

## Research Article

# Psychopathological Dimensions in Portuguese Subjects with Transthyretin Familial Amyloid Polyneuropathy

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### What Is It about?

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a fatal, chronic, progressive disease. It is a rare hereditary amyloidosis, which manifests as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood. There are very few studies about psychopathology in these patients and asymptomatic carriers. The present study evaluated psychopathological dimensions in this particular population. It concluded that many FAP patients and carriers had more psychopathological symptoms than the general population, when Brief Symptom Inventory (BSI) was applied. It also concluded that patients have higher risk for most of psychopathological dimensions. In addition, women are more vulnerable, and with time, patients have more psychological distress.

### Keywords

Transthyretin familial amyloid polyneuropathy · Familial amyloid polyneuropathy · Psychosocial issues · Psychopathology · Psychiatric issues

### Abstract

**Background:** Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a fatal, chronic, progressive disease. It is a rare hereditary amyloidosis, which manifests as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood. **Aims and Methods:** Our aim is to evaluate psychopathological dimensions in a population attending a consultation center for TTR-FAP. Two hundred and nine subjects (symptomatic and asymptomatic carriers), 84 men and 127, women participated in the study. Most subjects were married (67.1%) and most of them were still working; 33% were retired from work or on a sick leave. A sociodemograph-

ic questionnaire and The Brief Symptom Inventory (BSI) were applied. Statistical analysis was performed (descriptive analysis, Mann-Whitney, Wilcoxon, and Spearman tests). **Results:** The Global Symptom Index (GSI) was significantly higher in patients ( $p = 0.001$ ). Considering GSI, 32.7% of total subjects were above the median for general population. When subgroups were evaluated, 25.6% of symptomatic carriers, 26.3% of subjects without established diagnosis, and 39.1% of patients were above median. GSI was significantly higher in patients ( $p = 0.001$ ). Some BSI dimensions were also significantly higher in the patient group (somatization, depression, anxiety, and psychoticism) when compared with carriers. Women scored higher than men. Sick women scored higher for all dimensions except somatization. Asymptomatic carriers scored statistically higher for phobic anxiety ( $p = 0.01$ ), interpersonal sensitivity, anxiety, and depression. In patients, most dimensions and GSI ( $\rho = 0.33$ ,  $p = 0.002$ ) had positive correlations with years of disease. **Conclusions:** TTR-FAP patients and carriers are a very vulnerable group for psychological distress and psychopathological problems. Women and patients are at higher risk.

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## Introduction

Chronic diseases have important psychosocial consequences that demand significant psychological adaptive processes. They represent permanent threats and challenges for these patients, which must be addressed by an emotional balance that may be missing on several occasions. Chronic diseases impose diagnosis doubts, incapacities, loss of autonomy and quality of life, uncertainty about the future along with social and familial changes.

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare and fatal inherited amyloidosis of adult onset. Age at onset is variable and unpredictable, and the disease may have early or late onset (after 50s) [1–3]. It is a chronic, progressive disorder caused by generalized deposition of mutated TTR [4–8]. The disease is transmitted in an autosomal dominant way, with a penetrance that approaches 100% in the areas of higher prevalence. Although TTR Val30Met mutation occurs worldwide, the largest focus is located in the north of Portugal [9–11]. Andrade [12] observed the first patient in 1939, and since then more than 3,700 patients have been registered at our center in Hospital Santo António, Porto.

TTR-FAP is a devastating disease leading to autonomy loss and causing death in around 11 years, when no treatment is implemented [13]. The clinical picture is dominated by a mixed sensory, motor, and autonomic neuropathy; severe nephrological, cardiac, ophthalmological, vesical, gastrointestinal, sexual, and central nervous system symptoms are related to systemic amyloid deposition [14–18].

For a long time, patients with TTR-FAP lived with a disease that had no treatment and had to face a chronic and catastrophic clinical evolution. The characteristics of heredity with variable age at onset in adulthood and variable symptomatic expression, and the chronic and devastating evolution pose a psychological burden on these patients and their families. The disease has a great impact on the mental and relational life of these patients [19].

Since the 1990s, liver transplantation is a possibility for these patients precluding the synthesis of abnormal protein. In recent years, tafamidis, a drug that prevents mutated protein deposition, became another available treatment. Both treatments slow down the disease progression and increase patient survival [20–24].

The following studies concerning psychosocial issues in TTR-FAP, included patients before and after liver transplantation, and in the genetic testing context. The need for psychological coping and psychiatric issues have been considered in liver transplantation [25, 26]. After transplantation, when comparing different etiologies of hepatic diseases, mental quality

of life improved for several hepatic diseases, but worsened for FAP patients. Some other studies found no differences in psychiatric diagnosis between patients with TTR-FAP and those with alcohol liver disease, while they were on the waiting list [27, 28]. A few phenomenological studies described the experience of Swedish TTR-FAP patients submitted to liver transplantation. According to these, the experience had a positive as well as a negative connotation: the threat of a fatal disease was gone, but in spite of liver transplantation, patients remained symptomatic and disabled needing continuous psychological and social support [29, 30].

Distress and psychopathological issues were studied in genetic screening, before and after presymptomatic testing. No negative outcomes were found in short-term psychosocial impact of genetic testing. Moreover, genetic screening seemed to improve the psychological well-being of persons at risk, and pretest levels of anxiety and depression were good predictors of that improvement. Apart from that, family dynamics seemed important in the pretest phase and for test uptake, lessening the psychological impact of testing results [31–33]. Medium- and long-term psychosocial impact of presymptomatic testing showed how depression and anxiety varied in subjects: depression occurred only when subjects had previously manifested the first symptoms of their neurological disease and the proximity to the age at symptom onset might be a trigger for anxiety [34, 35].

As a chronic, progressive and disabling disease, TTR-FAP imposes a psychological burden on patients and mutation carriers, and we may expect psychopathological problems in these subjects. Depression and anxiety have been reported as the most relevant symptoms reported in a liaison psychiatry consultation in a study that included 30 TTR-FAP patients [36]. Thus, the aim of present study is to evaluate psychopathological dimensions and symptoms in a consecutive sample of TTR-FAP patients and carriers, and compare them with the general population.

## Methods

### *Participants*

The study sample included 209 adults (85 men and 124 women) with the Val30Met mutation. They were followed in consultation at the Unidade Corino de Andrade of Centro Hospitalar do Porto. One hundred and nine participants had an established diagnosis of TTR-FAP in different evolution stages, 81 were proven asymptomatic carriers, and 19 had no established diagnosis since they had symptoms without a positive amyloid biopsy or a positive biopsy without symptoms. All subjects aged 18–65 years were eligible to be included in the study. Participants were recruited at their routine consultation and agreed to answer the study questionnaires. All procedures performed in this study were approved and in accordance with the ethical statements of the Centro Hospitalar do Porto Ethical Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All study participants gave written consent.

### *Instruments*

Two questionnaires were applied to all subjects: Brief Symptom Inventory (BSI-53) and a social demographic questionnaire that also included three questions addressing psychiatric issues, like attending or having attended psychiatric or clinical psychology appointments, previous or current use of any psychiatric drugs, and known psychiatric diagnoses the subject may have had.

The BSI-53 is a screening tool used for detecting psychopathological symptoms as indicators of emotional distress. It consists of a self-rated questionnaire with 53 items that are

answered on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (extremely). The BSI-53 has nine subscales, which assess nine domains of psychopathology: Somatization, Obsessive-compulsive, Interpersonal sensitivity, Depression, Anxiety, Anger-hostility, Phobic anxiety, Paranoid ideation, and Psychoticism. Three global indices of distress were computed: Global Symptom Index (GSI), Positive Symptom Index (PSI), and Positive Symptom Total (PST). GSI represents a combined assessment of intensity of distress and the number of symptoms; PSI gives a media of intensity for all symptoms and PST represents the number of signalized symptoms.

Derogatis developed the BSI in 1982 [37, 38]. The validated Portuguese version of BSI-53 was used in this study [39]. The mean values of global indices obtained for the Portuguese population were 0.83 (standard deviation, SD = 0.48) for GSI, 26.99 (SD = 11.72) for PSI, and 1.56 (SD = 0.38) for PST.

Subjects filled out the forms in the presence of the same investigator, who assisted in the process of filling, solving doubts that respondents might have.

### *Statistical Analysis*

Preliminary tests for normal distribution, outliers, and missing data were conducted. Descriptive analysis included frequency and percentage, mean and SD, or median and interquartile range. Cronbach's  $\alpha$  statistics measured internal consistency of the BSI-53 scale as a whole and each of its nine subscales. Guttman split-half statistic further evaluated the BSI-53 internal reliability. Data were nonnormally distributed for all BSI dimensions. Several attempts were done to normalize data without success; thus, nonparametric tests were used in most analyses. Correlations with and among the BSI scales were computed using Spearman correlation ( $\rho$ ). For continuous variables, groups were compared with the Mann-Whitney  $t$  test.

Multivariable logistic regression was performed to determine whether selected variables were associated with higher scores of GSI, PST, and PSI as dependent binary variables (higher or lower than the means levels achieved for Portuguese population). The independent variables included in the models were tested to evaluate their effect on the occurrence of psychological symptoms evaluated by GSI, PST, and PSI. Multivariate linear regression analysis was applied to investigate possible related variables with each BSI dimension as the dependent variable. Statistical significance was defined as  $p < 0.05$ , and all analyses were done with the statistical package SPSS version 23.0.

## **Results**

There were 209 subjects (86 men; 123 women) included in this analysis: 81 carriers (nonsymptomatic), 109 patients, and 19 with no established diagnosis. This is a group of participants, positive for TTR-FAP, regularly followed at our center for evaluation; they have not yet a defined status of having initiated the disease. They may have symptoms that sometimes may be confounding and have not positive biopsies for amyloid. They were included in present research because we were not making clinical research about the beginning of disease, but in the psychosocial aspects of having a genetic disease of late onset. Besides these particular clinical aspects, they share all other investigated issues with patients and carriers without disease.

The mean age at participation was 37 (SD = 9.7) years, with 50% of the sample being 35 years old or younger. The mean age was lower for carriers (34 years, SD = 9.8) and higher for subjects with no established diagnosis (41 years, SD = 14), with a mean age of 38 years (SD = 8.1) for FAP patients. In FAP patients, the median time of disease evolution was 4 years (range: 1–28 years).

**Table 1.** Internal consistency of the nine BSI-53 dimensions and the total score

	Cronbach's $\alpha$
Somatization (BSI.S)	0.89
Obsession-compulsion (BSI.OC)	0.80
Interpersonal sensitivity (BSI.IS)	0.82
Depression (BSI.D)	0.88
Anxiety (BSI.A)	0.83
Hostility (BSI.H)	0.79
Phobic anxiety (BSI.PA)	0.79
Paranoid ideation (BSI.PI)	0.80
Psychoticism (BSI.P)	0.68

Most of the subjects were married or lived with a partner (68.4%), and most of them were still working (67%); 15.8% were retired from work or on a sick leave (4.8%). The majority of participants (59.3%) completed the basic education (9th year of schooling), 17.2% completed the high school, and 21.5% had a college degree. Four participants (1.9%) were illiterate.

#### *Scale Reliability: Internal Consistency*

The total BSI-53 score demonstrated good reliability (Cronbach's  $\alpha = 0.97$ ; Guttman split half reliability = 0.87). The internal consistency of the nine subscale scores was examined by using Cronbach's  $\alpha$ . The lower Cronbach's  $\alpha$  was 0.68 for psychoticism, and the remaining coefficients ranged from 0.78 to 0.9 (Table 1).

#### *BSI-53 Global Indices (GSI, PST, and PSI)*

The mean GSI score was 0.76 (SD = 0.63), median = 0.58. Considering the mean levels of Portuguese general population [39], 35.4% were above the mean levels for general population (mean = 0.83, SD = 0.48). Considering the subgroups, 28.2% of nonsymptomatic carriers, 29.4% of subjects without established diagnosis, and 41.7% of patients were above mean levels of GSI. The mean PST levels for the global sample were 22.9 (SD = 14.1), median = 21.0, and 38.4% were above mean levels for general population (mean = 27.0, SD = 11.7). Considering the subgroups, 29.5% of nonsymptomatic carriers, 41.2% of subjects without established diagnosis and 44.7% of patients were above mean levels of PSI. The mean PSI scores for the total sample were 1.59 (SD = 0.56), median = 1.50, and 44.4% were above mean levels for general population. Considering the subgroups of subjects, 39.7% of nonsymptomatic carriers, 52.9% of subjects without established diagnosis, and 46.6% of patients were above mean levels of general population.

#### *BSI-53 Comparisons*

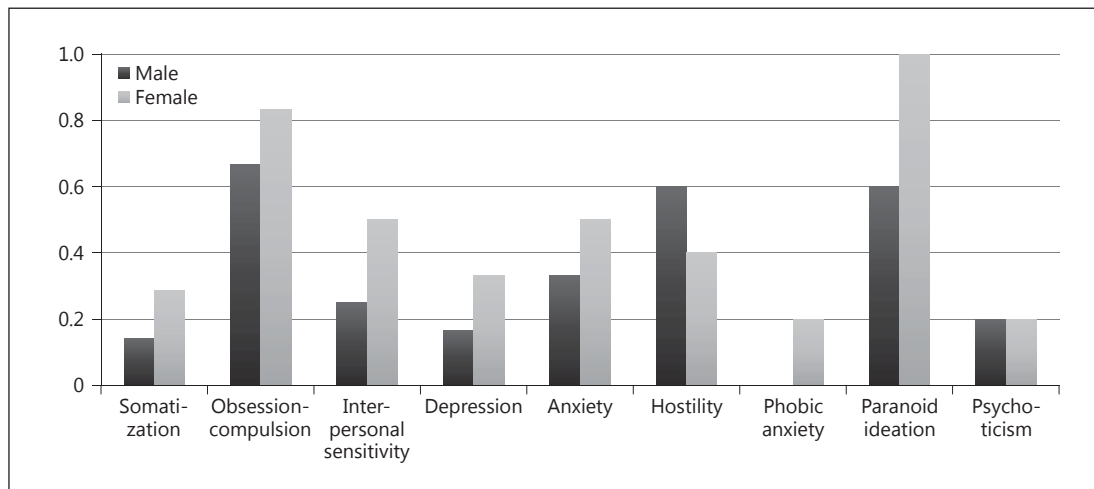
##### Subgroups of Subjects (Nonsymptomatic Carriers, Symptomatic Carriers, and Subjects with No Established Diagnosis)

Descriptive statistics for BSI dimensions and global indices for nonsymptomatic and symptomatic carriers are presented in Table 2. Median levels of all dimensions of BSI were higher in the group of patients when compared with that of the carriers, but only somatization, depression, anxiety, and psychoticism showed a statistically significant difference. The median levels of GSI and PST were significantly higher in patients than in carriers, but not PSI. The sample of subjects with no established diagnosis was also compared with nonsymptomatic carriers. No significant differences were found in the median score of any of the BSI dimensions or global indexes, except for PSI with lower median levels for subjects with no established diagnosis (0.66 [0.26–1.0] vs. 1.46 [1.14–1.78],  $p = 0.02$ ). We did not find significant differences between subjects with no established diagnosis and FAP patients.

**Table 2.** Descriptive statistics for BSI dimensions and global indices for nonsymptomatic and symptomatic carriers

	Nonsymptomatic median (IQ)	FAP patients median (IQ)	<i>p</i>
Somatization	0.29 (0.00–0.71)	0.86 (0.29–1.43)	<b>&lt;0.001**</b>
Obsession-compulsion	0.83 (0.46–1.21)	1.00 (0.50–1.50)	0.368
Interpersonal sensitivity	0.50 (0.00–1.25)	0.50 (0.00–1.25)	0.899
Depression	0.33 (0.17–1.00)	0.67 (0.17–1.67)	<b>0.006*</b>
Anxiety	0.50 (0.17–0.83)	0.83 (0.17–1.33)	<b>0.044*</b>
Hostility	0.50 (0.20–1.20)	0.60 (0.40–1.40)	0.137
Phobic anxiety	0.00 (0.00–0.40)	0.20 (0.00–0.60)	0.409
Paranoid ideation	0.80 (0.35–1.60)	0.80 (0.40–1.60)	0.539
Psychoticism	0.20 (0.00–0.60)	0.40 (0.00–0.80)	<b>0.019*</b>
GSI	0.44 (0.21–0.93)	0.68 (0.38–1.25)	<b>0.014*</b>
PST	16 (10–31)	24 (15–37)	<b>0.010*</b>
PSI	1.46 (1.14–1.78)	1.53 (1.21–1.95)	0.108

GSI, Global Symptom Index; PST, Positive Symptoms Total; PSI, Positive Symptoms Index.



**Fig. 1.** Differences in BSI dimensions, considering gender, in symptomatic carriers only.

### Gender

When we considered differences between gender, women who were asymptomatic carriers had statistically significantly more interpersonal sensitivity ( $p = 0.042$ ) and more phobic anxiety ( $p = 0.017$ ). There were no significant differences in GSI, PST, or PSI. In the group of patients, almost all dimensions were scored significantly higher for women, with the exception of somatization, which was almost significant ( $p = 0.052$ ). GSI, PST, and PSI were also significantly higher in women (Fig. 1).

### Marital Status

The median scores of the nine BSI subscales and global indices were compared between subjects married or living with a partner versus others (separated/divorced/single/widowed), but no significant differences were found either in patients or in asymptomatic carriers.

**Table 3.** Independent predictors of a GSI, PST, and PSI higher than the mean levels achieved for the Portuguese population in TTR-FAP patients

	OR adjusted	<i>p</i> value	95% CI
Independent predictors of GSI >0.83			
Gender (female vs. male)	3.55	0.004	1.51–8.35
Disease evolution time (per each year of increase)	1.07	0.026	1.01–1.14
Independent predictors of PST >26.99			
Gender (female vs. male)	3.79	0.002	1.60–8.98
Disease evolution time (per each year of increase)	1.09	0.007	1.03–1.17
Independent predictors of PSI >1.56			
Gender (female vs. male)	3.07	0.008	1.34–7.05
Disease evolution time (per each year of increase)	1.07	0.029	1.01–1.14

Results given by logistic regression (forward Wald test), considering the Global Symptom Index (GSI), Positive Symptom Total (PST), and Positive Symptom Index (PSI) categorized according the mean levels achieved for the Portuguese population (higher or lower) as the dependent variable. The subgroups of 19 subjects with no established diagnosis and 81 asymptomatic carriers were excluded in these analyses. The variables disease evolution time (years), age (continuous), gender, professional occupation (nonactive vs. active), marital status (married/living with a partner vs. others), and having children (yes vs. no) were included in the models. OR, odds ratio; 95% CI, 95% confidence interval; TTR-FAP, transthyretin familial amyloid polyneuropathy.

#### Professional Occupation

When we analyzed differences in BSI scores and global indices considering the professional occupation (still working vs. others, that is retired, unemployed, or on a sick leave), no significant differences were found in the group of asymptomatic carriers. In the group of patients, the subjects professionally active had significant lower BSI scores in somatization ( $p = 0.002$ ), obsessive-compulsive ( $p = 0.014$ ), depression ( $p = 0.040$ ), and phobic anxiety ( $p = 0.01$ ). The GSI and PSI global indices were also significantly lower in patients with an active professional situation versus others ( $p = 0.038$  and  $p = 0.002$ , respectively).

#### Correlations

In the group of patients, all BSI dimensions and GSI ( $\rho = 0.31$ ,  $p = 0.001$ ), PST ( $\rho = 0.29$ ,  $p = 0.003$ ), and PSI ( $\rho = 0.24$ ,  $p = 0.016$ ) had positive correlations with years of disease, except for interpersonal sensitivity.

#### *Independent Predictors of GSI, PST, and PSI in TTR-FAP Patients*

This analysis only included symptomatic patients. The variables disease evolution time (years), age (continuous), gender (female vs. male), professional occupation (nonactive vs. active), marital status (married/living with a partner vs. others), and having children (yes vs. no) were included in the models.

The independent predictors of GSI >0.83 were female gender (vs. male: OR = 3.55,  $p = 0.004$ ) and longer disease evolution time (per each year of increase: OR = 1.074,  $p = 0.026$ ). The independent predictors of PST >26.99 were female gender (vs. male: OR = 3.79,  $p = 0.002$ ) and longer disease evolution time (per each year of increase: OR = 1.095,  $p = 0.007$ ). Regarding PSI, the independent predictors of a PSI >1.56 were also female gender (vs. male: OR = 3.07,  $p = 0.008$ ) and longer disease evolution time (per each year of increase: OR = 1.073,  $p = 0.029$ ) (Table 3).

**Table 4.** Independent predictors of each BSI dimension in TTR-FAP patients

	Regression coefficient adjusted	p value	95% CI
<b>Independent predictors of BSI Anxiety</b>			
Gender (female vs. male)	0.579	<0.001	0.309–0.849
Disease evolution time (per each year of increase)	0.026	0.009	0.007–0.046
Marital status (married/living with a partner vs. others)	0.316	0.040	0.014–0.618
<b>Independent predictors of BSI Somatization</b>			
Gender (female vs. male)	0.378	0.017	0.068–0.688
Being professionally nonactive (yes vs. no)	0.358	0.032	0.032–0.683
Marital status (married/living with... vs. others)	0.334	0.017	0.014–0.618
Disease evolution time (per each year of increase)	0.043	0.001	0.019–0.067
<b>Independent predictors of BSI Obsession-compulsion</b>			
Gender (female vs. male)	0.615	<0.001	0.336–0.894
Being professionally nonactive (yes vs. no)	0.451	0.004	0.147–0.755
Marital status (married/living with... vs. others)	0.334	0.039	0.018–0.650
Disease evolution time (per each year of increase)	0.022	0.043	0.001–0.044
<b>Independent predictors of BSI Paranoid ideation</b>			
Gender (female vs. male)	0.414	0.008	0.110–0.717
Disease evolution time (per each year of increase)	0.024	0.033	0.002–0.046
<b>Independent predictors of BSI Hostility</b>			
Gender (female vs. male)	0.028	0.006	0.008–0.049
Disease evolution time (per each year of increase)	0.358	0.011	0.082–0.634
<b>Independent predictors of BSI Depression</b>			
Gender (female vs. male)	0.466	0.003	0.157–0.774
Disease evolution time (per each year of increase)	0.033	0.004	0.011–0.056
<b>Independent predictors of PSI Psychoticism</b>			
Gender (female vs. male)	0.289	0.009	0.073–0.505
Disease evolution time (per each year of increase)	0.018	0.030	0.002–0.033
<b>Independent predictors of BSI Interpersonal sensitivity</b>			
Gender (female vs. male)	0.536	<0.001	0.258–0.813
<b>Independent predictors of BSI Phobic anxiety</b>			
Gender (female vs. male)	0.462	<0.001	0.242–0.683
Being professionally non-active (yes vs. no)	0.381	0.001	0.154–0.607
Marital status (married/living with... vs. others)	0.254	0.049	0.001–0.507

#### *Independent Predictors of Each BSI Dimension in TTR-FAP Patients*

The independent predictors of higher BSI Somatization and BSI Obsession-compulsion were: disease evolution time (more years); female gender; having children; and being professionally nonactive. The results are summarized below and displayed in Table 4.

The independent predictor of higher BSI Interpersonal sensitivity was only the female gender. The independent predictors of higher BSI Depression, BSI Hostility, BSI Paranoid ideation and BSI Psychoticism were female gender and higher disease evolution time (years). The independent predictors of higher BSI Anxiety were female gender, marital status “married/living with a partner,” and greater disease evolution time (years). The independent predictors of higher BSI Phobic anxiety were female gender, marital status “married/living with a partner,” and being professionally nonactive.



### *Psychiatric and Psychological Problems*

Around 26.5% of subjects reported psychological or psychiatric problems in the past and 18.2% in the year before responding to the protocol; 21.2% were taking medication, namely antidepressive drugs and/or tranquilizers. The most frequent diagnosis established by a psychiatrist or family doctor was depression and anxiety, and 3 patients were diagnosed as having obsessive-compulsive disorder.

## Discussion

Chronic medical illness and chronic neurological diseases have been associated with depression, anxiety, and emotional distress [40–46]. Literature has shown that psychopathological comorbidities may worsen the prognosis and quality of life in patients with medical illnesses [47]. In these patients, an increase in mortality was found [48–50].

The criteria for psychiatric diagnosis may be very difficult when a patient has a comorbid medical disorder. In serious chronic medical conditions, medical and psychiatric symptoms may overlap and diagnostics may be complicated. Nevertheless, in these conditions, we must pay attention to emotional pain and emotional distress. In 1989, Derogatis and Wise raised the issue that in chronic medical illness, states of psychological distress, although not enough for a psychiatric diagnosis, are associated with high levels of discomfort and reduced quality of life.

The BSI questionnaire has been widely used not only in patients with psychiatric disorders but also patients with chronic medical illnesses to evaluate psychological and psychiatric comorbid symptoms and psychological distress [51–56].

According to its authors, BSI “possess a broad range of sensitivity to symptomatic manifestations, ranging from mild loss of well-being with few if any clinical implications through morbid distress states to symptom levels characteristic of formal psychiatric disorders. These instruments not only may help in operationalizing diagnostic status but are sensitive to a comprehensive range of psychological distress states” [57, p. 81].

In the present study, BSI-53 showed good reliability with internal consistency coefficient results that were similar to those reported by Canavarro’s group who performed a study to validate this questionnaire in a Portuguese community sample.

To our knowledge, beyond transplantation and genetic testing, no literature exists addressing psychopathology in TTR-FAP subjects. In liver transplantation, more mental problems and psychological constraints were reported in TTR-FAP patients when compared with subjects with other diagnosis [27, 28, 30]. In genetic testing, anxiety and depression may exist on several occasions during the procedure: when subjects are waiting for results, after disclosure, and in the years after testing when subjects become symptomatic [31–35].

The results of the present study showed that percentages ranging between 29 and 52% of patients and carriers were above the mean levels for the general population in GSI, PST, and PSI dimensions of BSI. The symptomatic and asymptomatic groups demonstrated in a considerable number of subjects more psychopathological symptoms. These results point to the existence of high levels of psychosocial distress in this specific population. When these two groups were compared, it was noticed that the group of patients had higher levels for psychopathological symptoms. The median levels of global severity symptoms, as well as some of BSI dimensions (somatization, depression, anxiety and psychoticism) were significantly higher in patients than in carriers.

Our findings concerning symptomatic subjects are in agreement with the literature, when other chronic medical conditions are considered. Katon et al. [40] showed that depression was 2–3 times more frequent in chronic medical diseases. The psycho-oncology

literature has shown that more than 30% of cancer patients meet the criteria for a mental condition diagnosis [58–60], and in chronic autoimmune diseases, psychiatric conditions and psychological distress are important associated problems [46, 47, 61–63]. Many chronic medical diseases are also associated with higher levels of mental problems [49, 64].

In this study, higher levels of psychopathological symptoms were also found in the asymptomatic group compared to the general population. Although these subjects do not have to face, yet, the disease and its consequences, they live with uncertainty about its onset, and most of them live or have lived with one or more sick relatives. This could concur with higher psychological distress among this group. In Huntington's disease, a late-onset neurological disorder that shares the characteristics of heritability and incurability with TTR-FAP, similar results were found. More cases of major depressive disorder and obsessive compulsive disorder were found in both presymptomatic and symptomatic mutation carriers than in the general population; psychiatric disorders were more prevalent in mutation carriers than in noncarriers [65, 66].

When gender was considered, sick women scored significantly higher on global BSI indices, and all other dimensions, except somatization. Asymptomatic women had significantly higher scores in interpersonal sensitivity and phobic anxiety. These values demonstrated that women are more at risk for psychopathological symptoms than men, and this was more evident when they were already sick. These results were supported by multivariable analysis, after adjusting for other social demographic variables. These findings are in accord with the epidemiology for mental health diseases that show a higher vulnerability, namely for anxiety and depression, in females [67–70].

All BSI dimensions and global indices positively correlated with years of disease. Similar findings were found in a study with Huntington disease where disease stage predicted anxiety and depression; however, sex did not [71]. Multivariable logistic regression analyses identified the independent predictors for BSI global indices higher than the mean levels found in general population. Being a woman and years of disease predicted higher levels in all three BSI global indices.

When subjects were asked about a history of psychological problems, depression and anxiety were the most referred diagnoses. These results are similar to those found in other chronic diseases where depression and anxiety are the most prevalent psychological/psychiatric problems.

A chronic physical illness must be considered more than a sum of signs and physical symptoms. Dekkers [72] pointed out to the fact that these patients have to face not only the diagnosis crisis but a series of crisis throughout the course of their illnesses. Adjustments must continuously be made as the illness progresses. Chronic illness is not static and imposes a permanent need of restructuring one's life [73, 74].

## Conclusions

Results of the present study point to important vulnerabilities to psychological distress and psychiatric disease of asymptomatic and symptomatic carriers of TTR-FAP with the mutation Met30Val.

Becoming sick, years of disease, and female gender seem to play a major role in psychological associated symptoms in subjects with TTR-FAP.

Depression and anxiety were psychopathological dimensions observed in sick subjects, and they were the most frequently made diagnoses.

In TTR-FAP amyloidosis, like in other progressive chronic illness, patients must live with the uncertainty of how and when symptoms will begin, need to cope with permanent changes

in functioning, body image, permanent threats to self-esteem and disruption of social roles as well as plans for future [75, 76].

In TTR-FAP patients and at-risk subjects, several factors are implicated in psychological distress and psychiatric disorders, and these certainly are multiple and complex. Some of them like being already sick, disease stage, and sex may be recognized, which may act as major stressors and be associated with psychological distress. Many subjects with this mutation experience, from very early in their lives, changes in family functioning, disease in close relatives, and parental loss, among others, as disease consequences. However, early-life events were not considered in this current analysis.

As in other chronic illnesses, psychological and psychiatric support is very important to these patients and at-risk subjects. Therefore, multidisciplinary teams that assist these populations should include professionals of these areas.

#### *Study Limitations*

The study sample included only Portuguese subjects with TTR-FAP V30M. Because of that, its results cannot be extrapolated to other amyloidosis cases whether with the same variant but in different countries or cultures or with genetic variants with different clinical problems and different outcomes.

The approach to psychopathological issues provided by BSI may have limitations as psychiatric diagnosis cannot be made. Further research is needed to address more accurate psychiatric diagnosis in these subjects.

#### **Statement of Ethics**

All procedures performed in this study were approved and in accordance with the ethical standards of the Centro Hospitalar do Porto Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

#### **Disclosure Statement**

A. Lopes has received honoraria from Pfizer for presentations at courses of TTR-related FAP. T. Coelho has received support from Pfizer, Ionis Pharmaceuticals, and Alnylan Pharmaceuticals to attend scientific meetings, integrates the speaker's bureau of Pfizer, and received honoraria. J. Sequeiros received honoraria from Pfizer for presentations on genetic counselling of TTR-related FAP and courses, as well as preparation of leaflets and webinars on genetic counselling.

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