of depression and PTSD in individuals with HHT.

2. Methods

2.1. Participants and recruitment

Individuals with an established diagnosis of HHT were included in this cross-sectional survey. Participants were first recruited via email using the email contact list (which includes 8000 individual email addresses) of CureHHT, run by HHT Foundation International, an international non-profit organization dedicated to supporting patients and families affected by HHT, educating medical professionals and supporting research. The survey was also posted on the CureHHT website and administered from October 10, 2015 to November 30, 2015. 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 [10]. The institutional review board at Vanderbilt University approved this study.

2.2. Survey instrument

The instrument for this study had three major components (see Appendix A; Survey Instrument): (i) Baseline participant characteristics: age, sex, educational level, current employment status, details of HHT diagnosis, clinical manifestations and history of depression, PTSD, anxiety disorder or other mental health illnesses (using questions that inquired about whether a patient had ever been diagnosed with specific psychiatric conditions by a healthcare professional). Participants were asked to identify any episode of their illness that had caused significant anxiety or distress. They were given the opportunity to give a short narrative of the incident. (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 [11]. 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. This cutoff has a sensitivity of 85% and specificity of 91% for the diagnosis of PTSD [12]. A provisional diagnosis can be 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. (iii) Beck Depression Inventory II (BDI-II): the BDI-II is an extensively validated self-administered screening tool for depression [13]. 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 test developers, Beck and Steer. 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, 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. At a cutoff of 14 and above, various studies have reported that the BDI-II detects depression with a sensitivity of 87.7%–92% and specificity of 74%–83% [14].

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; 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, clinical manifestations of HHT and history of depression and other mental illnesses. Variables that reached a significance of $p < 0.20$ on univariate analyses were tested in the multivariable model. The proportional hazards assumption was assessed, and Martingale and deviance residuals were used to assess model assumptions and the effect of outlier cases. We used the Spearman correlation test to evaluate correlations between PCL-5 and BDI-II scores. We used the chi-squared test to evaluate the association of mild, moderate or severe depression with a positive screen for PTSD. All p-values are two sided, and values < 0.05 were considered statistically significant. SPSS version 23 (IBM Corp, USA) was used to perform all analyses.

3. Results

Two hundred and twenty two individuals with HHT responded to the survey between October 10, 2015 and November 30, 2015. Of these, 37 participants completed only the baseline information while 185 completed at least one of the mental health screening tools (PCL-5 or BDI-II). These 185 participants were included in the analysis. The 37 patients who completed demographics only were not different from those included in the analysis in terms of age and sex distribution, education or employment status. They did not complete the questions regarding clinical symptoms and mental health. We are unable to calculate a response rate since the survey was posted online (in addition to being distributed via email) and we do not have an estimate of the total number of eligible individuals that it reached; however, the 222 responses in this study are comparable to a preliminary feasibility survey that yielded 210 responses.

Participants had a median age of 54 years [interquartile range (IQR) 44, 62] and 142 (76.8%) were female. They reported the following symptoms of HHT: nosebleeds, 179 (96.8%); telangiectasia, 168 (90.8%), shortness of breath, 121 (65.4%), abdominal pain, 58 (31.4%),