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## Long-term predictors for psychological outcome of pre-symptomatic testing for late-onset neurological diseases

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### ABSTRACT

This longitudinal study aimed at determining predicting variables for middle and long-term psychological disturbance due pre-symptomatic testing (PST) for two late-onset neurological diseases, Huntington disease (HD) and TTR (transthyretin protein) familial amyloid polyneuropathy (FAP) Val30Met (now classified as Val50Met). 196 clinical records of persons who performed PST at least three years ago and answered to the two stages of evaluation (before PST and least 3 years after disclosure of results) were analysed. For this purpose, regression analysis was performed, showing that the Positive Symptom Distress Index (PSDI), psychoticism, somatization and paranoid ideation dimensions assume predictive value in the middle and long-term impact for total anxiety and PSDI. The result of PST was not a relevant predictor. The application of an evaluation instrument of various psychopathological dimensions played a fundamental role in the detection of clinical situations that may arise several years later after PST. Attention should be paid to providing psychological support to persons at-risk who, at the pre-test phase, present some psychopathology indices before pursuing with genetic testing.

### 1. Introduction

A pre-symptomatic testing (PST) protocol of genetic counselling and psychosocial evaluation and follow-up for late-onset neurological disorders (LONDs), such as Huntington's disease (HD), has been implemented and adapted for other diseases with late-onset (Hawkins et al., 2011). HD is a monogenic, autosomal and dominant disease with a severe neurodegenerative evolution and no effective treatment or cure. It is initially manifested by the development of chorea, involuntary movements leading to a progressive deterioration of motor skills and accompanied by progressive dementia and psychiatric disorders; patients also manifest a progressive cognitive deterioration. TTR (transthyretin protein) familial amyloidotic polyneuropathy (FAP) Val30Met (now classified as Val50Met) is an autosomal dominant form of systemic amyloidosis manifesting predominantly as a sensitive, motor and autonomic neuropathy. TTR-FAP is a severe and incapacitating disease, with no effective cure, caused by an abnormal transthyretin (TTR), deposited in various organs as amyloid (Saraiva and Costa, 1986; Leite et al., 2017b). Liver transplantation began by the 90's (Herlenius et al., 2004; in Coelho et al., 2012) and the new drug tafamidis (Coelho et al., 2012) have been used to prevent disease

progression, but are not adequate or effective in a large proportion of patients.

A PST protocol was designed (adapted from those used in HD) and implemented since 1995 (Sequeiros et al., 2006; Leite et al., 2016; Leite et al., 2017a). Along the last decades, there have been several studies showing that the psychosocial short-term (one-year) impact of PST did not reach a significant negative impact, including in these two neurological diseases, concerning psychopathological, depression or anxiety indicators (Rolim et al., 2006; Tibben, 2007; Lêdo et al. 2013a, 2013b). Similar results were found concerning the middle to long-term psychosocial impact of PST (Almqvist et al., 2003; Decruyenaere et al., 2003; Decruyenaere et al., 2004; Timman et al., 2004; Lickleder et al., 2008; Gargiulo et al., 2009; Gonzalez et al., 2012; Lêdo, Leite, Souto, Dinis and Sequeiros, 2016a; Lêdo et al., 2016b; Leite et al., 2017c,d), except in carriers who were already presenting symptoms of the disease (Lickleder et al., 2008; Lêdo et al., 2016a, 2016b) or, as Lêdo et al. (2016a) have suggested concerning the improvement of anxiety levels, when carriers approach of the onset's age disease.

At the Center for Predictive and Preventive Genetics (CGPP), at Institute for Molecular and Cell Biology (IBMC), a national reference protocol was developed for genetic counselling and PST (Sequeiros,

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1996; Rolim et al., 2006). Lêdo and colleagues (2013) studied the psychopathological impact on this population and noticed that psychopathological indices decreased significantly one year after one year after PST, regardless of its result. The same was found for middle (4 years) to long-term (7–10 years) PST psychological impact (Lêdo et al., 2016a, 2016b), and comparable with the findings of the few such studies in HD (Decruyenaere et al., 2003, 2004; Timman et al., 2004; Gargiulo et al., 2009; Crozier et al., 2015). There were three main common conclusions that those studies reached: (1) while asymptomatic, testees do not present significant psychological disturbance; (2) “mutation” carriers could present some psychological disturbance only when they already have symptoms of the disease; (3) those who presented any short or long-term psychological disturbance, already had some psychological signs at pre-test.

According to Codori et al. (1997), the best predictors of psychological disorder post-disclosure of results could be the baseline levels of the same variables. In this study, were analysed possible pre-test predictors of post-testing adjustment in participants who received a result of “carrier” or “non-carrier” for HD or TTR-FAP, at least 3 years ago. Thus, the main aim of this study was to find predictive variables that may assist this field of research and increase our knowledge and prepare follow-up by investigating the long-term consequences of PST, as also suggested by Timman et al. (2004) when they emphasized the importance of follow-up studies investigating the long-term consequences of PST so that the adjustment of psychological support can be possible.

## 2. Methods

### 2.1. Type of study

A longitudinal study was designed based on data collected from medical records, at the time of the first evaluation (before PST), for two autosomal dominant late-onset diseases, HD and TTR-FAP. Participants who accepted undergoing the one-year PST protocol were previously informed about the purpose of this research and signed a written informed consent. The project was approved by the IBMC Ethics Committee. The only inclusion criteria was that participants had completed the PST protocol at least three years before, having received either a result of mutation *carrier* or *non-carrier*.

### 2.2. Participants

The first assessment was conducted with 686 participants when they perform the PST, at CGPP, but before they know the test result (pre-test). The second assessment was conducted by mail, with the same 686 participants, several years after de first one. Participants were asked to complete a sociodemographic questionnaire and respond to three psychological tools. Out of those, 203 answered in useful time, and 7 were excluded because the questionnaires were not filled in properly. The study sample included 196 effective participants, aged 21–78 years ( $M = 37$  years,  $SD = 12.3$  years). Most were female (58%), and single (55%) or married/in a couple (42%). Years after PST ranged 3 to 11 ( $M = 6.5$  years,  $SD = 2.2$ ). In the group at-risk for TTR-FAP (85%), the majority (56%) were carriers, and in the group at-risk for HD (15%), approximately half (53%) were carriers (Table 1).

### 2.3. Study variables and tools

Social and demographic data, as *sex*, *age* and *marital status*, and clinical variables, as *years after PST*, *test result*, *disease (HD or TTR-FAP)* and *current clinical status*, were collected from a questionnaire sent to carriers and non-carriers.

(1) *Anxiety* was assessed using the Portuguese version (Vaz Serra et al., 1982) of the original Zung Self-Rating Anxiety Scale (SAS) (Zung, 1975), composed by 20 items rated on a four points Likert scale

**Table 1**

Sample characterization (n = 196) at pre-test stage.

| Variable                            | n (%)      |
|-------------------------------------|------------|
| <i>Sex</i>                          |            |
| Female                              | 114 (58.2) |
| Male                                | 82 (41.8)  |
| <i>Marital Status</i>               |            |
| Single                              | 107 (54.6) |
| Married/Union                       | 82 (41.8)  |
| Divorced                            | 5 (2.6)    |
| Widow                               | 2 (1.0)    |
| <i>Type of disease</i>              |            |
| TTR-FAP                             | 167 (85.2) |
| HD                                  | 29 (14.8)  |
| <i>Test result</i>                  |            |
| Non-carrier                         | 88 (44.9)  |
| Carrier                             | 108 (55.1) |
| <i>Current Clinical Status</i>      |            |
| Non-carrier                         | 88 (44.9)  |
| Asymptomatic carrier                | 71 (36.2)  |
| Symptomatic carrier (affected)      | 28 (14.3)  |
| Liver transplant (TTR-FAP affected) | 9 (4.6)    |

(ranging from 1 = “rarely or never” to 4 = “most or all the time”). SAS measures anxiety, based on the description of its most common symptoms and signals for four dimensions (subscales): *cognitive* (items 1 to 5), for a maximum of 20 points; *motor* (items 6 to 9), maximum of 16 points; *vegetative* (items 10 to 18), maximum of 36 points; and *central nervous system (CNS)* (items 19 and 20), maximum of 8 points. The score thus ranges 20 through 80, with a cut-off point set at 40 (Vaz Serra et al., 1982). (2) *Depression* was assessed using the Portuguese version (Vaz Serra and Pio-Abreu, 1973a, 1973b) of the Beck Depression Inventory (BDI) (Beck et al., 1961; Beck et al., 1996), a self-response record with 21 items. BDI is divided in two subscales, cognitive-affective and somatic or performance subscales; each item has four to six statements, sorted according to severity (none = 0, mild = 1, moderate = 2 and severe = 3). The cut-off point is set at 12, above which the difference to the normal population is established. (3) *Psychopathological symptoms* were assessed by the Portuguese version (Canavarró, 1999, 2007) of the Brief Symptom Inventory (BSI, Derogatis, 1993), composed of 53 items rated on a Likert scale of five grades, ranging from 0 (“rarely”) to 4 (“very often”), nine dimensions - *somatization*, *obsessive-compulsive*, *interpersonal sensitivity*, *depression*, *anxiety*, *hostility*, *phobic anxiety*, *paranoid ideation* and *psychoticism* - and three global indices, *Global Severity Index (GSI)* which is the mean of all of the subscale scores, *Positive Symptom Total Index (PSTI)* which is the number of items endorsed at a level higher than zero and *Positive Symptom Distress Index (PSDI)*, which corresponds to the sum of all items values divided by the PSTI. All this indices express psychometric ratings of emotional distress.

### 2.4. Data analysis

Descriptive statistics were used to report baseline characteristics; *t*-tests were employed to identify significant differences between psychological dimensions and related subscales at the pre-test and post-test stages; a reliability analysis checked for internal consistency of the scales; and a multiple regression analysis with stepwise variables selection was used to identify social and demographic characteristics and psychological dimensions at the pre-test stage that could predict the dimensions at the second stage. Results were considered statistically significant at the 5% standard significance level. All statistical analyses were performed using SPSS software version 24 (IBM, 2016).

## 3. Results

Differences of psychological variables at the pre-test (1st) and post-

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