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Long-term Negative Psychological Impact of Presymptomatic Testing for Huntington ’s disease

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This research has been carried out in Institute for Molecular and Cell Biology (IBMC), Centre for Predictive and Preventive Genetics (CGPP).

Abstract
Presymptomatic Testing (PST) for Huntington’s disease (HD) is available since 1986 and its impact on carriers and non-carriers is not yet fully clear. It is important to understand its psychological impact so that the PST protocols are best suited to the subjects at-risk. Preventing a negative psychological impact is the ultimate purpose of the genetic counselling process. This study addresses the long-term negative psychological impact assessment of PST for HD. The sample consisted of 29 subjects that were 50% at-risk for HD, and had performed the PST for at least three years ago. Participants answered the sociodemographic questionnaire and the Brief Symptom Inventory, the Zung Self-Rating Anxiety Scale, and the Beck Depression Inventory. Although most of the sample does not present clinically significant psychopathology values, 6 subjects present a Positive Symptoms Distress Index value which is equal to or greater than 1.7; 7 subjects present a value which is equal to or greater than 40 of anxiety; and 7 subjects present mild depression. Symptomatic carriers, who underwent the PST less time ago, present worse psychopathological symptoms, depression and anxiety. Subjects with this profile should have a more intense and personalized psychological and social support, aiming to prevent the risk of suicide and to improve the quality of their lives.
Keywords: Presymptomatic Testing (PST), Preditive genetic testing, Huntington´s Disease (HD), Long-term Psychological Impact, Late-onset disease

1. Introduction

Huntington´s Disease (HD) is a rare autosomal-dominant inherited progressive neurodegenerative disorder of the central nervous system, characterized by unwanted choreatic movements, behavioral and psychiatric disturbances, and dementia[1]. HD is caused by an expansion of a CAG repeat in the Huntingtin (HTT) gene, which leads to an expanded polyglutamine tract in the pervasive expressed HTT protein[2]. An excessive number

of CAG repeats in the gene results in a protein containing an excessive number of glutamine units and the expanded polyglutamine sequence in the Huntingtin protein is toxic to brain cells. The prevalence of this disease is 3-7: 100.000 whereas nearly 20: 100.000 are carriers of the gene responsible for the disease[3].

There is a prodrome of HD, that is, symptoms of the presence of a disease prior to the development of the full clinical syndrome, that may appear up to several years before the onset of motor symptoms[4]. There is also a triad of clinical impairments in HD patients: motor, cognitive and emotional features. The psychiatric manifestations cause significant morbidity and encompass the full spectrum of psychiatric illnesses[5]. HD is associated with affective disorders, irritability, apathy and psychosis[5]. However, high rates of psychiatric disturbances have also been observed in HD family members who do not carry the genetic mutation[6]. Some authors have also reported psychiatric and behavioral comorbidities in these subjects[7,8], including the risk of suicidal behavior[9-12]. It is, however, difficult to prove that suicide may be a consequence resulting from the impact of the predictive test and not from the disease itself. In a study[11], it was found that the number of deaths due to suicide among subjects with HD is almost four times greater than the corresponding proportion for the U.S. Caucasian population. However, there seems to be no consensus regarding the stages where this suicide risk is increased. In another study[12], it was found that suicide may occur more frequently in the early stages of the illness, but other authors have identified two critical periods for increased risk of suicide in HD: immediately before receiving a diagnosis of HD and in the middle stage of the disease, when independence diminishes[9]. Suicide occurred more frequently in the early to middle stages of the illness[11]. Possibly due to that, suicide has not been identified as the most serious manifestation of the negative psychological impact of Presymptomatic Testing (PST) for HD.

The first symptoms of HD usually begin at the age of 35–45 years, but there is a wide variation in its onset. There is no cure for HD, nor treatment that can delay or slow the progression of the disease and so HD can only be treated to alleviate the symptoms[13].

Genetic counseling provides information and support to people who have been, or may be, at-risk for genetic disorders. The practice of genetic counselling gives rise to many ethical dilemmas, and counsellors need to be aware of the principles of biomedical ethics, which are: respect for autonomy, beneficence, non-maleficence and justice. PST guidelines for HD were published by an *Ad Hoc* Committee in 1994[14]. In 2011, at the World Congress Meeting on HD, a proposal was made for the guidelines to be reviewed every two years in conjunction with the World Congress Meeting.

The experience of genetic counselling is seen as an opportunity for discussing problems or is associated with feelings of disempowerment. Thus, PST may be a journey of empowerment, an ambivalent process or a poor experience[15]. Many people who seek genetic counseling decide not to know the results of the genetic testing. Analyzing why there are persons who reject the predictive testing and others no, it was studied the determinants for undergoing or not undergoing the PST: maturity of the individual at risk (related to age); ability to cope with a positive test result; experience of living with HD sufferers; information about testing and psychological support; attitude of the family; social visibility of genetic testing; personality and temperament of each subject at risk of HD[16]. Receiving a test result is one of the transition points in the life of an individual at-risk for any genetic disease. In fact, the emotional impact of the test result is not always in accordance to the test result itself, because some mutation carriers may feel relieved after knowing their status[15, 17].

Several different authors studied the PST psychosocial impact in a middle and long-term period of time[18-21]. They all found mostly no evidence of negative psychological impact of the PST in the middle and long-term. However, a minority of subjects in this study presents values indicating negative psychological impact of the PST. That is why it is so important to determine which are the most affected subjects, aiming an adequate psychological intervention in order to avoid the risk of suicide.

2. Materials and Methods

2.1 Object of the study

This quantitative study addresses the assessment of PST long-term psychological impact for HD, studying psychopathological, depression and anxiety symptoms.

2.2 Participants

The sample consisted of 29 subjects, aged over 20 years, that were 50% at-risk for HD, and had performed the PST for at least three years ago (Table 1).

Table 1 presents the sociodemographic characteristics of the sample of this study, which is mostly female, married or in unmarried unions, with an average age of 44.52 years, composed by housekeepers, carriers and having performed the PST for about 5.72 years, on average.

2.3 Measures

The instruments used in this study were a sociodemographic questionnaire, the Brief Symptom Inventory

(BSI)[22,23], the Zung Self-Rating Anxiety Scale (SAS)[24,25]; and the Beck Depression Inventory (BDI)[26,27].

The sociodemographic questionnaire included questions regarding gender, age, marital status, profession, PST result - non-carrier or carrier, current status - non-carrier, asymptomatic carrier or symptomatic carrier, and time after PST result. BSI aimed to assess psychopathological symptoms, SAS aimed to assess anxiety and BDI aimed to assess depression.

2.4 Procedures

The guidelines for this investigation were accepted by the Institute for Molecular and Cell Biology (IBMC) Ethics Committee. The guarantee of the confidentiality of the data was made clear. Additionally, the informed consent to voluntary collaborate in the research was obtained.

In this study, all subjects had previously attended genetic counseling consultations in the Center for Preventive and Predictive Genetics (CGPP), IBMC, between January 2005 and July 2015, in order to know their genetic status for HD. The only inclusion criteria in this study was that the participants had completed the one year PST protocol in CGPP service, for at least three years, before participating in the study.

Participants were contacted by mail, one time only, to answer the sociodemographic questionnaire and the BSI, SAS, and BDI instruments. A six-month time frame was respected to receive the participant´s responses by mail.

Table 1
Sociodemographic characterization of the sample (n = 29)

Variables	Total (n = 29)
Gender	
Female	16 (55.2%)
Male	13 (44.8%)
Age	M = 44.52; SD = 14.21
Minimum	21
Maximum	71
Marital status	
Single	9 (31.0%)
Married or unmarried union	16 (55.2%)
Divorced or separated	2 (6.9%)
Widow or Widower	2 (6.9%)
Profession	
Pensioner	9 (31.0%)
Unemployed	2 (6.9%)
Student	2 (6.9%)
Employed	16 (55.2%)
PST result	
Non-carrier	14 (48.3%)
Carrier	15 (51.7%)
Current status	
Non-carrier	14 (48.3%)
Asymptomatic carrier	10 (34.5%)
Symptomatic carrier	5 (17.2%)
Time in years after PST result	M = 5.72 [3-10]; SD = 2.02
Less or equal to 5	15 (51.7%)
6 or more	14 (48.3%)

M = Mean; SD = Standard deviation

2.5 Data Analysis

Since the sample of this study follows a non-normal distribution, confirmed using the Kolmogorov-Smirnov test (K–S test or KS test) [0.379 (24) = 0.000], and since the sample size is small, non-parametric test for independent samples were used: the Mann-Whitney test for dichotomous variables, and the Kruskal-Wallis test for non-dichotomous variables. Correlations were calculated through the Spearman's rank correlation coefficient or Spearman's rho.

Collected data were quantitatively analyzed using the SPSS IBM software, version 22.

3. Results

In Table 2, normative means of BSI scales and indices[22] are presented to the general Portuguese population and

to the Portuguese population presenting emotional disturbances, as well as for the population in this study, i.e., subjects who took the PST for HD at least 3 years ago.

Table 2

Comparison of BSI scales and indices mean for the general Portuguese population, the Portuguese population with emotional disturbances and the population of the present study

	General Portuguese population Canavarro[22]			Portuguese population with emotional disturbances		Population of the present study		
BSI scales and indices	*M*	*SD*	*α*	*M*	*SD*	*M*	*SD*	*α*
Somatization	0.573	0.916	0.80	1.355	1.004	0.571	0.711	0.88
Obsessive-compulsive	1.290	0.878	0.77	1.924	0.925	1.012	0.855	0.88
Interpersonal Sensitivity	0.958	0.727	0.76	1.597	1.033	0.565	0.777	0.87
Depression	0.893	0.722	0.73	1.828	1.051	0.667	0.762	0.86
Anxiety	0.942	0.766	0.77	1.753	0.940	0.641	0.651	0.81
Hostility	0.894	0.784	0.76	1.411	0.904	0.763	0.859	0.93
Phobic Anxiety	0.418	0.663	0.62	1.020	0.929	0.222	0.494	0.80
Paranoid Ideation	1.063	0.789	0.72	1.532	0.850	0.704	0.619	0.71
Psychoticism	0.668	0.614	0.62	1.403	0.825	0.482	0.566	0.65
GSI	0.835	0.480	-	1.430	0.705	0.638	0.595	-
PSTI	26.993	11.724	-	37.349	12.166	19.172	13.385	-
PSDI	1.561	0.385	-	2.111	0.595	1.502	0.540	-

M = Mean; *SD* = Standard deviation; *α* = Cronbach's alpha; GSI = General Severity Index; PSTI = Positive Symptoms Total, PSDI = Positive Symptom Distress Index

When comparing the normative values of the general population of the BSI Portuguese version[22] with the values of the present study, it can be concluded that the present sample has lower values than those of the general population in all of the BSI scales and in all indices. Cronbach's alpha (*α*) values of the present sample are all higher than those found by the author of the Portuguese version (Table 2), except with regard to the paranoid ideation subscale.

Of the 29 subjects of the sample, 23 (79.3%) present a Positive Symptom Distress Index (PSDI) value below the cutoff point proposed by the author (1.7)[22] and 6 subjects (20.7%) a value equal to or greater than 1.7. Of these 6 subjects, 5 are carriers - 2 are asymptomatic and 3 are symptomatic.

A comparison between the BSI scales and General Severity Index (GSI), Positive Symptoms Total (PSTI) and PSDI values in relation to the independent variables of this study was carried out. Only statistically significant results are presented. Students and employees present significantly lower values of the PSDI that pensioners and the unemployed ($p = 0.046$). Unemployed and employed present significantly lower levels of phobic anxiety than pensioners and students ($p = 0.015$). Regarding PST result, carriers present higher values than non-carriers, in what respects obsessive-compulsive ($p = 0.018$), depression ($p = 0.020$), and anxiety scales and PSDI. Regarding current status, symptomatic carriers present significantly higher values than asymptomatic carriers and then non-carriers, both regarding the obsessive-compulsive scale ($p = 0.015$) and PSDI ($p = 0.004$).

Regarding the time after PST result (that refers to the number of years that the subjects performed the PST when this study was carried out and that was converted into a variable which splits the number of years in two groups - ≤ 5 years and ≥ 6 years), subjects which underwent the PST a smaller number of years ago (≤ 5) present higher levels of somatization ($p = 0.017$), anxiety ($p = 0.044$), GSI ($p = 0.038$), PSTI ($p = 0.049$), and PSDI ($p = 0.049$) than those who underwent the PST more years ago (≥ 6).

In Table 3, normative means of BDI scales and total BDI[26] are presented to the general Portuguese population, as well as for the population in this study, i.e., subjects who took the PST for HD at least 3 years ago.

Table 3
Comparison of BDI scale sand Total BDI mean for the general Portuguese population and the population of the present study

	General Portuguese population Vaz Serra and Pio Abreu[26]					Population of the present study		
BDI scales and total BDI	Absence of depression	Mild depression	Moderate depression	Severe depression	α	*M*	*SD*	α
Cognitive-affective depression	-	-	-	-	-	0.331	0.422	0.86
Somatic or performance depression	-	-	-	-	-	0.341	0.437	0.72
Total BDI	0 – 12	12 - 18	18 - 24	> 24	0.81	7.039	8.553	0.90
n_i (present study)	22 (75.9%)	4 (13.8%)	1 (3.4%)	2 (6.9%)	-	-	-	-

M = Mean; *SD* = Standard deviation; α = Cronbach's alpha; n_i = absolute frequency

When analyzing Table 3, alpha values are quite high, except with respect to the somatic or performance subscale. As shown in Table 3, the authors of BDI[26] consider different levels of depression. The majority of the sample shows absence of depression, while 24.1% (7 subjects) of the sample present depression. 6 of these 7 subjects are carriers - 3 are asymptomatic carriers and 3 are symptomatic carriers.

A comparison between the BDI scales and total BDI median values in relation to the independent variables of this study was carried out: pensioners and unemployed present significantly higher values than the students and employed people regarding somatic or performance (p = 0.018) and total BDI (p = 0.027). Regarding the PST result, carriers present higher values than non-carriers with regard to cognitive-affective depression (p = 0.001), somatic or performance (p = 0.028) and total BDI (p = 0.002). Regarding current status, carriers present significantly higher values than non-carriers in relation to cognitive-affective depression (p = 0.003), somatic or performance (p = 0.014) and total BDI (p = 0.004). Compared to carriers, symptomatic carriers have higher values than asymptomatic carriers. Regarding the time after PST result, subjects who underwent the PST a smaller number of years ago ($\leq$ 5) present higher levels of cognitive affective depression (p = 0.041) and total depression (p = 0.040) than those who underwent the PST for more years ($\geq$ 6).

In Table 4, normative means of SAS scale and total SAS[24,25] are presented to the general Portuguese population and to the Portuguese population with anxiety, as well as for the population in this study, i.e., subjects who took the PST for HD at least 3 years ago.

When comparing the normative values of the general population of the SAS Portuguese version[24] with the values of the present study, it can be stated that the present sample has lower values than those of the general population in all of the SAS scales and in total SAS, except in Central Nervous System Anxiety subscale, as it can be observed in Table 4. α values of the present sample are good - total SAS; questionable - motor anxiety; poor - cognitive anxiety and vegetative anxiety; and unacceptable - Central Nervous System Anxiety[25].

Table 4
Comparison of SAS scales and Total SAS means for the general Portuguese population, Portuguese population with emotional disturbances and the population of the present study

	General Portuguese population Ponciano et al.[24]		Portuguese population with anxiety Ponciano et al.[24]		Population of the present study		
SAS scales and total SAS	*M*	*SD*	*M*	*SD*	*M*	*SD*	α
Cognitive Anxiety	8.759	2.303	-	-	7.560	2.002	0.55
Motor Anxiety	6.824	2.047	-	-	6.680	2.231	0.61
Vegetative Anxiety	14.587	2.705	-	-	13.840	3.287	0.55
Central Nervous System Anxiety	3.237	1.278	-	-	3.400	1.190	0.14
Total SAS	33.406	6.611	46.03	9.591	31.480	7.422	0.83

M = Mean; *SD* = Standard deviation; α = Cronbach's alpha

The authors of SAS[24] consider that the cutoff point is set to the value of 40. However, the value of 37 already suggests a serious likelihood that the subject is pathologically anxious. Of the 29 subjects of the sample, 22 (75.9%) present a value equal to or less than 39 and 7 subjects a value equal to or higher than 40. From these 7 subjects, 5 are carriers - 3 are symptomatic and 2 are asymptomatic.

A comparison between the SAS scales and total SAS median values in relation to the independent variables of this study was carried out: carriers have higher values than non-carriers with regard to cognitive

anxiety (p = 0.000), vegetative anxiety (p = 0.000), motor anxiety (p = 0.009), and total SAS (p = 0.000). Regarding carriers, symptomatic carriers have higher values than asymptomatic carriers.

Spearman's rank correlation coefficient between BSI, BDI and SAS was calculated. The studied dimensions present mostly positive and statistically significant correlations between them (r = 0.399-.952). The dimensions presenting the least significant correlations with the other dimensions are the phobic anxiety (BSI) (r = 0.041-0.464), then the central nervous system anxiety (SAS) (r = 0.247-0.652). The dimensions vegetative anxiety (SAS) and motor anxiety (SAS) also present less significant correlations.

The authors of this study wanted to know the correlations between the sociodemographic and clinical variables and the studied instruments, having found statistically significant results on the socio-demographic variable profession and on the clinical variables time after PST result, PST result and current status (Table 5). Only statistically significant results are presented.

Analysing Table 5, it is possible to verify that the socio-demographic variable profession has a negative and significant correlation with anxiety (BSI), GSI (BSI), PSDI (BSI) and all BDI dimensions. Regarding the clinical variables, time after PST result, PST result and current status show significant correlations: time after PST result correlates negatively and significantly with somatization (BSI), all BSI indices (GSI, PSTI and PSDI), total BDI and the variable cognitive-affective depression (BDI). The PST result and the current status correlated positively and significantly with the same variables: obsession-compulsive, depression, anxiety, GSI and PSDI indices from BSI, all the dimensions of BDI and SAS, with the exception of the central nervous system anxiety (SAS). The result of the predictive test also correlates positively and significantly with hostility (BSI).

Table 5

Spearman's rank correlation coefficient or Spearman's rho for sociodemographic and clinical variables and BSI, BDI and SAS scales, indices and totals

	Profession	*Time after PST result*	PST result	Current status
1 - BSI Somatization		-.468* .017		
2 - BSI Obsessive-compulsive			.464* .015	.541** .004
3 - BSI Interpersonal Sensitivity				
4 - BSI Depression			.458* .016	.461* .015
5 - BSI Anxiety	-.390* .049		.425* .031	.440* .024
6 - BSI Hostility			.382* .049	
7 - BSI Phobic Anxiety				
8 - BSI Paranoid Ideation				
9 - BSI Psychoticism				
10 - BSI GSI	-.425* .030	-.415* .035	.410* .037	.440* .025
11 - BSI PSTI		-.371* .047		
12 - BSI PSDI	-.523** .007	-.402* .046	.617** .001	.670** .000
13 - BDI Cognitive-affective depression	-.442* .024	-.412* .036	.671** .000	.683** .000
14 - BDI Somatic or performance depression	-.422* .032		.438* .025	.536* .005
15 - Total BDI	-.497** .010	-.411* .037	.612** .001	.660** .000
16 - SAS Cognitive Anxiety			.790** .000	.783** .000
17 - SAS Vegetative Anxiety			.697** .000	.727** .000
18 - SAS Motor Anxiety			.506** .007	.578** .002
19 - SAS Central Nervous System Anxiety				
20 – Total SAS			.752* .000	.783** .001

GSI = General Severity Index; PSTI = Positive Symptoms Total,
PSDI = Positive Symptom Distress Index
**Significant correlation to level 0.01/ * Significant correlation to level 0.05

4. Discussion

The sample in this study is mostly female, married or in unmarried unions, with a mean age of 44.52 years, housekeeper, carrier and having performed the PST for about 5.72 years on average. Previous studies on middle and long-term PST psychological impact[20,28] have suggested that female population – both carrier and non-carrier - had higher values of psychopathology and tend to score higher in somatization, phobic anxiety and hostility dimensions[28]. However, in the present study, no differences in relation to gender were found.

The majority of the sample did not reveal clinically significant psychopathological values, which is nonetheless surprising, since asymptomatic carriers generally have the prodrome of HD that may appear up to several years before the onset of motor symptoms[4]. Furthermore, carriers usually present psychiatric disorder, as HD is associated with affective disorders, irritability, apathy and psychosis[6]. However, this sample is composed by carriers and non-carriers and not just carriers.

Although as a whole the sample does not show high values of psychopathology, depression and anxiety, there is disturbing data present. In particular, 6 subjects (20.7%) present a value equal to or greater than 1.7 of PSDI (BSI); 7 subjects (24.1%) have depression (BDI); and 7 subjects (24.1%) present a value equal to or greater than 40 of anxiety (SAS); and the overwhelming majority of these individuals is a carrier. That is, carriers, and primarily symptomatic carriers, clearly show higher values than non-carriers and even than asymptomatic carriers in the studied dimensions. These data corroborate the ones obtained by a study[29], which suggests that subjects experiencing real symptoms are focalized on their physical sensations, leading them to feel worse than those subjects who have not yet experienced symptoms.

Symptomatic patients present a higher PSDI, as well as higher values of obsession-compulsive than those of asymptomatic carriers and non-carriers. Moreover, carriers present higher values than non-carriers with regard to cognitive anxiety, vegetative anxiety, motor anxiety and total anxiety, and symptomatic carriers have higher values than asymptomatic carriers, for the same dimensions. The same can be said regarding the cognitive-affective depression, somatic or performance and total depression (BDI). These data are corroborated by the correlations between the current status and the studied dimensions.

The subjects who underwent the PST for a smaller period of time present higher levels of cognitive-affective depression and total depression than those who underwent the PST a higher period of time ago. The subjects who underwent the PST less time ago present a higher PSDI, as well as higher levels of somatization, anxiety and GSI. In several studies[28], higher values of depression, anxiety and psychopathological symptoms were found in subjects who underwent the PST for fewer years, which confirms the results resulting from the present study.

Pensioners and the unemployed present a higher PSDI and higher levels of somatic or performance depression and total depression. Pensioners and students present more phobic anxiety. These data are also corroborated by the correlations between the profession and the studied dimensions.

It can be stated that carriers, especially symptomatic carriers, who underwent the PST less time ago, pensioners and unemployed are the ones that, in this sample, present worse psychopathological symptoms, depression and anxiety. It is difficult to distinguish in these carriers the psychopathological symptoms arising from the fact of knowing that they are carriers of this devastating disease and the psychopathological symptoms of the manifestation of the disease itself. In fact, although the specific psychopathology of these subjects is well documented[5,6], the psychopathology comorbidity is also present[7,8]: suicidal ideation in HD frequently occurs and its assessment is a priority in mutation carriers with a depressed mood[30]. Furthermore, knowledge about the high suicide risk in this disease is important for genetic counselling[10].

5. Conclusion

In the middle and long-term after receiving the PST result, subjects with this profile should have a more intense and personalized psychological and social support, aiming to prevent the risk of suicide and to improve the quality of their lives.

Future research should focus on the relationship between the quality of PST protocols and its psychological impact.

6. Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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