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%),

gastrointestinal bleeding, 65 (35.1%); headaches, 107 (57.8%), seizures, 23 (12.4%); AVMs in the lung, liver or brain, 115 (62.2%). Eighty-one (43.8%) patients had a prior diagnosis of depression (made by a health-care provider), of which 61 were receiving pharmacologic therapy for depression. Sixteen patients (8.6%) had a prior diagnosis of PTSD; 59 (31.9%) had a diagnosis of anxiety disorder, 5 (2.7%) had a history of adjustment disorder, and 5 (2.7%) had a diagnosis of bipolar disorder. Forty (21.6%) and 32 (17.3%) patients reported that they were unemployed due to HHT and reasons other than HHT, respectively. Detailed demographic and clinical data are provided in Table 1.

One hundred and sixty two (87.6%) patients identified a significant stressor or traumatic event related to HHT. This was related to severe epistaxis in social or professional situations in 110 patients (67.9%). Others reported severe gastrointestinal bleeding (n = 16), losing consciousness due to excessive hemorrhage (n = 9), stroke (n = 12), seizures (n = 5), cerebral abscesses (n = 8), losing family members to HHT (n = 12), and major surgery including gastrectomy or craniotomy (n = 9).

One hundred and sixty participants completed the BDI-II. This included 70 individuals who reported a prior diagnosis of depression. The median score was 23 [IQR 17, 32]. A total of 142 (88.7%) respondents had at least mild depressive symptoms (BDI II > 13) (Table 2). BDI-II scores > 13 were present in 97.1% (68/70) of patients with a reported depression history and 82.2% (74/90) without such a history. Median score on the somatic scale was 13 (IQR 10, 15) and on the cognitive/affective scale was 11 (IQR 7, 18). On an average, somatic scores contributed to 53% of the total score. In a multivariable model adjusted for sex, history of depression, history of anxiety disorder and being unemployed due to any cause, only a prior history of depression was associated with a BDI II score > 13 [OR 2.50 (95% CI 1.18–5.32); p = 0.017]. Age, educational level, anemia or particular symptoms such as nosebleeds, shortness of breath, gastrointestinal bleeding, headache, seizures or stroke were not significantly associated with a BDI II score > 13.

One hundred and eighty five participants completed the PCL-5. The median score was 24 (IQR 14, 39). Fifty-two (28.1%) had a PCL-5 score ≥ 38, meeting criteria for a positive screening test. This included the 16 patients with a prior diagnosis of PTSD. Forty-one (22.1%) met criteria for provisional diagnosis of PTSD based on the DSM 5 diagnostic rule which requires a score of 2 or higher on at least 1 cluster B item, 1 cluster C item, 2 cluster D items and 2 cluster E items. In a multivariable logistic regression model, a history of 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 due to any cause [OR 2.234 (95% CI 1.46–4.714), p = 0.019) were associated with a positive PCL-5 screen for PTSD. Sex was included in this model but was not associated with PTSD [OR 1.78 (95% CI 0.87–3.71); p = 0.703]. Age, educational level anemia or particular symptoms such as nosebleeds, shortness of breath, gastrointestinal bleeding, headache, seizures or stroke were not significantly associated with PCL-5 scores indicative of PTSD.

Of the 160 patients who completed both surveys, 39 (24.4%) of patients had co-morbid depression and PTSD assessed by the BDI II and PCL-5, respectively. Scores on BDI II correlated closely with the PCL-5 score (R = 0.691, p < 0.001) by Spearman's correlation test. Severity of depression (by BDI II score ranges) was associated with a PCL-5 score ≥ 38; of the 160 patients who completed the BDI II, none of the patients without depressive symptoms (0%), 2 (5.4%) patients with mild depression, 6 (13%) of patients with moderate depression and 31 (52.5%) of patients with moderate depression, and 39 (24.4%) of patients with severe depression had PCL-5 score ≥ 38 (p < 0.001 by the Chi squared test).

Table 1
Baseline demographic and clinical characteristics of participants (n = 185).

	N (%)
Age, median (range)	54 years (17–81 years)
Female sex	142 (76.8)
Highest educational level attained	
Completed eighth grade	1 (0.5)
Completed high school	67 (36,2)
Completed college	82 (44.3)
Master's degree	27 (14.6)
Doctoral degree	7 (3.8)
Employment status	
Working full time	73 (39.5)
Working part time	19 (10.3)
Student	7 (3.8)
Homemaker	8 (4.3)
Unemployed (due to reasons other than HHT)	32 (17.3)
Unemployed due to reasons related to HHT	40 (21.6)
Clinical manifestations of HHT	
Recurrent nosebleeds	179 (96.8)
Telangiectasias	168 (90.8)
Shortness of breath	121 (65.4)
Exercise intolerance	113 (61.1)
Abdominal pain	58 (31.4)
Intestinal bleeding	65 (35.1)
Headaches	107 (57.8)
Seizures	23 (12.4
Anemia	131 (70.8)
AVMs in the lung, liver, or brain	115 (62.2)
Previous psychiatric diagnoses made by a physician	
Previous diagnosis of PTSD	16 (8.6)
Previous diagnosis of depression	81 (43.8)
Previous diagnosis of anxiety disorder	59 (31.9)
Previous diagnosis of adjustment disorder	5 (2.7)
Previous diagnosis of bipolar disorder	5 (2.7)

HHT, hereditary hemorrhagic telangiectasia; AVM, arteriovenous malformation; PTSD, post-traumatic stress disorder.

Table 2
Depression and PTSD outcomes in individuals with HHT.

Outcome	
Depression (n = 160)	
BDI II score, median (IQR)	23 (17,32)
Somatic, median (IQR)	13 (10,15)
Cognitive/affective, median (interquartile range)	11 (7,18)
No depression (0–13), n(%)	18 (11.3%)
Mild depression (14–19), n(%)	37 (23.1%)
Moderate depression (20–28), n(%)	46 (28.75%)
Severe depression (29–63), n(%)	59 (36.8%)
PTSD (n = 185)	
PCL-5 scores, median (IQR)	24 (14,39)
PCL-5 score ≥ 38	52 (28.1%)
Provisional diagnosis of PTSD, n(%)	41 (22.1%)

4. Discussion

This large cross-sectional survey has yielded two important sets of observations regarding mental health in individuals with HHT. First, we found a high prevalence of depressive symptoms in individuals with HHT, a majority of which were previously undiagnosed. This is higher than the 23.2% prevalence reported in primary care outpatients using the same cutoff [15]. Second, an overwhelming majority of participants were able to identify a 'traumatic episode' related to their disease that caused significant anxiety and distress. A significant proportion of these had PCL-5 scores ≥ 38 (positive screening test for PTSD) and 22% met criteria for a provisional diagnosis of PTSD based on DSM-5. This is also higher than the 6.5%–12.3% estimates from studies using self-report measures of PTSD, including previous versions of the PTSD checklist (PCL), in various primary care populations [16–18], and higher than the 3.5% past-1-year prevalence of PTSD estimated by the National Comorbidity Survey that used structured diagnostic interviews [19]. Depression is closely associated with PTSD and 21% patients had comorbid depression and PTSD in this cohort. A prior diagnosis of anxiety disorder and unemployment due to any cause were also associated with PTSD in

a multivariable model. We did not observe a relationship between age, sex, or specific clinical manifestations with the outcomes of interest. The absence of an association of depression and PTSD with age, in particular, is surprising given that the symptoms of HHT increase with age and nearly all individuals manifest disease by the age of forty. This may be explained by the fact that 82.1% of respondents in our study were over 40 years of age. Therefore, younger individuals contributed fewer responses and our study may have been underpowered to detect age related differences.

Our investigation highlights the finding that a large proportion of individuals with HHT have at least mild depressive symptoms (88.7%); almost half of them do not have an existing diagnosis of depression from a healthcare provider. In our sample, depressive symptoms were independent of other known risk factors. We found that more severe depressive symptoms are a risk factor for PTSD in this population. Importantly, our data indicate that the prevalence of somatic and cognitive/affective symptoms are comparable in individuals with HHT supporting the hypothesis that both somatic and affective components contribute to depression in this population. Other studies in populations of medically ill patients such as post-myocardial infarction, chronic obstructive pulmonary disease, and survivors of critical illness have reported that somatic symptoms contribute disproportionately to the burden of depression [20–22]. Some sources have argued that medically ill individuals with chronic physical problems may be misdiagnosed as having depression when their complaints may be illness-driven [23]. Part of the depressive symptoms in our sample may be attributable to physical symptoms such as fatigue caused by anemia. It is of utmost importance to identify patients with potentially treatable mood disorders. A recent Cochrane review of 51 studies including 3603 participants concluded that antidepressants are effective in improving depressive symptoms in patients with physical illness. While the BDI II is not a definitive diagnostic tool, and should not replace a clinician assessment, a high score may draw attention to depression and other emotional disturbances, especially in clinical situations where mood is not routinely assessed.

This is the first study to report point prevalence of symptoms of PTSD associated with HHT. PTSD is an adverse reaction to traumatic experiences in which patients typically re-experience the traumatic event (for example, recurring thoughts or dreams), avoid reminders to the event and endure symptoms of hyperarousal (for example, irritability and sleeping difficulties) and negative effects on cognition/functioning, all of which contribute to poor quality of life. PTSD is traditionally thought of in association with violence, accidents and natural disasters; however, several studies have reported that experiences related to chronic illness can also be perceived as traumatic by patients and may be associated with PTSD symptomatology [24,25]. Approximately 22% of participants in our study met criteria for a provisional diagnosis of PTSD. This is in line with other studies that have reported the association of PTSD with medical illnesses such as chronic obstructive pulmonary disease [26], inflammatory bowel disease [27], human immunodeficiency virus infection [28,29], cardiac disease [30–33], stroke [34–36], variceal hemorrhage [37], and critical illness requiring admission to the intensive care unit [21,38–40]. Clinicians should be aware that a considerable number of patients perceive HHT as psychologically traumatic. A high burden of PTSD symptoms indicated by a high PCL-5 score is a reasonable trigger to alert clinicians to the need for more thorough assessment through the Clinician Administered PTSD scale for DSM-5, the gold standard for current or lifetime PTSD diagnosis. PTSD and PTSD symptoms are associated with worse self-reported health and health-related quality of life [33,41]. Diagnosing and treating depression and PTSD in individuals with HHT presents an untapped an opportunity to improve quality of life [42]. Depression and PTSD often overlap, particularly in the context of high symptom severity, and individuals with severe depression and PTSD may be the group that would benefit most from intervention. We suggest that individuals with a BDI-II score > 13 or a PCL-5 score ≥ 38 should be referred to a mental health provider for more thorough evaluation and, if indicated, treatment that would optimally involve a combination of counseling and pharmacotherapy. An interesting finding was that a large number of individuals were able to identify a stressful trigger that precipitated psychological distress. Future studies may be warranted to evaluate the benefit of supportive interventions at the time of the traumatic experience in order to prevent depression/PTSD.

While several investigators have reported decreased health-related quality of life in individuals with VWD, particularly menstruating women, and hemophilia [43–46], few previous studies have addressed the prevalence of depression and PTSD among these individuals. Ianonne et al. reported a 37% prevalence of depression in adults with hemophilia using the Patient Health Questionnaire 9 as a screening tool [47]. In the Hemophilia Experiences, Results and Opportunities (HERO) study, 43% of young adults (18–30 years) with Hemophilia reported a psychological or psychiatric morbidity (including stress, anxiety, depression or insomnia); 26% attributed their symptoms to hemophilia [46]. A higher proportion (88.7%) of respondents in our study screened positive for depression. This may be due to the almost daily symptoms associated with HHT, anxiety regarding multi-organ complications and dealing with a rare disorder with which their primary physicians may not be familiar. Additionally, responder bias may have led to a higher prevalence in our study.

The strengths of our study are a relatively large sample size and the use of instruments with robust psychometric properties, which have been used extensively in medically ill patients. For example, the BDI II has high internal consistency, and good discriminant and convergent validity. It has been validated in medical cohorts including cardiac, HIV, chronic fatigue, and general medical outpatients [14]. The PCL-5 also has good internal consistency, test-retest reliability and discriminant and convergent validity [48]. We used a more stringent cutoff of 38 on the PCL-5 to avoid over-estimating prevalence of PTSD symptoms.

This study has several limitations. First, the individual members of the Cure HHT foundation may be different from an unselected HHT population and represent individuals whose experiences have led them to seek out a support group due to psychological stress. Also, voluntary patient surveys are inherently prone to bias since those who respond, versus non-responders, represent a self-selected population that is likely enriched in individuals who are already concerned about the topics of the survey, depression and PTSD in this case. We are unable to determine an accurate response rate since the survey was posted online in addition to being distributed through email. We also had a moderate non-completion rate (37 of 222 respondents), which may reflect that the individuals who completed the survey had more marked symptoms. Additionally, women were disproportionately represented in our sample. This is likely reflective of the well-established fact that women are more likely participate in scientific studies [49]. However, female sex is an independent risk factor for depression and for developing PTSD after trauma, which may have led to a higher prevalence rate in this study [50–52]. Second, we did not collect information regarding other comorbidities and exposure to military, sexual or other trauma that may be associated with the outcomes of interest. However, we have no reason to believe that there is a higher incidence of these exposures in our sample compared to the general population. Third, since an online survey was the most efficient design for this exploratory study, we relied on self-reported diagnoses of HHT and existing psychiatric diagnoses. Finally, our assessment of depressive and PTSD symptoms was limited to a single point in time and we have no information regarding stability or trajectory of symptoms. However, this assessment allowed a preliminary demonstration of the value of assessing such symptoms. Additional studies in unbiased observational cohorts are indicated to confirm our findings.

In conclusion, this study provides evidence in support of a high prevalence of depression and PTSD symptoms in individuals with HHT. Clinicians who care for these patients should remain vigilant for signs of emotional distress and consider screening for PTSD and depression.

Conflict of interest statement

The authors have no conflicts of interest to report.

Acknowledgements

SC and KM designed the study, SC, OO, MC and NS performed the research, SC analyzed the data, SC and KM wrote the paper, and all authors reviewed the manuscript prior to submission. The authors stated that they had no interests, which might be perceived as posing a conflict or bias.

We would like to recognize the contributions of CureHHT and the patients who participated in this study. This work was supported in part by NIH U34 HL123416 (to KRM) and an ASH RTAF (to SC). The RedCap tool used for this study is supported by NCATS/NIH UL1 TR000445 (Vanderbilt Institute for Clinical and Translational Research).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2017.03.003.

References

[1] J. McDonald, P. Bayrak-Toydemir, R.E. Pyeritz, Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis, Genitourin. Med. 13 (2011) 607–616.
[2] S. Dupuis-Girod, S. Bailly, H. Plauchu, Hereditary hemorrhagic telangiectasia: from molecular biology to patient care, J. Thromb. Haemost. 8 (2010) 1447–1456.
[3] M.E. Porteous, J. Burn, S.J. Proctor, Hereditary haemorrhagic telangiectasia: a clinical analysis, J. Med. Genet. 29 (1992) 527–530.
[4] L.A. Higa, J. McDonald, D.O. Himes, et al., Life experiences of individuals with hereditary hemorrhagic telangiectasia and disclosing outside the family: a qualitative analysis, J. Community Genet. (2015).
[5] U.W. Geisthoff, K. Heckmann, R. D'Amelio, et al., Health-related quality of life in hereditary hemorrhagic telangiectasia, Otolaryngol. Head Neck Surg. 136 (2007) 726–733 (discussion 734-725).
[6] A.O. Geirdal, S. Dheyauldeen, G. Bachmann-Harildstad, et al., Quality of life in patients with hereditary hemorrhagic telangiectasia in Norway: a population based study, Am. J. Med. Genet. A 158A (2012) 1269–1278.
[7] P.A. Lennox, A.E. Hitchings, V.J. Lund, et al., The SF-36 health status questionnaire in assessing patients with epistaxis secondary to hereditary hemorrhagic telangiectasia, Am. J. Rhinol. 19 (2005) 71–74.
[8] G. Pasculli, F. Resta, E. Guastamacchia, et al., Health-related quality of life in a rare disease: hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease, Qual. Life Res. 13 (2004) 1715–1723.
[9] C.A. Merlo, L.X. Yin, J.B. Hoag, et al., The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia, Int Forum Allergy Rhinol 4 (2014) 921–925.
[10] P.A. Harris, R. Taylor, R. Thielke, et al., Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inform. 42 (2009) 377–381.
[11] C.A. Blevins, F.W. Weathers, M.T. Davis, et al., The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation, J. Trauma. Stress. 28 (2015) 489–498.
[12] J.H. Wortmann, A.H. Jordan, F.W. Weathers, et al., Psychometric analysis of the PTSD checklist-5 (PCL-5) among treatment-seeking military service members, Psychol. Assess. (2016).
[13] A.T.S.R. Beck, M.G. Carbin, Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation, Clin. Psychol. Rev. 8 (1988) 77–100.
[14] Y.P. Wang, C. Gorenstein, Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II, Clinics (Sao Paulo) 68 (2013) 1274–1287.
[15] R.C. Arnau, M.W. Meagher, M.P. Norris, et al., Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients, Health Psychol. 20 (2001) 112–119.
[16] H. Thulesius, A.K. Alveblom, A. Hakansson, Post-traumatic stress associated with low self-rated well-being in primary care attenders, Nord. J. Psychiatry 58 (2004) 261–266.
[17] H.S. Resnick, D.G. Kilpatrick, B.S. Dansky, et al., Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women, J. Consult. Clin. Psychol. 61 (1993) 984–991.
[18] E.A. Walker, E. Newman, D.J. Dobie, et al., Validation of the PTSD checklist in an HMO sample of women, Gen. Hosp. Psychiatry 24 (2002) 375–380.
[19] R.C. Kessler, W.T. Chiu, O. Demler, et al., Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication, Arch. Gen. Psychiatry 62 (2005) 617–627.
[20] P. de Jonge, J. Ormel, R.H. van den Brink, et al., Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis, Am. J. Psychiatry 163 (2006) 138–144.
[21] J.C. Jackson, P.P. Pandharipande, T.D. Girard, et al., Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study, Lancet Respir. Med. 2 (2014) 369–379.
[22] J.N. de Voogd, J.B. Wempe, G.H. Koeter, et al., Depressive symptoms as predictors of mortality in patients with COPD, Chest 135 (2009) 619–625.
[23] S.W. Perry, D.F. Cella, Overdiagnosis of depression in the medically ill, Am. J. Psychiatry 144 (1987) 125–126.
[24] J.E. Tedstone, N. Tarrier, Posttraumatic stress disorder following medical illness and treatment, Clin. Psychol. Rev. 23 (2003) 409–448.
[25] A.A. Alonzo, The experience of chronic illness and post-traumatic stress disorder: the consequences of cumulative adversity, Soc. Sci. Med. 50 (2000) 1475–1484.
[26] M.C. Chung, R.C. Jones, S.A. Harding, et al., Posttraumatic stress disorder among older patients with chronic obstructive pulmonary disease, Psychiatr Q. (2015).
[27] R.J. Camara, M.L. Gander, S. Begre, et al., Post-traumatic stress in Crohn's disease and its association with disease activity, Front. Gastrointest. 2 (2011) 2–9.
[28] B.O. Olley, M.D. Zeier, S. Seedat, et al., Post-traumatic stress disorder among recently diagnosed patients with HIV/AIDS in South Africa, AIDS Care 17 (2005) 550–557.
[29] R. Kimerling, K.S. Calhoun, R. Forehand, et al., Traumatic stress in HIV-infected women, AIDS Educ. Prev. 11 (1999) 321–330.
[30] P. Bennett, M. Conway, J. Clatworthy, et al., Predicting post-traumatic symptoms in cardiac patients, Heart Lung 30 (2001) 458–465.
[31] P. Bennett, S. Brooke, Intrusive memories, post-traumatic stress disorder and myocardial infarction, Br. J. Clin. Psychol. 38 (Pt 4) (1999) 411–416.
[32] E. Shemesh, A. Rudnick, E. Kaluski, et al., A prospective study of posttraumatic stress symptoms and nonadherence in survivors of a myocardial infarction (MI), Gen. Hosp. Psychiatry 23 (2001) 215–222.
[33] B.E. Cohen, C.R. Marmar, T.C. Neylan, et al., Posttraumatic stress disorder and health-related quality of life in patients with coronary heart disease: findings from the Heart and Soul Study, Arch. Gen. Psychiatry 66 (2009) 1214–1220.
[34] S. Sembi, N. Tarrier, P. O'Neill, et al., Does post-traumatic stress disorder occur after stroke: a preliminary study, Int. J. Geriatr. Psychopharmacol. 13 (1998) 315–322.
[35] I.M. Kronish, D. Edmondson, J.Z. Goldfinger, et al., Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks, Stroke 43 (2012) 2192–2197.
[36] J.Z. Goldfinger, D. Edmondson, I.M. Kronish, et al., Correlates of post-traumatic stress disorder in stroke survivors, J. Stroke Cerebrovasc. Dis. 23 (2014) 1099–1105.
[37] R.E. O'Carroll, G. Masterton, R. Gooday, et al., Variceal haemorrhage and post-traumatic stress disorder, Br. J. Clin. Psychol. 38 (Pt 2) (1999) 203–208.
[38] G. Schelling, C. Stoll, M. Haller, et al., Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome, Crit. Care Med. 26 (1998) 651–659.
[39] P. Scragg, A. Jones, N. Fauvel, Psychological problems following ICU treatment, Anaesthesia 56 (2001) 9–14.
[40] C. Jones, R.D. Griffiths, G. Humphris, et al., Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care, Crit. Care Med. 29 (2001) 573–580.
[41] R.B. Hidalgo, J.R. Davidson, Posttraumatic stress disorder: epidemiology and health-related considerations, J. Clin. Psychiatry 61 (Suppl. 7) (2000) 5–13.
[42] M.H. Rapaport, C. Clary, R. Fayyad, et al., Quality-of-life impairment in depressive and anxiety disorders, Am. J. Psychiatry 162 (2005) 1171–1178.
[43] S. Von Mackensen, Quality of life in women with bleeding disorders, Haemophilia 17 (Suppl. 1) (2011) 33–37.
[44] C. Rae, W. Furlong, J. Horsman, et al., Bleeding disorders, menorrhagia and iron deficiency: impacts on health-related quality of life, Haemophilia 19 (2013) 385–391.
[45] R.A. Kadir, C.A. Sabin, D. Pollard, et al., Quality of life during menstruation in patients with inherited bleeding disorders, Haemophilia 4 (1998) 836–841.
[46] M. Witkop, C. Guelcher, A. Forsyth, et al., Treatment outcomes, quality of life, and impact of hemophilia on young adults (aged 18–30 years) with hemophilia, Am. J. Hematol. 90 (Suppl. 2) (2015) S3–10.
[47] M. Iannone, L. Pennick, A. Tom, et al., Prevalence of depression in adults with haemophilia, Haemophilia 18 (2012) 868–874.
[48] M.J. Bovin, B.P. Marx, F.W. Weathers, et al., Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental disorders-fifth edition (PCL-5) in veterans, Psychol. Assess. (2015).
[49] S. Galea, M. Tracy, Participation rates in epidemiologic studies, Ann. Epidemiol. 17 (2007) 643–653.
[50] N. Breslau, R.C. Kessler, H.D. Chilcoat, et al., Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma, Arch. Gen. Psychiatry 55 (1998) 626–632.
[51] N. Breslau, The epidemiology of posttraumatic stress disorder: what is the extent of the problem? J. Clin. Psychiatry 62 (Suppl. 17) (2001) 16–22.
[52] J. Angst, A. Gamma, M. Gastpar, et al., Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies, Eur. Arch. Psychiatry Clin. Neurosci. 252 (2002) 201–209.