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Original Paper

The Effect of Biopsychosocial Variables in Fatigue in Patients with Hemoglobinopathies

Eleni F. Aslani[1,2], Georgios N. Lyrakos[1,3*], Dimitra Vini[2], Marouso Drosou-Servou[2] & Maria Tsironi[1]

[1] Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of the Peloponnese, Sparti, Greece

[2] Thalassemia Transfusion Unit, General Hospital of Nikaia, "Agios Panteleimon", Nikaia, Greece

[3] Psychiatric Department, General Hospital of Nikaia, "Agios Panteleimon", Nikaia, Greece

[*] Georgios N. Lyrakos, Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of the Peloponnese, 18454, Sparti, Greece

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Abstract

Purpose*: The purpose of the present study was to explore the biopsychosocial variables affecting fatigue in patients with hemoglobinopathies.* ***Methods****: 102 patients undergoing transfusion treatment from one hospital in Athens, Greece participated in the study. Fatigue was measured with the Multidimensional Fatigue Inventory (MFI), quality of life with the Euro5D thermometer as self-perceived health and psychological variables with the Depression, Anxiety and Stress Scale (DASS 21). Statistical analysis was performed with SPSS21.* ***Results****: 63 were females (61,4%) and 39 males (38,6%). The mean age of the sample was 41.7±9.2 years, while the majority of participants were patients with a diagnosis of homozygous β-Thalassemia (81.4%). Multivariate analysis revealed 6 independent models for each dimension of fatigue, while every one of the five dimensions of MFI as well the total score of the inventory, revealed a different model of correlations with mixed variables, related with disease complications, adherence to treatment, sex, the self-perceived quality of life, as well as the qualitative characteristics of fatigue related with disease complications.* ***Conclusions****: Fatigue has been identified as a very common symptom in patients with thalassemia with many variables affecting it in this population. Our results broadens the evidence regarding fatigue in hemoglobinopathies and leads us to the need for distinguishing the etiologies leading to fatigue in hemoglobinopathies since it is an important factor affecting HPQoL. Longitudinal studies are needed in order to understand the path of fatigue and the factors influencing the condition.*

Keywords

fatigue, hemoglobinopathies, thalassemia, quality of life, adults, self-perceived health, regression analysis

1. Introduction

Haemoglobinopathies (thalassemia and sickle cell disease [SCD]) are the most common hereditary diseases in the Greek population. Their current trait incidence in general population is ~8 % and ~1-2%, respectively, while during the previous years it had reached up to 15-20%, in certain geographic areas (Schizas et al., 1977). According to the new national registry, four thousand thirty-two patients has been included in the Greek hemoglobinopathies National registry, while more than half of them has thalassaemia major. Compared to the previous report (Voskaridou et al., 2012), a reduction is evident in the total number of all hemoglobinopathies, except for hemoglobinopathy "H" (Voskaridou et al., 2018). Based on this report, most patients had low or moderate liver iron concentration (LIC) values, while only a non-negligible proportion of them had high LIC. The burden due to heart iron overload was less prominent while the major causes of morbidity and mortality are Cardiac- and liver-related complications. Although, from 2000 to 2015, researchers observed a decrease in heart-related deaths along with an increase in liver-associated fatalities (Voskaridou et al., 2018).

The introduction of oral iron chelators, including deferiprone in 2000, initially as monotherapy and then in combination with deferoxamine, and deferasirox in 2007, has significantly enhanced the efficacy of chelation therapy (Tanner et al., 2007), and according to Voskaridou et al. (2018), the Hellenic Prevention Program along with the advances in chelation regimens and iron status monitoring have resulted in improved patient outcomes.

Fatigue on the other hand is a nonspecific symptom, because it can be indicative of many causes or conditions that includes physiological states such as sleep deprivation or excessive muscular activity, as well as medical conditions such as chronic inflammatory conditions, autoimmune illnesses, bacterial or viral infections. It can also be indicative of psychiatric disorders such as major depression, anxiety disorders, and somatoform disorders (Manu, Lane, & Matthews, 1992), while it is sometimes defined as "tiredness", feeling tired, being fatigued, feeling weak in part of the body, tired or lacking in energy, or experiencing "everything as an effort" (Cope, 1992, p. 273).

Over the last thirty years, fatigue has come to be recognized as a serious symptom of many illnesses that can significantly impair a person's functioning and have a negative impact on quality of life in many chronic illnesses, including after cancer treatment (Bartsch, Weis, & Moser, 2003; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Smets et al., 1993), systemic lupus erythematosus (SLE) (Jacobson, Gange, Rose, & Graham, 1997), multiple sclerosis (Schwid, Covington, Segal, & Goodman, 2002), Human Immunodeficiency Virus (HIV) infection, viral and cholestatic liver diseases, rheumatoid arthritis (Swain, 2000) and recently, it has been reported in patients with SCD as one of the major symptoms along with pain (While & Mullen, 2004), and thalassemia intermedia patients (Tabei

et al., 2013). Fatigue has been examined mostly in children's populations (Panepinto et al., 2014; Dampier et al., 2016), as a symptom that affects quality of life in these patients (Dampier et al., 2010; Ameringer et al., 2014).

However, understanding fatigue in chronic medical disease, remains difficult to prove and even though it is considered a primary or a common symptom, such as in multiple sclerosis or SLE, fatigue often does not correlate with disease status or physiological findings (Schwid et al., 2002; Krupp et al., 1990; Wang et al., 1998; Omdal et al., 2003). Even though, fatigue has been identified as a major symptom, affecting both health and quality of life in patients with sickle cell disease, and has been recognised as a major symptom affecting the quality of life in patients with thalassemia major as well (Lyrakos et al., 2012), until now, there is no study exploring the factors affecting fatigue in patients with hemoglobinopathies under transfusion treatment, according to the biopsychosocial model of health.

The purpose of the present study was to investigate the factors affecting the symptom of fatigue in patients with hemoglobinopathies under transfusion therapy, including both symptoms of the disease, as well as psychological factors and sociodemographic characteristics, according to the biopsychosocial model of health and illness.

2. Method

2.1 Participants

This analysis included participants enrolled in a Thalassemia Transfusion Department at General Hospital of Nikaia "Ag. Panteleimon" (GHN), Greece, between 2016 and 2018. The study assessed common measures of fatigue, anxiety, depression and stress, hematological biomarkers, hemosiderosis level, chelation therapy, adherence to treatment and Health related quality of life (HRQoL) as well as socio-demographic characteristics in adult patients (>18 years) with hemoglobinopathies. The protocol was approved by the Hospital Scientific Board at General Hospital of Nikaia "Ag. Panteleimon" (G.H.N.). Written informed consent was obtained from all patients before their participation in the study.

2.2 Measurements

2.2.1 Multidimensional Fatigue Inventory (MFI)

The MFI-20 comprises five subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (Smets et al., 1995). Each subscale includes four items with five-point Likert scales. General fatigue includes general statements about fatigue and decreased functioning and was designed to encompass both physical and psychological aspects of fatigue. Physical fatigue concerns physical sensations related to fatigue. Mental fatigue pertains to cognitive functioning, including difficulty concentrating. Reduced activity refers to the influence of physical and psychological factors on the level of activity. Reduced motivation relates to lack of motivation for starting any activity. Scores on each subscale range from 4 to 20, with higher scores indicating greater fatigue.

2.2.2 Depression Anxiety Stress Scale 21 (DASS21)

DASS-21 is a quantitative measure of distress on the basis of three subscales of depression, anxiety (eg, symptoms of psychological arousal), and stress (e.g., cognitive, subjective symptoms of anxiety) (Lovibond, P. F. & Lovibond, S. H., 1995). It is the short form of DASS 42 and it was used for this study because it is a measurement that has been validated in the Greek population and has been used in chronic patients as well (Lyrakos et al., 2011). Each subscale has 7 questions that respondents answered according to a Likert-type scale ranging between 0 (“does not apply to me at all”) to 3 (“applies to me very much, or most of the time”).

2.2.3 Haematological Biomarkers

Haemoglobin before transfusion and Serum ferritin concentration which is a useful but rather rough estimate of total body iron load, were measured the day of the interview.

2.2.4 Magnetic Resonance Imaging

Levels of T2* for heart and liver of the last five years were retrieved from patients files. This was decided because T2* imaging provides a precise quantification of myocardial and hepatic iron load and has become a useful tool for the evaluation of patients and for the therapeutic guidance and follow-up of iron chelation therapy (T2* reference values: normal, >25 ms; mild/moderate iron load, 8 to 20 ms; severe iron load, <8 ms) (Tanner et al., 2007).

2.3 Statistical Analysis

Statistical analysis was performed using programs available in the SPSS statistical package (SPSS 10.6, Chicago, USA). All variables were tested for normal distribution of the data. Data are shown as mean ± SD, unless it is stated otherwise.

Univariate linear regression analysis was performed to look for the relationship between the total score of MFI and the five main domains of the inventory; General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Activity and Reduced Motivation and the variables of interest in the sample population. Then, multivariate linear regression analyses were performed to look for independent associations between the five main domains of the MFI and the variables of interest, one for every domain of MFI (General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity) and one for the total score of the inventory. The variables that were used in the models included the demographic characteristics of the sample (sex, age, education, marital status, place of residence), hematological biomarkers (hemoglobin and serum ferritin), magnetic reasoning markers (T2 * liver, T2 * heart), treatment variables like adherence to chelation treatment, frequency of transfusion per days, HRQoL as it was measured by the current health status, the kind of diagnosis, the type of chelation therapy, levels of anxiety, stress and depression, and qualitative characteristics of fatigue which included the cause of fatigue according to the patient, existence of fatigue before transfusion, and increase of fatigue during the last month. All independent variables in the multivariate analyses models were tested for multicolinearity. $p<0.05$ (two-tailed) was considered statistically significant.

3. Result

The sample consisted of 63 females (61,4%) and 39 males (38,6%). The age of the sample ranged from 19 to 72 years. The average age of the sample was 41.7 years with a standard deviation of 9.2 years, while the majority of participants were patients with a diagnosis of homozygous β-Thalassaemia (bT) (81.4%). Finally present health status had a mean of 69.9 with a SD 19.3, with minimum value 10 and maximum 100. The level of education, marital status, place of residence and diagnosis characteristics are presented in table 1, while means and standard deviations for fatigue, depression, anxiety, stress, hematological and magnetic reasoning markers are presented in Table 2 respectively.

Table 1. Descriptive Summary Scores for the Demographic Characteristics of the Sample

Variable	N	%
Sex		
Males	39	38.6
Females	63	61.4
Total	102	100
Educational level (n=102)		
Primary school	13	12,9
Elementary school	8	7,9
High school	37	36,6
University or college	40	39,6
MSc- PhD	4	3,0
Marital status (n=101)*		
Single	36	35,6
Married	51	50,5
Divorced	12	11,9
Widow	2	2,0
Place of residence (n=102)*		
Athens	84	84,0
Rural area	16	16,0
Diagnosis (n=102)		
Thalassemia major	78	76,5
Thalassemia intermedia	17	16,7
Sickle -beta Thalassemia	7	6,9

N: number of participants; %: percent of total sample;

*missing values are due to participants not answering the specific questions.

Table 2. Means and Standart Deviations of the Sample Variables

	N	Min	Max	M	SD
Age	102	27	72	44,73	9,59
Hb	100	7,90	11,10	9,72	0,63
Serum ferritin	100	20,70	10562	1539,82	1891,18
T2 * liver	88	0,70	37,50	11,39	10,21
T2 * heart	88	4,10	41,30	30,86	9,26
Transfusion frequency	101	10	32	19,09	5,54
Present health	100	10	95	66,42	19,56
Depression	101	0	38	8,75	9,93
Anxiety	100	0	40	6,26	7,02
Stress	101	0	38	12,44	9,04
General fatigue	100	4,00	20	12,14	3,22
Physical fatigue	100	4,00	20	11,71	3,54
Reduced activity	100	4,00	20	10,77	3,52
Reduced motivation	100	4,00	17	9,85	3,12
Mental fatigue	100	4,00	20	10,06	2,69

M: Mean; SD: Std. Deviation; Min: Minimum; Max: Maximum.

Sex, location, chelation treatment and existence of fatigue distribution were similar among the participants with thalassemia major, intermedia and sickle beta thalassemia (all comparisons were no significant). Significant differences were found in marital status between the 3 groups with the majority of thalassemia intermedia patients being marred (82.4%), while only 44,2% of thalassemia major patient were married. Age and transfusion frequency distribution had significant differences between participants (F=9.901, p=0.001 and F=38.938, p=0.001 respectively, while hemoglobin, ferritin, T2 * liver and T2 * heart distributions were similar among the participants with thalassemia major, intermedia and sickle beta thalassemia (all comparisons were non-significant) (Table 3).

Table 3. Sample Distribution and Differences According to the Type of Hemoglobinopathy for the Independent Variables of Interest

		Thalassemia major	Thalassemia intermedia	Sickle-beta Thalassemia	Test/p value
Gender	*Males*	31	8	1	5.003*/0.082
	Females	46	9	7	
Location	*Athens*	65	14	5	0.989*/0.610
	Elsewhere	12	3	2	
Chelation	*Deferoxamine*	21	6	1	9.060*/0.170

	Deferasirox	15	5	3	
	Desferrioxamine	7	3	2	
	*Combination***	34	3	2	
Existence of fatigue	*Yes*	64	12	7	3.369*/0.184
	No	14	5	0	
Age	*(Mean/SD)*	42.6 ±8.3[a]	50.5 ±9.7[b]	54.3 ±12.6[c]	[a-b]-7.855/**0.004** [a-c]-11.670/**0.003**
Hemoglobin	*(Mean/SD)*	9.8 ±0.5	9.5 ±0.6	9.3 ±1.2	F=3.065/0.051
Ferritin	*(Mean/SD)*	1699.8 ±2086	963.1 ±911.4	1202.8 ±1891	F=1.178/0.312
T2 * liver	*(Mean/SD)*	11.7 ±10.5	10.8 ±9.1	11.4 ±0.3	F=0.518/0.598
T2 * heart	*(Mean/SD)*	29.9 ±10.1	34.5 ±3.2	35.1 ±0.2	F=1.825/0.167
Transfusion frequency per days	*(Mean/SD)*	17.2 ±3.6[a]	23.7 ±6.6[b]	29.1 ±3.2[c]	[a-b]-6.550/**0.001** [a-c]-11.987/**0.001** [b-c]-5.437/**0.014**

*: chi square test or else F for ANOVA; ** Desferrioxamine & Deferoxamine; p value in bold if p<0.05; For ANOVA significant mean differences were calculated with the use of Bonferonni post hoc test.

3.1 Multivariate Analysis

The final model of multivariate analysis with the use of stepwise method using as dependent variable the total score of the MFI and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in Table 4.

Table 4. Multifactorial Analysis with Dependent Variable Total Fatigue (Total Score of MFI)

Final model with the independent variables contributing to the variance of the Total fatigue						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	62,426	4,312		14,477	0,000	53,843	71,009
Health Thermometer	-0,174	0,060	-0,290	-2,923	**0,005**	-0,292	-,056
Fatigue before the transfussion< week	8,411	2,694	0,308	3,122	**0,003**	3,049	13,774
Non adherence to chelation therapy after doctor's orders	4,969	2,359	0,209	2,106	**0,038**	0,273	9,665

a. Dependent variable: Total fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 23% of the variance in general fatigue (R^2=0,231, p=0,038) is related with the current state of health as it is measured by the EQ-5D health thermometer (β=-0,290, p=0.005), existence of fatigue before transfusion for less than a week (β=-0.308, p=0.003) and non-adherence to chelation therapy for long periods of time following physician's order (β=-0.209, p=0.038).

The final model of multivariate analysis with the use of stepwise method using as dependent variable General fatigue and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in Table 5.

Table 5. Multifactorial Analysis with Dependent Variable General Fatigue

Final model with the independent variables contributing to the variance of the General Fatigue						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	16,519	1,293		12,771	0,000	13,944	19,093
Health Thermometer	-0,060	0,018	-0,346	-3,330	**0,001**	-0,097	-0,024
Subcutaneous chelator	-2,390	1,009	-0,242	-2,369	**0,020**	-4,399	-0,382
Fatigue from 2 weeks to 1 month before transfusion	-3,140	1,407	-0,233	-2,231	**0,029**	-5,941	-0,338

a. Dependent variable: General fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 18% of the variance in General fatigue (R^2=0,183, p=0,029) is related with the current state of health as measured by the EQ-5D health thermometer (β=-0.346, p=0.001), the use of subcutaneous chelation therapy (Desferrioxamine) (β=-0.242, p=0.02) and existence of fatigue before the transfusion for a period of two weeks to 1 month (β=-0.233, p=0.029).

The final model of multivariate analysis with the use of stepwise method using as dependent variable Physical fatigue and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in Table 6.

Table 6. Multifactorial Analysis with Dependent Variable Physical Fatigue

Final model with the independent variables contributing to the variance of the Physical fatigue						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	16,064	1,373		11,703	0,000	13,331	18,797
Health Thermometer	-,077	,019	-0,402	-4,042	**0,000**	-0,116	-,039
Fatigue from 2 weeks to 1 month before transfusion	-3,528	1,492	-0,237	-2,364	**0,021**	-6,499	-,557
Combination chelation therapy	1,679	0,716	0,231	2,344	**0,022**	0,253	3,106
Fatigue before transfusion< week	1,796	0,864	0205	2,080	**0,041**	0,077	3,516

a. Dependent variable: General fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 26% of the variance in Physical fatigue (R^2=0,266, p=0,04) is related to the current state of health as measured by the EQ-5D health thermometer (β=-0.402, p=0.001), existence of fatigue for a period of two weeks to one month before the transfusion (β=-0.237, p=0.021), use of combination chelation therapy (Desferrioxamine & Deferoxamine) (β=0.231, p=0.022) and existence of fatigue before transfusion for less than a week (β=0.205, p=0.041).

The final model of multivariate analysis with the use of stepwise method using as dependent variable Reduced activity and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in Table 7.

Table 7. Multifactorial Analysis with Dependent Variable Reduced Activity

Final model with the independent variables contributing to the variance of Reduced activity						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	8,740	0,510		17,150	0,000	7,726	9,755
Fatigue before transfussion< week	2,833	0,844	0,330	3,356	**0,001**	1,153	4,514
Sex	1,832	0,709	0,259	2,582	**0,012**	0,420	3,244
Non adherence to chelation therapy after doctors' orders	1,652	0,748	0,221	2,208	**0,030**	0,163	3,140

a. Dependent variable: General fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 24% of the variance in reduced activity (R^2=0.330, p=0.001) is related with existence of fatigue during the last days of the week before the transfusion (β=-0,330, p=0.005), gender and in particular being a woman (β=0.259, p=0.012) and non-adherence to chelation therapy for long periods of time following physician's order (β=-0.221, p=0.030).

The final model of multivariate analysis with the use of stepwise method using as dependent variable Reduced motivation and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in table 8.

Table 8. Multifactorial Analysis with Dependent Variable Reduced Motivation

Final model with the independent variables contributing to the variance of Reduced motivation						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	9,000	0,401		22,450	0,000	8,202	9,798
Non adherence to chelation therapy after doctors' orders	2,115	0,708	0,313	2,990	**0,004**	,707	3,524
Fatigue due to working conditions	4,500	2,140	0,220	2,103	**0,039**	,241	8,759

a. Dependent variable: General fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 13% of the variance in reduced motivation (R^2=0,132, p=0,039). Is related with non-adherence to chelation therapy for long periods of time following physician's order (β=-0,313, p=0.004) and fatigue due to the working conditions of the patient (β=0.220, p=0.039).

Finally, The final model of multivariate analysis with the use of stepwise method using as dependent variable Mental fatigue and independent variables sex, age, education, marital status, place of residence, hemoglobin, serum ferritin, T2 * liver, T2 * heart, ejection fraction of heart, frequency of transfusion per days, current health status, diagnosis, type of chelation therapy, anxiety, stress, depression, adherence to chelation treatment, cause of fatigue, existence of fatigue before transfusion, and increase of fatigue in the last month is presented in Table 9.

Table 9. Multifactorial Analysis with Dependent Variable Mental Fatigue

Final model with the independent variables contributing to the variance of Mental fatigue						95,0% confidence intervals for B	
	B	SE	Beta	t	p value	Lower bound	Higher bound
(Constant)	11,513	0,891		12,928	0,000	9,741	13,285
Fatigue before transfussion < week	3,010	0,579	0,490	5,195	**0,000**	1,857	4,163
Health Thermometer	-,031	0,013	-0,231	-2,454	**0,016**	-0,057	-0,006

a. Dependent variable: General fatigue; In bold statistical significant values for p<0.05.

Multivariate analysis showed that 29% of the variance in mental fatigue (R^2=0,290, p=0,016) is associated with existence of fatigue before transfusion for less than a week (β=0.490, p=0.001) and with the current state of health as it is measured by the health thermometer of the EQ-5D (β=-0.231, p=0.016).

4. Discussion

The aim of this study was to investigate the factors that explain the variance of fatigue through the biopsychosocial model for health and illness. The first result, regarding the type of hemoglobinopathy, was that there were no differences between thalassemia major, intermedia and sickle beta thalassemia patients in most of the variables, except the frequency between transfusions, which is a logical difference since every hemoglobinopathy has a different treatment pattern. The second difference was found in the mean age of the three groups, a result that has to do with the fact that both thalassemia intermedia as well as sickle beta thalassemia patients are starting transfusion therapy later in their life than thalassemia major patients.

Regarding fatigue, analysis revealed that it was related with several variables, mostly physical. In fact every one of the five dimensions of MFI show a different model of correlations with mixed variables related with disease complications, adherence to treatment, sex, the self-perceived quality of life, as well as the qualitative characteristics of fatigue, something that leads us to a first conclusion that fatigue in hemoglobinopathies is multidimensional.

As expected, our findings suggest that patients with hemoglobinopathies experiences fatigue, as it was measured with the MFI and different factors affect different dimension of fatigue.

One of the major factors which had a significant effect in the total score of the questionnaire as well as in general and physical fatigue, was the health related quality of life, as it was measured with the thermometer of the EuroQ5D. This result is consistent with results of previous studies showing that fatigue is one of the factors affecting the quality of life in patients with hemoglobinopathies and vice versa (Dampier et al., 2010; Dampier et al., 2016; Ameringer, Elswick, & Smith, 2014; Lyon et al.,

2014).

Another important factor, which was revealed from the analysis, was the effect of adherence to chelation therapy and specifically, non-adherence to it for long periods of time, following physician's order. This variable appeared to be one of the statistically significant independent variables in multifactorial regression models in more than one of the MFI scales and the present result comes to reinforce the results of previous studies, showing that noncompliance to chelation treatment is correlated with decreased quality of life in patients with hemoglobinopathies, since fatigue is one of the major factors that negatively affects HRQoL (Trachtenberg et al., 2011; Lurakos et al., 2012).

Gender was also found to affect fatigue, with a higher percentage of women reporting fatigue than men. This result in relation to gender was expected, since it is not the first time that higher rates of fatigue in women have been found in patients with hemoglobinopathies (Dampier et al., 2016). Also, it has been found before that gender is one of the factors that affect the quality of life of patients with hemoglobinopathies (Sobota et al., 2011).

As expected from previous reports, chelation therapy was one of the main factors that contributed to the regression models for fatigue. As we can see from the final models in the regression analysis, the use of combination chelation therapy (Desferrioxamine & Deferoxamine) had a positive effect in physical fatigue, which means that it correlates with reduced fatigue, while the use of subcutaneous chelation therapy (Desferrioxamine) had a negative effect in general fatigue and was correlated with increased fatigue. Our results supports the findings of other studies that different types of chelation therapy have a significant effect on health self-assessment, with patients receiving oral chelation therapy reporting better HRQoL (Lourenco et al., 2005) and is consistence with other studies that suggests that the quality of life of beta thalassemia major patients is dependent on type of iron chelation treatment which they received (Seyedifar et al., 2016; Karnon et al., 2008; Goulas, Kourakli-Symeonidis, & Camoutsis, 2012). Also, according to previous studies, patients receiving Desferrioxamine were more likely to suffer from fatigue, as well as depression, dyspnea, and decreased physical functioning (Abetz et al., 2006; Pakbaz et al., 2005)

Another important factor explaining fatigue, seems to be the qualitative characteristics of fatigue, which was revealed from the opposite correlation, between the variables "existence of fatigue for a period between two weeks and a month" with "existing fatigue before transfusion for less than seven days". This result regarding physical fatigue can be interpreted if we understand that the more recent the feeling of fatigue in the patients, the greater the level of fatigue they score in the inventories.

Another interesting factor affecting reduced motivation was "fatigue due to working conditions". This result though, was expected, since reduced motivation has to do with the patient's inability to do things he used to do before, and work is an aggravating factor when fatigue coexists. This result supports previous findings in studies concerning patients with other chronic diseases, which found that when individuals suffers from fatigue as a result to working conditions, they score higher in the scales that evaluates fatigue (Weijman et al., 2004).

5. Conclusions

In conclusion, as shown by all the models in multivariate analysis, the current self-evaluation off health, regarding physical health with its complications in people with hemoglobinopathies is the main factor affecting fatigue, noncompliance to chelation therapy is the second factor which is also known to be associated with hepatic and kidney hemosiderosis, higher serum ferritin values and reduced compliance to treatment, while chelation therapy is the third most important factor contributing negative to fatigue, as has been seen in previous studies as well (Porter et al., 2011; Tools & Therapy, 2013; Lyrakos et al., 2011; Lyrakos et al., 2012).

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