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Letter

Symptoms of depression and anxiety in patients with thalassemia: Prevalence and correlates in the thalassemia longitudinal cohort †

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Abstract

Thalassemia is an inherited blood disorder that requires lifelong adherence to a complicated and burdensome medical regimen which could potentially impact emotional functioning of patients. The importance of understanding and promoting healthy emotional functioning is crucial not only to psychological well-being, but also to physical health as it has been shown to impact adherence to medical regimens [1–4]. The current study aimed to [1] determine the prevalence of depressive and anxiety symptoms in adolescent and adult patients with thalassemia; and [2] explore possible demographic, medical, and psychosocial correlates of these symptoms in 276 patients (14–58 years

old, M age = 27.83; 52% female). Overall, most patients did not report experiencing significant symptoms of anxiety and depression (33% of participants indicated experiencing symptoms of anxiety and 11% symptoms of depression). Females and older patients were more likely to experience these symptoms than males and younger patients. Symptoms of anxiety and depression were positively associated with self-report of difficulty with adherence and negatively associated with quality of life. Given these findings, regular screening for anxiety and depression symptoms could help to identify at-risk individuals to provide them with appropriate psychological support with the goal of improving both emotional and physical health. Am. J. Hematol., 2010. © 2010 Wiley-Liss, Inc.

Literature examining psychological functioning in individuals with thalassemia indicates that this population is vulnerable to experiencing psychological adjustment problems, such as symptoms of depression and anxiety [5–9]. However, except for one study conducted with adult patients in Italy [7], these studies are generally limited to small, homogeneous samples of children [8, 9]. Because of advances in medicine over the past few decades, patients with thalassemia are living longer than ever before, and thus understanding how thalassemia and its treatment differentially affects adults is essential. It is also important to understand which demographic, medical, and psychosocial variables are related to the experience of psychological distress so that we can identify individuals at risk and develop targeted interventions.

The current study includes a subset of 276 patients enrolled in the Thalassemia Longitudinal Cohort (TLC), a multi-center multinational study conducted by the NHLBI-sponsored Thalassemia Clinical Research Network (TCRN), who had completed self-report measures on symptoms of anxiety and depression (HADS) and quality of life (SF-36) at baseline. Participants ranged in age from 14- to 58-years old (M = 29.38). Fifty-two percent of the participants were female, and 55% indicated they were Caucasian, with another 41% reporting Asian ethnicity. Table I provides more detailed demographic and medical information.

Table I. Patient Demographics

Demographic or medical item	*n*(%) of 276
Gender	
Female	144 (52)
Age	
≥18	235 (85)
Race	
Caucasian	148 (55)
Asian	112 (41)

Other	11 (4)
Chelator type	
Deferoxamine	65 (24)
Oral chelator	153 (55)
Combination	37 (13)
None	21 (8)
Thalassemia diagnosis	
B-thal regularly transfused[a]	213 (78)
B-thal intermittently transfused[b]	24 (9)
B-thal nontransfused[c]	3 (1)
HbH CS	4 (1)
E-B-thal regularly transfused[a]	22 (8)
E-B-thal intermittently transfused[b]	6 (2)
E-B-thal nontransfused[c]	1 (0.36)
Alpha-thal	2 (0.73)
Ferritin	M ± SD, Median (range)
	2,220 ± 2,530, 1,387 (67–23,71
Country	
United States	201 (73)
Canada	36 (13)
United Kingdom	39 (14)

a At least eight transfusions in past year

b One to seven transfusions in past year.

c No transfusions in past year in past year.

Utilizing the cut-off score of 8 described in the HADS manual [10], 33% of participants described experiencing significant symptoms of anxiety. Specifically, 20% of participants indicated experiencing mild symptoms of anxiety, 12% indicated moderate symptoms, and 1% indicated severe symptoms. Using the same cut-off for the depression items, 11% of participants indicated experiencing significant depressive symptoms, with 8% indicating mild symptoms, 2% moderate symptoms, and 1% severe symptoms (see Table II). It is possible that patients report experiencing more anxiety than depression due to the relatively new care initiatives and treatments that have developed over the past decade and the uncertainty that can sometimes be associated with trying new things.

Table II. Descriptive Data From the HADS

HADS	Anxiety (M ± SD or %)	Depression (M ± S
Across entire sample	6.31 ± 3.72	3.42 ± 3.02
Percent mild[a]	20	8
Percent moderate[b]	12	2
Percent severe[c]	1	1

Males	5.62 ± 3.31	3.17 ± 2.7
Females	6.93 ± 3.96	3.66 ± 3.27
Age group		
14–17	4.60 ± 2.99	1.82 ± 1.86
18–24	6.10 ± 3.49	3.14 ± 2.54
25–34	7.10 ± 3.67	4.01 ± 2.86
35–44	6.68 ± 4.02	3.60 ± 3.69
45–54	6.15 ± 4.31	4.25 ± 3.14
55–64	9.00 ± 3.61	7.67 ± 5.13

Note: HADS scores range from 0 to 21

a Scores of 8–10

b Scores of 11–14.

c Scores of ≥15.

Overall, these finding suggest that the majority of patients diagnosed with thalassemia do not experience significant symptoms of anxiety or depression. This is in contrast to results of the Messina et al. [7] study conducted with adults in Italy, which suggested that most of the patients diagnosed with thalassemia had severe psychosocial problems, including depression and anxiety. It is likely that these conflictual findings are the result of differences in the two samples and the measurement tools used. Specifically, the Messina et al. study was conducted with a homogeneous group and relied on a measure that assesses multiple elements of an individual's functioning, whereas the sample in the

current study includes greater heterogeneity and relied on a measure which focuses solely on symptoms of anxiety and depression. Given the specificity of the measure used in the current study, as well as the larger sample size and greater heterogeneity, it is probable that the current assessment is a more accurate estimate of the prevalence of symptoms of anxiety and depression than the study conducted by Messina et al.

A review of previously conducted research that utilized the HADS with various samples indicates that the current sample of patients with thalassemia experience similar rates of anxiety symptoms (32%), but lower rates of depressive symptoms (22%) compared to a sample of patients with diabetes [11], and higher rates of symptoms of anxiety (21%) and similar rates of symptoms of depression (10%) compared to a sample of patients diagnosed with cystic fibrosis [12].

Comparison with general population samples was more challenging, due to the wide range of results found in research using the HADS to examine prevalence estimates in normative samples. Specifically, studies utilizing the HADS in general population samples have found between 7 and 33% of individuals endorse significant symptoms of anxiety and 5 and 11% endorse significant symptoms of depression [13–15]. This suggests that individuals with thalassemia are as likely as or more likely to experience symptoms of anxiety and depression than individuals without chronic medical conditions.

Bivariate associations between socio-demographic and medical variables and the HADS indicated several significant relationships. Specifically, there was a significant difference in symptoms of anxiety and depression by age, with older participants (≥18) endorsing more symptoms of anxiety ($P < 0.005$) and depression ($P < 0.001$) than younger patients (<18). This finding is likely the result of the cumulative burden associated with longer disease duration in older patients. Moreover, research conducted in the general psychiatric literature indicates that psychological disorders are more prevalent in adults than in adolescents [16, 17], which is consistent with our finding.

There was also a significant difference in symptoms of anxiety by gender, with females endorsing more symptoms than males ($P < 0.005$; symptoms of depression were also greater in females, but not statistically different). This finding is consistent with the psychiatric literature that suggests that compared to men, women report experiencing more symptoms of depression and anxiety, with woman being diagnosed with anxiety disorders and depression approximately two times as often as men [18–21]. No significant differences were indicated by ethnicity, diagnosis, type of chelator, or transfusion status.

In regards to the adherence data, after controlling for age and gender, when using the mean for all of the adherence items, both symptoms of anxiety and depression were significantly correlated with adherence difficulty ($P < 0.05$; $P< 0.001$ respectively; See Table III). This finding that self-report of adherence difficulty is associated with psychological functioning is supported by previously conducted research with other chronic illness populations [1–4].

Table III. Correlations With HADS Depression and Anxiety Subscales and Variables of Interest, Controlling for Age and Gender

	Depression
Adherence	

Mean adherence difficulty score (all items)	0.31***
Had a problem remembering to take the chelator	0.21**
Questions only for patients taking oral chelators	
Had a problem taking the chelator	0.16*
Questions only for patients taking deferoxamine	
Had a problem preparing deferoxamine	0.24*
Had a problem sticking yourself	0.33**
Had a problem wearing the pump	0.39***
Ferritin	0.06
Quality of life (SF-36)	
Physical component summary score	−0.42***
Mental component summary score	−0.59***
Disease severity	
Number of secondary complications	0.10
Number of iron related complications	0.08
Number of transfusion related complications	0.02

Note: HADS anxiety and depression: higher = more symptoms of anxiety and depression. Adherence: higher = m adherence. SF-36: higher = better quality of life. Disease severity: higher = greater severity.

*** $P < 0.001$,

** $P < 0.01$,

* $P < 0.05$.

When examining the adherence items separately, difficulty remembering was significantly correlated with depression ($P < 0.01$), but not anxiety. These differences are likely the result of the diminished ability to think or concentrate, fatigue, and hopelessness, which are more commonly symptoms of depression and not anxiety. In fact, having a small amount of anxiety may be protective to individuals as it will help them to be vigilant with following their medical regimen.

For the item that asked individuals taking an oral chelator if they had "a problem taking" the chelator, a significant relationship was found for depression ($P < 0.05$), but not anxiety. Interestingly, although there was no significant difference in report of symptoms of anxiety and depression by chelator type, those individuals taking Deferoxamine who indicated more symptoms of anxiety and depression were also more likely to endorse difficulty sticking oneself ($P < 0.005$), problems wearing the pump for many hours ($P < 0.001$), and problems preparing the medication ($P < 0.05$).

Utilizing ferritin level as a biological indicator of adherence, a significant relationship with symptoms of anxiety or depression was not indicated. It is possible that we did not find a relationship between ferritin and symptoms of anxiety and depression because ferritin is only a crude estimate of overall adherence and the current study only examined ferritin at one time point.

Experiencing more symptoms of both anxiety and depression were associated with poorer functional health and well being (quality of life; $P < 0.001$; see Table III). This finding is consistent with research conducted with children and adolescents diagnosed with thalassemia [6, 9] and with research conducted with other illness groups [22].

Finally, we did not find a significant relationship between disease severity (as measured by number and type of secondary complications) and experiencing symptoms of depression and anxiety (see Table III). It is possible that a relationship between these variables was not found because we are not adequately capturing disease severity with the number and type of secondary complications. It is also possible that as seen in other illness populations, it is not the severity of the illness, but rather the perceived impact on functioning, intensity of the medical regimen, and ability to control the condition that contribute to experiencing symptoms of anxiety and depression [22, 23].

While the results of the current study provide useful information about the prevalence and correlates of experiencing symptoms of anxiety and depression in patients diagnosed with thalassemia, there are several limitations that should be noted.

First, the current study involves a heavy reliance on self-report measures which are vulnerable to subject bias. Data collection through other informants or methods (e.g., physician's report of severity and/or adherence) would further validate the findings of the current study. Future studies also should include a standardized measure of adherence.

A further limitation of the current study is the inability to make causal inference. Specifically, because the findings are based on cross-sectional, correlational data, we are unable to determine if experiencing symptoms of depression and anxiety lead to poorer quality of life and decreased adherence or vice versa. Future research utilizing longitudinal designs will help to clarify this relationship.

Methods

Anxiety and depression symptoms.

Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS; 10). The HADS is a 14-item self-report measure in which participants are asked to respond to items using a four-point Likert scale ranging from 0 to 3, with higher scores reflecting higher occurrence of symptoms of depression and anxiety. In this sample, the internal consistency (Cronbach's alphas) of the HADS-A subscale was 0.80 and 0.76 for the HADS-D subscale.

Quality of life.

Functional health and well being was measured using the SF-36 version 2 [24]. The SF-36 is a 36 item self-report measure which yields a physical component summary (PCS) and mental component summary (MCS) score. Higher scores indicate higher quality of life. In the current sample internal consistencies (Cronbach's alphas) for the subscales that make up the PCS ranged from 0.82 to 0.95. For the subscales that are included in the MCS, internal consistencies ranged from 0.78 to 0.95.

Adherence to chelation.

Patients prescribed Deferoxamine were asked to indicate on a five-point Likert scale (1 = never and 5 = a lot) how often they (1) had a problem remembering to do Deferoxamine; (2) had a problem preparing Deferoxamine; (3) had a problem sticking yourself for Deferoxamine; and (4) had a problem wearing your pump for so many hours. Patients prescribed an oral chelator were asked to indicate on a five-point Likert scale (1 = never and 5 = a lot) how often they (1) had a problem remembering to take the oral chelator; and (2) had a problem taking the oral chelator. Patients prescribed both Deferoxamine and an oral chelator answered all questions.

A mean score including responses to all relevant questions was calculated for each participant. Higher scores indicate more difficulty with adherence.

Ferritin levels taken at the date closest to data collection were obtained from the patient's medical record.

Disease severity.

Disease severity was assessed by the number and type of secondary complications. Specifically, to calculate number of complications, a summary score of 14 potential complications was created for each person. The 14 complications included cardiac complications (congestive heart failure, ventricular arrhythmia, low cardiac T2* by MRI), endocrine complications (diabetes Type I, diabetes Type II, growth

hormone deficiency, hypothyroidism, hypoparathyroidism, hypogonadotropic hypogonadism), liver disease (cirrhosis), and transfusion-related complications and infections (alloimmumization, active hepatitis C, chronic active hepatitis B, HIV). A second variable was created which indicated whether the participant's secondary complications were iron-related, transfusion-related, or both.

Demographic and medical information.

As part of the larger TLC study, demographic (e.g., age, ethnicity, gender) and medical data (e.g., ferritin, method of chelation, frequency of transfusions) were collected through self-report and medical chart review.

Analytic strategy.

Initial descriptive statistics were calculated for socio-demographic and medical variables; independent variables: measures of adherence, quality of life, and disease severity; and outcome variables: HADS-A and HADS-D.

Bivariate associations between socio-demographic and medical variables, HADS-A, and HADS-D were conducted. Bivariate associations with anxiety symptoms were examined using student's *t* test or analysis of variance (ANOVA). Bivariate associations with depressive symptoms were examined using Wilcoxon or Savage tests.

Partial correlations and analysis of covariance, controlling for significant socio-demographic and medical variables, were conducted to examine the associations between the HADS-A, HADS-D, and measures of adherence, quality of life, and disease severity.

Appendix

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Thalassemia Longitudinal Cohort data reported in this article.

Children's Hospital, Boston (*N* = 38): Ellis Neufeld, MD, PhD, Principal Investigator, Jennifer Braunstein, NP, Research Nurse, Amber Smith, Study Coordinator, Latoya Lashley, Study Coordinator; Satellite: University of Texas Southwestern Medical Center at Dallas (*N* = 12), Charles Quinn, MD, MS, Principal Investigator, Deborah Boger, RN, MSN, PNP, Study Coordinator, Leah Adix, Study Coordinator, Sandra Richardson, Study Coordinator; Children's Healthcare of Atlanta (*N* = 16), Jeanne Boudreaux, MD, Principal Investigator, Leann Hassen, Study Coordinator; Baylor College of Medicine (*N* = 6), Brigitta Mueller, MD, Principal Investigator, Bogden Dino, Study Coordinator. Weill Medical College of Cornell University (*N* = 59): Patricia Giardina, MD, Principal Investigator, Elizabeth Evans, Study Coordinator; Satellite: Winthrop University Hospital (*N* = 6), Mark Weinblatt, MD, Principal Investigator, Linda Skelly, Study Coordinator. The Children's Hospital of Philadelphia (*N* = 59): Janet Kwiatkowski, MD, Principal Investigator, Marie Martin, RN, Research Nurse, Owen Beams, Study Coordinator; Satellite: Children's Memorial Hospital, Chicago, IL (*N* = 39), Alexis Thompson, MD, Principal Investigator, Janice Beatty, RN, Research Nurse, Tiffany Drinkwater, Study Coordinator. Children's Hospital at Oakland (*N* = 52): Elliott Vichinsky, MD, Principal Investigator, Dru Foote, NP, Research Nurse, Nancy Sweeters, Study Coordinator, Olivia Vega, Study Coordinator; Satellites: Children's Hospital of Los Angeles (*N* = 12),

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