Anxiety and pre-symptomatic testing for neurodegenerative disorders

Lêdo Susana[1,2,3*], Leite Ângela[1,4,5], Jorge Sequeiros[1,2]

[1]Centre for Predictive and Preventive Genetics (CGPP), IBMC—Institute for Molecular and Cell Biology, Porto, Portugal
[2]ICBAS, Universidade do Porto, Porto, Portugal
[3]ISCS-Norte (CESPU), Porto, Portugal
[4]ISCET—Instituto Superior de Ciências Empresariais e do Turismo, Porto, Portugal
[5]ULP—Universidade Lusófona do Porto, Porto, Portugal
Email: *susanaledo@gmail.com

ABSTRACT

In this retrospective study we have investigated the anxiety as an impact of pre-symptomatic testing (PST) for 3 autosomal dominant late-onset diseases: Huntington disease (HD), Machado-Joseph disease (MJD) and familial amyloidotic polyneuropathy (FAP) V30M TTR. The study included 686 subjects: 586 (85.4%) were the offspring at risk for FAP, 92 (13.4%) for HD and 8 (1.2%) to MJD. Of these, 352 received the carrier result and 305 the non-carrier result. As indicator of anxiety distress was taken the Self-Rating Anxiety Scale of Zung (SAS), applied in the pre-test and the three post-test moments: three weeks, 6 months and one year after notification of test results. Values decreased significantly along the four evaluation moments, regardless the studied disease or test result. For female population, SAS means cores revealed results of clinical anxiety at pre-test, only decreasing to non clinical scores a year after PST disclosure.

Keywords: Anxiety; Subscales; SAS; Psychological Impact; FAP; HD; MJD

1. INTRODUCTION

There are numerous diagnostic or pre-symptomatic tests (PST) for hereditary diseases [1-3] Machado-Joseph disease (MJD) or amyloidotic polyneuropathy (FAP) TTR V30M, all late onset autosomal dominant diseases, the PST can predict if, in future more or less distant, the person will develop the symptoms of the disease [2,4].

It's in this field of monogenic autosomal dominant late onset diseases, that the Center for Predictive and Preven-tive Genetics (CGPP) at Institute for Molecular and Cell Biology (IBMC), Oporto University, provides a multi-disciplinary approach for HD, PAF and MJD PST.

A Predictive protocol for neurodegenerative diseases implemented in CGPP is a national reference model for genetic counseling and psychosocial support for people at risk of suffering such progressive and debilitating dis-eases without effective treatment and cure until the pre-sent days [2].

The Studied Diseases

HD, MJD and FAP are three examples of monogenic au-tosomal dominant of late onset, clinically considered as neurodegenerative diseases, incurable and highly debili-tating and that may take a broad spectrum of symptoma-tic manifestations.

Huntington's disease [5,6] is the most studied, largely due to the discovery by Guselli and colleagues, of its ge-netic marker since 1983 [7]. Thus, the predictive test for Huntington's disease began to be held in Canada in 1986 and US [1,8], with over the 90's progress and the new laboratory techniques for mutation detection [5,6].

MJD and FAP are very specific Portuguese diseases, that also have a severe neurodegenerative pathway, and for which there is still no effective treatment or cure. In 1993, the MJD gene was finally located on chromosome 14 by a group of researchers led by Shoji Tsuji, later con-firmed in the Portuguese households by Sequeiros and colleagues [9]. The genetic mutation present in FAP leads to the production of an amyloid protein, immunologi-cally related to transthyretin (TTR) that is abnormally de-graded, precipitated and stored in tissues as amyloid sub-stance [10], deposited in the tissues of various organs leading these patients for a progressive limitation [11,12].

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*Corresponding author.

Pre-symptomatic diagnosis is available since 1984 [11]. Several psychosocial studies have been done with families and their descendants at risk for neurodegenerative diseases diagnosed in CGPP [13-15].

Lêdo [13] studied FAP carriers after a year of knowledge of their genetic status, and concluded there had been no presence of emotional distress and feelings of hopelessness.

Other studies with subjects at risk for FAP, HD and MJD pointed to the existence of psychological well-being and better health perception than the control subjects [14]. Also in this field, there have been published psychosocial genetic studies related to the experience of more than 10 years in the counseling of individuals at risk [16], as well as studies about the importance of contact time with the disease or affected father figure in the psychological impact of PST [15].

Despite the different approaches that have been made, there are still issues to be elucidated regarding the impact of the application of PST to diseases with common starting symptoms at the early adulthood and a degenerative path, but with different treatment options and clinical outcomes (e.g. the psychiatric disorders, unique to Huntington's disease, and for MJD frequent signs of cerebellar ataxia, progressive external ophthalmoplegia and pyramidal signs [9,17,18].

On the other hand, it continues to be relevant studies related to psychological impact of test results, mainly the anxiety indexes because this is one of the most expressed feelings at the first evaluation. In this sense, we established as objectives of this research: 1) the anxiety indexes observed before and after completion of the PST, and 2) the differences on anxiety indexes related to types of disease, carrier or non carrier status, and some demographic variables.

2. MATERIAL AND METHODS

It was designed a retrospective study of clinical files of subjects who underwent pre-symptomatic testing for genetic autosomal dominant diseases with late onset (MJD, HD and FAP), in CGPP, between 2000 and 2010. These files contained psychological evaluations data conducted along the four moments of the general psychological evaluation protocol: 1) 1st moment, pre-test, prior to the genetic test; 2) 2nd moment of evaluation, three weeks after receiving the test result and knowing genetic status; 3) 3rd moment, six months after disclosure; 4) 4th moment, one year after disclosure.

2.1. Subjects

The initial sample (**Table 1**) is constituted by 686 subjects at base line: 586 (85.4%) attended the service to accomplish the pre-symptomatic test for FAP, 92 (13.4%) for HD and 8 (1.2%) for MJD. Subjects underwent the evaluation protocol voluntarily when they were informed they were 50% at-risk for these diseases and were informed about the purpose of the research, simultaneously with PST protocol procedure and signed a written consent for the use of their data with the finality of scientific research. 58.6% of the complete sample were women. It was found that 51.3% of the subjects were single, 44.7% were married. Of the total initial subjects, 29 did not appear to know their test result, 352 (51.6%) received the result of carriers and 305 (44.7%) received the result of non-carriers. Along the four moment of the general protocol, subjects were given up. This is why we witnessed a sharp decline in the subject number at the post-test one year later.

Men and women have proven to be equivalent in their distribution regarding the age ($X^2 = 636.939$; df = 625; p

Table 1. Sample characteristics along the four moments of the general psychological evaluation protocol.

	Pre-test a (N = 686)			Post-test b (N = 290)			Post-test c (N = 143)			Post-test d (N = 54)		
	FAP	**HD**	**MJD**	**FAP**	**HD**	**MJD**	**FAP**	**HD**	**MJD**	**FAP**	**HD**	**MJD**
N	586	92	8	248	38	4	114	25	4	40	13	1
Gender	F 340 M 246	F 54 M 38	F 8 M 0	F 146 M 102	F 20 M 18	F 4 M 0	F 64 M 50	F 14 M 11	F 4 M 0	F 25 M 15	F 7 M 6	F 1 M 0
Mean Age	35.09	43.69	38.75	34.83	46.45	48.00	34.68	45.24	48.00	31.85	45.46	37.00
Marital Status	S 320 M 239 D 10 W 8	S 27 M 59 D 0 W 0	S 2 M 6 D 0 W 0	S 134 M 104 D 3 W 3	S 13 M 23 D 1 W 1	S 1 M 3 D 0 W 0	S 59 M 52 D 0 W 1	S 9 M 14 D 1 W 1	S 1 M 3 D 0 W 0	S 22 M 17 D 0 W 0	S 2 M 11 D 0 W 0	S 0 M 1 D 0 W 0
Test Result	NC 311 C 254 DK 17	NC 39 C 45 DK 8	NC 2 C 6 DK 0	NC 124 C 117 DK 5	NC 16 C 21 DK 1	NC 0 C 4 DK 0	NC 47 C 62 DK 3	NC 5 C 19 DK 1	NC 0 C 4 DK 0	NC 10 C 29 DK 0	NC 2 C 9 DK 2	NC 0 C 1 DK 0

Gender (**F**emale; **M**ale); Marital Status (**S**ingle; **M**arried; **D**ivorced; **W**idow); Test Result (**N**on Carrier; **C**arrier; **D**on't **k**now).

= 0.362), marital status ($X^2 = 5.733$; df = 2; p = 0.057), and test result ($X^2 = 2.446$; df = 2; p = 0.294).

2.2. Procedure

The PST protocol queries for neurodegenerative diseases in CGPP have been published elsewhere [2].

In the context of the protocol, each subject answered the anxiety scale evaluation along four stages: 1) pre-test: the first psychological evaluation, it was done the survey and evaluation of the motivations that led the person to pre-symptomatic test, exploring his/her own decision making processes and detection of emotional states that might jeopardize a good adjustment to the predictive test result (hereafter designated 1st moment); 2) post-test: three weeks after receiving the test result post-test (hereafter designated 2nd moment); 3) six months after disclosure (hereafter designated 3rd moment); 4) one year after reporting the genetic test result (hereafter designated 4th moment).

The socio-demographic variables (gender, age and marital status) and medical history were collected at the first psychological evaluation.

The anxiety variable was collected by the application of the Portuguese version [19] of the Self-Rating Anxiety Scale of Zung (SAS) [20]. This scale is composed of 20 items rated on a Likert scale of four grades (1 "rarely or never" to 4 "most or all of the time") and measure the anxiety clinical symptoms.

Anxiety is evaluated from the description of its most common symptoms and signals through four anxiety components (subscales): cognitive (items 1 - 3, 4 and 5) which can reach a maximum of 20 points, motor (items 6, 7, 8 and 9) which can reach a maximum of 16, vegetative (items 10 - 16, 17 and 18) that can reach a maximum of 36 and central nervous system—CNS—(items 19 and 20) with a maximum value of 8 points. The score ranges between 20 and 80 and the cut point is 40 [19].

2.3. Data Analysis

The statistical analysis was performed with the software PASW Statistics 19.0 [21]. We carry out procedures related to descriptive statistics (frequencies, mean, standard deviation, minimum, maximum), bi-variate statistics (mean, ANOVA, correlation bi-varied); prediction of numerical results (multiple linear regression, stepwise) predicting for the identification of groups (factor analysis and discriminant analysis).

3. RESULTS

3.1. Descriptive Analysis for the Four Evaluation Moments

We analyzed the mean and standard deviation of the results obtained from the application of SAS in the four moments considered, for the total sample and for female and male subsamples.

Reading **Table 2**, it can be seen that, along the four moments, women had always higher averages than men. For both genders, 1st moment revealed higher mean values (male: M = 39.6, SD = 8.07; female: M = 43.7, SP = 8.87), however, in women, there is a slight increase in average from the second to the third moment of data collection.

3.2. Descriptive Statistics of the 20 SAS Items for the Four Stages of Evaluation

We proceeded to the descriptive analysis for the 20 items of the scale (mean, standard deviation and percentage of symptomatic responses, *i.e.*, those scored with 2, 3 or 4 points) for the total sample and male and female subsamples, for four moment's evaluation. We can see that, at first assessment (**Table 3**), *i.e.*, before genetic testing (1st moment), women, in general, have significantly higher averages in some of the items that described anxiety symptoms, for example, restlessness and fear, headaches, neck and back pain and stomachache, or more nightmares.

At post-test, three weeks after the communication of the PST result (2nd moment), it was found, with statistically significant results, that women continued to show a greater tendency to feel more nervous and anxious than men and have higher sleep disturbance (**Table 4**).

Regarding **Table 5**, six months after knowing test result (3rd moment), women fell more scared for no reason and have hands dry and warm more often than men; furthermore, men fell that things will be all right more than women.

Reading **Table 6**, at 4th moment, there are no statistically significant differences between female and male subsamples.

3.3. Comparison of the Total Means along the Four Evaluation Moments

We found that the for the total anxiety average decreased over the four moments. In almost all moments compared, except between the 1st and the 3rd moments, and the 2nd and 3rd moments, the mean values obtained from the application of SAS decreased significantly with a p value less than 0.05 (see **Table 7**).

3.4. Comparison of the SAS Subscales Means along the Four Evaluation Moments

We observed a decrease in all SAS subscales over the four moments of our evaluation as we can see from the reading **Tables 8-11**.

In **Table 8**, we found statistically significant differences between 1st and 2nd moments, 1st and 3rd moments,

and 2nd and 3rd moments regarding motor anxiety subscale.

In **Table 9**, we found statistically significant differences between 1st and 2nd moments, and 1st and 4th moments regarding cognitive anxiety subscale.

In **Table 10**, we found statistically significant differ-

ences between 1st and 2nd moments, 1st and 4th moments, and 3rd and 4th moments regarding vegetative anxiety subscale.

In **Table 11**, we found statistically significant differences between 1st and 3rd moments, and 1st and 4th moments regarding CNS anxiety subscale.

Table 2. Total SAS results (mean, standard deviation) for the four moments evaluated (1st, 2nd, 3rd, 4th), for the total sample and female and male subsamples.

	Total Sample		Female		Male	
	M	*SD*	*M*	*SD*	*M*	*SD*
SAS	41.9	8.75	43.7	8.87	39.6	8.07
1st moment	($n = 653$; $\alpha = 0.80$)		($n = 378$; $\alpha = 0.79$)		($n = 275$; $\alpha = 0.78$)	
SAS	40.2	8.21	41.4	8.45	38.6	7.61
2nd moment	($n = 232$; $\alpha = 0.82$)		($n = 135$; $\alpha = 0.82$)		($n = 97$; $\alpha = 0.79$)	
SAS	41.0	9.87	43.0	10.10	38.4	9.05
3rd moment	($n = 85$; $\alpha = 0.83$)		($n = 48$; $\alpha = 0.82$)		($n = 37$; $\alpha = 0.85$)	
SAS	36.7	8.10	37.2	7.40	35.8	9.02
4th moment	($n = 62$; $\alpha = 0.83$)		($n = 35$; $\alpha = 0.79$)		($n = 27$; $\alpha = 0.87$)	

Table 3. Results of the items of the SAS 1st moment (mean, standard deviation, and percentage of symptomatic responses) for the total sample and female and male subsamples.

Item	Total Sample			Female			Male		
	M	*SD*	%	*M*	*SD*	%	*M*	*SD*	%
1—I feel more nervous and anxious than usual.[**]	1.86	0.82	62.6	1.96	0.80	70.4	1.72	0.83	51.4
2—I feel afraid for no reason.[*]	1.39	0.65	31.1	1.44	0.66	35.9	1.32	0.63	24.4
3—I get upset easily or feel panicky.	1.22	0.53	17.7	1.24	0.55	19.0	1.20	0.50	15.2
4—I feel like I'm falling apart and going to pieces.	1.40	0.66	31.3	1.43	0.66	34.8	1.35	0.65	26.4
5—I feel that everything is all right and nothing bad will happen.[**]	2.58	0.95	85.6	2.67	0.93	88.0	2.46	0.97	82.0
6—My arms and legs shake and tremble.[*]	1.42	0.62	35.9	1.47	0.62	40.4	1.35	0.61	29.7
7—I am bothered by headaches neck and back pain.[**]	1.70	0.77	54.1	1.80	0.79	60.6	1.56	0.71	45.2
8—I feel weak and get tired easily.[*]	1.44	0.67	34.6	1.49	0.72	37.1	1.36	0.59	31.1
9—I feel calm and can sit still easily.[**]	2.41	1.04	76.7	2.51	1.02	81.2	2.26	1.04	70.6
10—I can feel my heart beating fast.	1.42	0.62	357	1.45	0.63	38.2	1.37	0.60	32.2
11—I am bothered by dizzy spells.	1.25	0.52	21.1	1.27	0.53	23.9	1.21	0.52	17.2
12—I have fainting spells or feel like it.	1.08	0.32	7.2	1.10	0.36	8.9	1.06	0.26	5.0
13—I can breathe in and out easily.[**]	1.70	1.02	38.5	1.79	1.05	42.7	1.57	0.95	31.8
14—I get feelings of numbness and tingling in my fingers & toes.	1.36	0.64	29.3	1.39	0.67	30.6	1.33	0.58	27.5
15—I am bothered by stomach aches or indigestion.[**]	1.43	0.70	33.6	1.50	0.75	38.7	1.33	0.61	26.8
16—I have to empty my bladder often.	1.75	0.78	56.6	1.78	0.81	57.9	1.70	0.75	54.6
17—My hands are usually dry and warm.	2.81	1.09	83.4	2.87	1.08	85.1	2.74	1.10	81.1
18—My face gets hot and blushes.[**]	1.95	0.86	66.8	2.08	0.91	71.5	1.77	0.76	60.2
19—I fall asleep easily and get a good night's rest.[**]	1.98	1.05	55.5	2.07	1.07	58.9	1.85	1.00	50.7
20—I have nightmares.[**]	1.39	0.66	31.6	1.46	0.70	36.4	1.30	0.58	24.9

Note: [*]Differences between men and women to p < 0.05; [**]Differences between men and women to p < 0.01.

Table 4. Results of the items of the SAS 2nd moment (mean, standard deviation, and percentage of symptomatic responses) for the total sample and female and male subsamples.

Item	Total Sample			Female			Male		
	M	SD	%	M	SD	%	M	SD	%
1—I feel more nervous and anxious than usual.*	1.58	0.73	45.4	1.66	0.78	50.5	1.46	0.65	38.1
2—I feel afraid for no reason.	1.32	0.58	26.1	1.36	0.62	29.4	1.25	0.51	21.5
3—I get upset easily or feel panicky.	1.20	0.45	17.9	1.21	0.46	18.9	1.18	0.43	16.6
4—I feel like I'm falling apart and going to pieces.	1.32	0.59	26.2	1.34	0.63	27.2	1.29	0.54	24.8
5—I feel that everything is all right and nothing bad will happen.*	2.46	0.93	83.1	2.56	0.90	86.5	2.31	0.95	78.5
6—My arms and legs shake and tremble.	1.33	0.54	30.0	1.36	0.55	32.6	1.30	0.53	26.4
7—I am bothered by headaches neck and back pain.	1.64	0.73	50.6	1.66	0.74	51.8	1.60	0.71	48.8
8—I feel weak and get tired easily.	1.43	0.70	33.0	1.46	0.76	33.0	1.39	0.61	33.0
9—I feel calm and can sit still easily.	2.39	1.00	75.9	2.48	0.96	80.0	2.26	1.04	69.3
10—I can feel my heart beating fast.	1.37	0.57	32.3	1.40	0.58	35.3	1.33	0.57	28.1
11—I am bothered by dizzy spells.	1.27	0.55	22.1	1.29	0.62	21.8	1.23	0.42	22.5
12—I have fainting spells or feel like it.	1.09	0.32	7.9	1.11	0.37	9.4	1.06	2.23	5.8
13—I can breathe in and out easily.	1.59	0.96	33.6	1.58	0.97	31.7	1.60	0.94	36.4
14—I get feelings of numbness and tingling in my fingers & toes.	1.28	0.53	24.1	1.25	0.52	21.2	1.32	0.53	28.3
15—I am bothered by stomach aches or indigestion.	1.43	0.65	35.4	1.44	0.64	35.9	1.43	0.66	34.7
16—I have to empty my bladder often.	1.71	0.75	55.6	1.72	0.77	55.3	1.70	0.72	55.8
17—My hands are usually dry and warm.	2.82	1.09	83.6	2.84	1.05	85.2	2.80	1.15	80.1
18—My face gets hot and blushes.	1.84	0.79	64.0	1.89	0.87	63.3	1.77	0.67	65.0
19—I fall asleep easily and get a good night's rest.*	1.97	1.01	57.0	2.08	1.02	62.3	1.82	0.98	49.6
20—I have nightmares.*	1.34	0.60	28.2	1.40	0.67	31.2	1.26	0.47	24.0

Note: *Differences between men and women to p < 0.05.

Table 5. Results of the items of the SAS 3rd moment (mean, standard deviation, and percentage of symptomatic responses) for the total sample and female and male subsamples.

Item	Total Sample			Female			Male		
	M	SD	%	M	SD	%	M	SD	%
1—I feel more nervous and anxious than usual.	1.77	0.76	57.7	1.81	0.75	61.3	1.71	0.78	53.2
2—I feel afraid for no reason.*	1.29	0.59	21.7	1.38	0.66	27.5	1.17	0.46	14.3
3—I get upset easily or feel panicky.	1.25	0.54	19.4	1.26	0.53	22.3	1.22	0.56	15.5
4—I feel like I'm falling apart and going to pieces.	1.43	0.63	35.1	1.49	0.64	40.8	1.34	0.61	27.6
5—I feel that everything is all right and nothing bad will happen.*	2.37	0.92	82.1	2.54	0.92	88.2	2.14	0.89	74.2
6—My arms and legs shake and tremble.	1.36	0.57	31.4	1.41	0.61	34.2	1.29	0.50	27.6
7—I am bothered by headaches neck and back pain.	1.69	0.78	52.6	1.69	0.79	52.0	1.69	0.75	53.5
8—I feel weak and get tired easily.	1.40	0.63	32.1	1.43	0.62	36.9	1.34	0.64	25.8
9—I feel calm and can sit still easily.	2.11	0.95	69.4	2.09	0.91	71.1	2.14	1.02	67.3
10—I can feel my heart beating fast.	1.37	0.51	35.1	1.43	0.55	40.8	1.28	0.45	27.6
11—I am bothered by dizzy spells.	1.36	0.64	27.5	1.36	0.67	26.3	1.36	0.61	29.3
12—I have fainting spells or feel like it.	1.13	0.47	9.7	1.20	0.59	13.1	1.05	0.22	5.2
13—I can breathe in and out easily.	1.66	0.95	39.6	1.71	0.99	42.1	1.59	0.90	36.3
14—I get feelings of numbness and tingling in my fingers & toes.	1.37	0.66	29.1	1.29	0.63	21.1	1.48	0.68	39.7
15—I am bothered by stomach aches or indigestion.	1.42	0.64	35.1	1.46	0.66	38.2	1.36	0.61	31.0
16—I have to empty my bladder often.	1.81	0.82	58.9	1.87	0.81	63.1	1.74	0.85	53.4
17—My hands are usually dry and warm.**	2.81	1.12	81.9	3.05	1.06	88.2	2.49	1.14	73.7
18—My face gets hot and blushes.	1.75	0.80	56.7	1.79	0.85	57.9	1.71	0.73	55.2
19—I fall asleep easily and get a good night's rest.	1.84	0.99	50.0	1.91	0.97	55.3	1.76	1.01	43.1
20—I have nightmares.	1.37	0.66	29.8	1.45	0.70	35.4	1.28	0.56	22.4

Note: *Differences between men and women to p < 0.05; **Differences between men and women to p < 0.01.

Table 6. Results of the items of the SAS d (mean, standard deviation, and percentage of symptomatic responses) for the total sample and subsamples female and male.

Item	Total Sample			Female			Male		
	M	SD	%	M	SD	%	M	SD	%
1—I feel more nervous and anxious than usual.	1.54	0.73	41.8	1.58	0.76	44.7	1.48	0.69	37.9
2—I feel afraid for no reason.	1.12	0.37	10.5	1.11	0.31	10.5	1.14	0.44	10.3
3—I get upset easily or feel panicky.	1.12	0.37	10.5	1.11	0.31	10.5	1.14	0.44	10.3
4—I feel like I'm falling apart and going to pieces.	1.27	0.59	20.9	1.24	0.49	21.0	1.31	0.71	19.8
5—I feel that everything is all right and nothing bad will happen.	2.25	0.05	70.2	2.39	1.00	76.3	2.07	1.10	62.0
6—My arms and legs shake and tremble.	1.28	0.60	22.4	1.29	0.57	23.7	1.28	0.65	20.6
7—I am bothered by headaches neck and back pain	1.66	0.69	53.7	1.74	0.72	57.9	1.55	0.63	48.3
8—I feel weak and get tired easily.	1.45	0.63	38.8	1.47	0.60	42.1	1.41	0.68	34.4
9—I feel calm and can sit still easily.	2.03	1.03	59.7	2.05	1.04	60.5	2.00	1.03	58.6
10—I can feel my heart beating fast.	1.34	0.59	28.4	1.45	0.65	36.8	1.21	0.49	17.2
11—I am bothered by dizzy spells.	1.16	0.48	12.0	1.21	0.53	15.8	1.10	0.41	6.8
12—I have fainting spells or feel like it.	1.01	0.12	1.5	1.03	0.16	2.6	1.00	0.00	0.0
13—I can breathe in and out easily.	1.36	0.71	25.4	1.24	0.49	21.0	1.52	0.91	31.0
14—I get feelings of numbness and tingling in my fingers & toes.	1.34	0.59	29.9	1.42	0.64	36.8	1.24	0.51	20.6
15—I am bothered by stomach aches or indigestion.	1.39	0.63	31.4	1.26	0.50	23.7	1.55	0.74	41.4
16—I have to empty my bladder often.	1.84	0.75	64.2	1.87	0.74	65.8	1.79	0.77	62.0
17—My hands are usually dry and warm.	2.60	1.11	79.2	2.82	1.11	81.6	2.31	1.07	75.9
18—My face gets hot and blushes.	1.94	0.87	62.7	1.97	0.89	63.1	1.90	0.86	62.0
19—I fall asleep easily and get a good night's rest.	1.52	0.74	38.8	1.53	0.76	39.4	1.52	0.74	37.9
20—I have nightmares.	1.40	0.68	31.4	1.42	0.64	34.2	1.38	0.73	27.5

Table 7. Comparison of the total obtained from the application of SAS in the first (1st), second (2nd), third (3rd) and fourth (4th) evaluation moments.

Comparison (moments)		Mean	N	t	d.f.	Sig. (2-tailed)
1st Moment* 2nd Moment	SAS 1st	41.70	219	3.508	218	0.001*
	SAS 2nd	40.07	219			
1st Moment* 3rd Moment	SAS 1st	42.17	80	1.297	79	0.198
	SAS 3rd	40.94	80			
1st Moment* 4th Moment	SAS 1st	41.86	59	4.614	58	0.000*
	SAS 4th	36.65	59			
2nd Moment* 3rd Moment	SAS 2nd	39.48	60	−0.807	59	0.423
	SAS 3rd	40.19	60			
2nd Moment* 4th Moment	SAS 2nd	39.81	45	2.342	44	0.024*
	SAS 4th	37.14	45			
3rd Moment* 4th Moment	SAS 3rd	39.55	33	2.960	32	0.006*
	SAS 4th	36.48	33			

3.5. Comparison of the Anxiety Rates Regarding Socio-Demographic Variables over the Four Moments Evaluated

We compared the SAS questionnaire total mean, as well as the subscales means regarding socio-demographic variables (age, gender, marital status, type of disease, genetic test result) and we found some significant values.

Thus, with respect to gender variable it was found that women had, over the several moments, significantly higher values than men (p < 0.050) for total SAS questionnaire and for motor anxiety subscale (1st moment), for cognitive anxiety subscale (1st, 2nd and 3rd moments), for vegetative anxiety subscale (1st and 3rd moment), and for CNS anxiety subscale (1st and 2nd moment) as we can see consulting **Table 12**.

Respecting to the age variable, when compared the mean of CNS anxiety (1st moment) we verify that subjects between 61 - 70 and 41 - 50 have higher values; when compared the motor anxiety subscale mean (2nd and 3rd moment), we found that older subjects (age be-

Table 8. Comparison of the total means for the SAS motor anxiety subscale in the first (1st), second (2nd), third (3rd) and fourth (4th) evaluation moments.

Comparison (moments)	Motor Anxiety	Mean	N	t	df	Sig. (2-tailed)
1st Moment* 2nd Moment	MASAS 1st	7.02	279	2.139	278	0.033*
	MASAS 2nd	6.76	279			
1st Moment* 3rd Moment	MASAS 1st	7.16	128	3.068	127	0.003*
	MASAS 3rd	6.57	128			
1st Moment* 4th Moment	MASAS 1st	6.92	66	1.878	65	0.065
	MASAS 4th	6.45	66			
2nd Moment* 3rd Moment	MASAS 2nd	6.97	118	2.096	117	0.038*
	MASAS 3rd	6.61	118			
2nd Moment* 4th Moment	MASAS 2nd	6.78	50	0.678	49	0.501
	MASAS 4th	6.54	50			
3rd Moment* 4th Moment	MASAS 3rd	6.38	45	−0.788	44	0.435
	MASAS 4th	6.62	45			

Table 9. Comparison of the total means for the SAS cognitive anxiety subscale in the first (1st), second (2nd), third (3rd) and fourth (4th) evaluation moments.

Comparison (moments)	Cognitive Anxiety	Mean	N	t	df	Sig. (2-tailed)
1st Moment* 2nd Moment	CASAS 1st	8.52	283	4.468	282	0.000*
	CASAS 2nd	7.85	283			
1st Moment* 3rd Moment	CASAS 1st	8.33	131	0.890	130	0.375
	CASAS 3rd	8.10	131			
1st Moment* 4th Moment	CASAS 1st	8.57	67	3.470	66	0.001*
	CASAS 4th	7.30	67			
2nd Moment* 3rd Moment	CASAS 2nd	7.84	116	−0.830	115	0.408
	CASAS 3rd	8.05	116			
2nd Moment* 4th Moment	CASAS 2nd	7.96	50	1.537	49	0.131
	CASAS 4th	7.42	50			
3rd Moment* 4th Moment	CASAS 3rd	7.93	45	1.375	44	0.176
	CASAS 4th	7.38	45			

Table 10. Comparison of the total means for the SAS vegetative anxiety subscale in the first (1st), second (2nd), third (3rd) and fourth (4th) evaluation moments.

Comparison (moments)	Vegetative Anxiety	Mean	N	t	df	Sig. (2-tailed)
1st Moment* 2nd Moment	VASAS 1st	14.70	274	2.012	273	0.045*
	VASAS 2nd	14.39	274			
1st Moment* 3rd Moment	VASAS 1st	14.79	129	0.752	128	0.454
	VASAS 3rd	14.60	129			
1st Moment* 4th Moment	VASAS 1st	14.85	65	2.672	64	0.010*
	VASAS 4th	13.92	65			
2nd Moment* 3rd Moment	VASAS 2nd	14.54	113	−0.664	112	0.508
	VASAS 3rd	14.71	113			
2nd Moment* 4th Moment	VASAS 2nd	14.24	50	0.768	49	0.446
	VASAS 4th	13.96	50			
3rd Moment* 4th Moment	VASAS 3rd	14.32	44	2.048	43	0.047*
	VASAS 4th	13.66	44			

Table 11. Comparison of the total means for the SAS CNS anxiety subscale in the first (1st), second (2nd), third (3rd) and fourth (4th) evaluation moments.

Comparison (moments)	CNS Anxiety	Mean	N	t	df	Sig. (2-tailed)
1st Moment* 2nd Moment	CNSSAS 1st	3.42	285	1.696	284	0.091
	CNSSAS 2nd	3.29	285			
1st Moment* 3rd Moment	CNSSAS 1st	3.54	132	2.581	131	0.011*
	CNSSAS 3rd	3.20	132			
1st Moment* 4th Moment	CNSSAS 1st	3.36	67	2.580	66	0.012*
	CNSSAS 4th	2.93	67			
2nd Moment* 3rd Moment	CNSSAS 2nd	3.37	118	1.185	117	0.238
	CNSSAS 3rd	3.25	118			
2nd Moment* 4th Moment	CNSSAS 2nd	3.04	50	0.118	49	0.907
	CNSSAS 4th	3.02	50			
3rd Moment* 4th Moment	CNSSAS 3rd	2.93	45	−0.133	44	0.895
	CNSSAS 4th	2.96	45			

Table 12. Comparison between SAS total and subscales mean values regarding variable gender over the several moments.

Total Scores SAS		Mean	N	F	Sig.
1st moment (SAS 1st)	Female	43.47	378	32.247	0.000
	Male	39.62	275		
2nd moment (SAS 2nd)	Female	41.36	135	6.680	0.010
	Male	38.57	97		
3rd moment (SAS 3rd)	Female	42.97	48	4.651	0.034
	Male	38.41	37		
SAS Subscales Scores		**Mean**	**N**	**F**	**Sig**
Motor Anxiety 1st moment (MASAS 1st)	Female	7.26	390	18.927	0.000
	Male	6.53	278		
Cognitive anxiety 1st moment (CASAS 1st)	Female	8.75	390	14.430	0.000
	Male	8.01	278		
Cognitive anxiety 2nd moment (CASAS 2nd)	Female	8.15	169	5.797	0.017
	Male	7.50	121		
Cognitive anxiety 3rd moment (CASAS 3rd)	Female	8.50	76	4.555	0.035
	Male	7.60	57		
Vegetative anxiety 1st moment (VASAS 1st)	Female	15.26	384	26.853	0.000
	Male	14.09	279		
Vegetative anxiety 3rd moment (VASAS 3rd)	Female	15.16	76	5.095	0.026
	Male	13.98	57		
CNS anxiety 1st moment (CNSSAS 1st)	Female	3.53	392	12.899	0.000
	Male	3.15	280		
CNS anxiety 2nd moment (CNSSAS 2nd)	Female	3.48	170	6.622	0.011
	Male	3.07	121		

tween 61 and 80 years) are those with higher average (**Table 13**).

Concerning marital status, it was found significant differences, at 1st moment, for vegetative anxiety subscale (t = 2.996; df = 4; p = 0.018): widow individuals had the highest average and, at 3rd moment, six months after disclosure, married subjects had the highest averages in the SAS total mean (**Table 14**).

Finally, it was found significant values when comparing the total SAS and subscales SAS means with the variable type of disease.

As shown by the observation of **Table 15**, at 1st moment, only the CNS anxiety subscale presents significant values, indicating that the subjects who performed the HD PST as having the highest values.

At 2nd, 3rd and 4th moments, after disclosure, MJD sub-

Table 13. Comparison between SAS total and subscales mean values regarding variable age over the several moments.

Moments	Subscales		Mean	N	F	Sig.
1st moment	CNS anxiety CNSSAS 1st	17 - 30	3.38	262		
		31 - 40	3.16	229		
		41 - 50	3.60	73	2.880	0.014
		51 - 60	3.51	55		
		61 - 70	3.94	33		
		71 - 80	3.43	7		
2nd moment	Motor Anxiety MASAS 2nd	17 - 30	6.82	111		
		31 - 40	6.38	99		
		41 - 50	7.18	28	2.247	0.050
		51 - 60	6.77	26		
		61 - 70	8.06	16		
		71 - 80	7.77	3		
3rd moment	Motor Anxiety MASAS 3rd	17 - 30	6.35	48		
		31 - 40	6.00	45		
		41 - 50	6.87	15	2.433	0.039
		51 - 60	7.50	14		
		61 - 70	8.29	7		
		71 - 80	8.00	1		

Table 14. Comparison between the mean values of the SAS subscales regarding the variable marital status over the several moments.

Moments	Subscales/Totals		Mean	N	F	Sig.
1st moment	Vegetative anxiety	*Single*	14.52	336		
		Married	14.94	294	2.996	0.018
		Divorced	13.92	12		
		Widow	17.10	10		
3rd moment	Total SAS	*Single*	38.48	46		
		Married	44.24	38	4.230	0.018
		Divorced	0	0		
		Widow	0	0		

Table 15. Comparison between the mean values of the SAS totals and subscales with the variable type of disease over the several moments.

Moments	Subscales/Totals		Mean	N	F	Sig.
1st moment	CNS anxiety	*FAP*	3.34	574		
		MJD	2.75	8	3.019	0.050
		HD	3.66	90		
2nd moment	Total SAS	*FAP*	39.80	195		
		MJD	51.25	4		
		HD	41.17	33	4.194	0.016
	Cognitive anxiety	*FAP*	7.83	247	3.839	0.023
		MJD	11.00	4		
		HD	7.82	39		
3rd moment	Motor Anxiety	*FAP*	6.28	104		
		MJD	8.50	4	5.154	0.007
		HD	7.48	25		
4th moment	CNS anxiety	*FAP*	2.73	49		
		MJD	5.00	2	5.183	0.008
		HD	3.25	16		

jects are those having significantly higher values in SAS subscales and also in the SAS total score, three weeks after disclosure, presenting total scores (>40 points) revealing clinical anxiety.

3.6. Predictors of the Self-Rating Anxiety Scale of Zung (SAS)

We intend to know the predictive value of some socio-demographic and other variables that could take an explicative character to the values found in the SAS scale over the four evaluation moment sand for the three studied diseases.

Thus, we performed the multiple linear regression analysis using stepwise estimation method [22] for the total scores of the SAS scale, as well as for cognitive, motor, vegetative and CNS SAS subscales. We consid-

ered the socio-demographic variables as independent variables.

Analyzing **Table 16**, we can see that gender is the variable that has a higher predictive value in the regression equation explaining 4% of the dependent variable Total SAS variance, at 1st moment. The final equation is made by the independent variables gender and test result ($R^2 = 0.51$, F = 17.849, df = 2, p = 0.000) explaining, overall, 5.1% of the total SAS score variance, at 1st moment (**Table 16**).

It was also found that the independent variable gender is the one with the most predictive power in the regression equation, explaining 2% of the dependent variable Total SAS variance, at 2nd moment; the final equation is made by the independent variables gender, type of disease and test result ($R^2 = 0.06$, F = 4.644, df = 3, p = 0.004) explaining, overall, 6% of the total SAS score variation, at 2nd moment (**Table 17**).

Analyzing **Table 18**, we can see that the independent variable, marital status, shows the highest predictive value in the regression equation, explaining 9% of the dependent variable Total SAS variance, at 3rd moment; the final equation is made by the independent variables marital status, gender and test result ($R^2 = 0.21$, F = 6.804, df = 3, p = 0.000) which explain, overall, 21% of the total SAS score variation, at 3rd moment (**Table 18**).

Then, we conducted linear regression analyzes for all SAS subscales and for all the evaluation moments considered. These analyze yielded the following significant results:

For the cognitive anxiety subscale, it was found that the independent variable gender was the only one that had predictive value in the regression equation ($R^2 =$

Table 16. Multiple linear regression analysis for variables predicting the Total SAS 1st moment.

MODEL	VARIABLE	B	SE	β
1	Gender	−3.817	0.688	−0.216**
2	Gender	−3.900	0.687	−0.220**
	Test Result	−1.327	0.612	−0.084*

$R^2 = 0.04$ step 1; $\Delta R^2 = 0.05$ step 2; **p < 0.010, *p < 0.050.

Table 17. Multiple linear regression analysis for variables predicting the Total SAS 2nd moment.

MODEL	VARIABLE	B	SE	β
1	Gender	−2.520	1.114	−0.151*
2	Gender	−2.412	1.105	−0.144*
	Type of Disease	2.767	1.276	0.143*
3	Gender	−2.611	1.103	−0.156*
	Type of Disease	3.161	1.283	0.164
	Test Result	−2.012	1.020	−0.132

$R^2 = 0.02$ step 1; $\Delta R^2 = 0.04$ step 2 $\Delta R^3 = 0.06$ step 3; **p < 0.010, *p < 0.050.

Table 18. Multiple linear regression analysis for variables predicting the Total SAS 3rd moment.

MODEL	VARIABLE	B	SE	β
1	Marital Status	5.577	2.021	0.293**
2	Marital Status	5.540	1.976	0.291**
	Gender	−4.514	2,064	−0.227*
3	Marital Status	6.237	1.927	0.324**
	Gender	−5.565	2.034	−0.280**
	Test Result	−5.589	2.153	−0.268*

$R^2 = 0.09$ step 1, $\Delta R^2 = 0.14$ step 2, $\Delta R^3 = 0.21$ step 3; **p < 0.010, *p < 0.050.

0.20, F = 13.032, df = 1, p = 0.000), explaining 2% of the variance at 1st moment. The same can be said, for the same dependent variable, at 2nd moment, the independent variable gender continued to explained 2% of the variance ($R^2 = 0.20$, F = 5.756, df = 1, p = 0.017). Concerning yet this dependent variable, at 3rd moment, we observed that the independent variable type of disease was the only one that explained 4% of the variance ($R^2 = 0,43$, F = 5,722, df = 1, p = 0,018).

It was verified that the independent variable gender was the only one that had predictive value in the regression equation ($R^2 = 0.27$, F = 18.018, df = 1, p = 0.000), by explaining 3% of the variance of the dependent variable motor anxiety subscale, at 1st moment. At 3rd moment, we found that the two independent variables type of disease and test results, together, explained 11% of the dependent variable motor anxiety subscale variance ($R^2 = 0.11$, F = 7.892, df = 2, p = 0.001).

For the dependent variable vegetative anxiety subscale, at 1st moment, the independent variables gender, test result, and marital status explained 6% of its variance ($R^2 = 0.06$, F = 12.670, df = 3, p = 0.000); at 3rd moment, the independent variables age and gender, together, explained 8% of the variance of this same dependent variable ($R^2 = 0.08$, F = 5.610, df = 2, p = 0.005); finally, at 4th moment, the independent variable marital status was the one that explained 9% of the variance.

At last, regarding the dependent variable CNS anxiety subscale, at 1st moment, the dependent variables gender and age, together, explained 3% ($R^2 = 0.03$, F = 8.817, df = 2, p = 0.000) of its variance; at 2nd moment, the independent variable gender, explained 2% of its variance ($R^2 = 0.02$, F = 4.729, df = 1, p = 0.031); finally, at 4th moment, the independent variable type of disease, explained 11% of its variance ($R^2 = 0.11$, F = 8.191, df = 1, p = 0.006).

4. DISCUSSION

We have found that the number of patients leaving the protocol over one year was quite high and this can be the principal limitation of this study; thus, this can bias the conclusions we draw from the data obtained. We found

that, proportionally, the number of carriers increases and non carriers decreases over protocol, *i.e.*, the carriers remain in the protocol more than non carriers; therefore, it is necessary to take into account this point as one of the limitations of this study.

The descriptive analysis, such as a previous study of measurement of scale to Portuguese population [19], revealed that female had higher values of anxiety symptoms. The pre-test (1st moment) recorded higher values for both genders, although for women values were indicative of clinical anxiety (score ≥ 40) and men were on the border between normal and pathological anxiety. For both groups it can be stated that anxiety decreased over four assessment moments.

We also obtained results quite acceptable for internal consistency, since the αvalues were always, for all moments and groups considered, very close to 0.80, leading us to conclude that this instrument is reliable for the studied population.

By examining the 20 items scale, we find that women, in the pre-test (1st moment), revealed a higher level of restlessness, pessimism and fear, and a greater pain associated with the presence of a higher generalized tension (head, neck and back); these findings seem to corroborate the presence of the total scores inducing anxiety symptoms, even before the completion of the TPS, as said in previous paragraph. Higher values of anxiety symptoms at the beginning of PST, in women, could mean that pre-test (1st moment) itself may bea trigger of anxiety disturbance, as well as other studies have mentioned, supporting the need for psychological support since the beginning of the genetic counseling PST process [23,24].

Three weeks after PST disclosure (2nd moment), women continued to show a greater presence of items answered with options-inducing presence of anxiety symptoms, in particular, revealing more likely to present sleep disorders.

These data, *i.e.*, the reduction of anxiety score during the protocol (mostly, from 1st moment to 2nd moment, first post-test immediately after the PST communication), also seem to indicate that the PST brings advantages in reducing the uncertainty and self control effects for the disease to which the at-risk individual decides to make the test [15,16,25].

Considering the anxiety total scores and subscales values regarding socio-demographic variables, some significant results were found:

Thus, with respect to gender variable it was found that women had, over the several moments, significantly higher values than men for total SAS questionnaire and for motor anxiety subscale (1st moment), for cognitive anxiety subscale (1st, 2nd and 3rd moments), for vegetative anxiety subscale (1st and 3rd moment), and for CNS anxiety subscale (1st and 2nd moment).

Respecting to the age variable, when compared the mean of CNS anxiety (1st moment) we verify that subjects between 61 - 70 and 41 - 50 have higher values; when compared the motor anxiety subscale mean (2nd and 3rd moment), we found that older subjects(age between 61 and 80 years) are those with higher average. This can be explained, first, according to the SAS scale normalization studies for the portuguese population, there is a greater tendency for older individuals present higher values of anxiety [26]; second, the age of these subjects (between 40 and 51 years) is approaching the age mean considered to the beginning of this late on-set diseases first symptoms, that can lead to higher anxiety values.

Considering marital status, we found a tendency for widow subjects had the highest average in the vegetative anxiety subscale at pre-test (1st moment); this result seems to point to the hypothesis that people at risk and more alone may have greater tendency for a higher level of anxiety symptoms. Widowhood maybe relates to the perceived lack of effective care, by becoming more difficult the existence of a future caregiver. The fact that, in the divorced group, we did not observe the same trend, canbe explained with the age factor, *i.e.*, widows tend to be older people. After 6months of PST disclosure (3rd moment), the married subjects group had higher total anxiety, compared with the single individuals (note that this moment assessed only subjects with these two marital status); therefore, it may be the existence of a partner or objectives of having a child, significant factors to induce higher values of anxiety, since it was widely studied the importance of partners in the at-risk and/or ill patients for HD [8,27].

Finally, when we compared the total scores and subscales means regarding the type of disease variable, we found significant values for the CNS anxiety subscale, in the pre-test, for HD; this may indicate greater anxiety for those at risk for this disease, given the severity of their clinical condition. This may also be related to some HD carriers psychopathological symptoms, that may already be manifesting at the beginning of the PST protocol (1st moment). This aspect concerning the disease severity might explain why, at all post-test moments (2nd, 3rd and 4th moments), the HD subjects continued to reveal superior anxiety results, only being surpassed by the MJD subjects (however, MJD group were not significant). Subjects who performed the test for FAP showed lower values, perhaps because they have hope on the drug treatment in the near future or in the currently available solution, the liver transplantation, in order to wage disease progression, both solutions nonexistent for HD or MJD [3,28].

Regarding test result variable, there were no statisti-

cally significant results, as previous studies were indicated for HD: knowledge of carrier or non-carrier status does not seem to bring a negative psychological impact on individuals [7,8,28].

Several studies have indicated the importance of the socio-demographic variables predictive character for population that performs the PST [3,6-8,16,28] for the establishment of more effective interventions in those individuals identified as vulnerable. This study identified variables such as gender, type of disease, marital status as having some predictive value with respect to what can be expected about future anxiety symptoms presented along the several assessed moments. For this reason, the need for a personalized and careful monitoring to each individual who performs a PST protocol remains a substantial ethical principle in conducting such genetic tests [2, 3].

5. CONCLUSIONS

We found a decrease in mean values over the four evaluations moments regarding total scores obtained by applying the Self-Ranting Anxiety Scale of Zung (SAS), evidencing that subjects have higher values before pre-symptomatic test (1st moment) than in the several post-testing moments (2nd, 3rd and 4th moments), mainly a year after knowing their genetic status. However, for the female population, the SAS means scores revealed a result of clinical anxiety (>40 points) from the pre-test (1st moment), only decreasing to non clinical scores a year after PST disclosure (4th moment).

The inherent characteristics of each disease here studied, as well as the knowledge of the genetic status—to be or not to be a carrier—do not appear to significantly influence the presence of anxiety disorder. However, we find a lower trend in subject's average who took the PST for FAP.

The variables gender, age and marital status, showed an oscillating weight in the anxiety scores verifying that female has higher values, as well as the older subjects or those who are closer to the beginning of the first symptoms; widows also had the highest anxiety scores.

Although, from a clinical point of view, we have not found values indicating anxiety disorder, we can conclude however that pre-symptomatic test for studying diseases causes a considerable anxiety level, since the averages were always very close to the cutoff point of the SAS.

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