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ORIGINAL RESEARCH

Presymptomatic Testing for Neurogenetic Diseases in Brazil: Assessing Who Seeks and Who Follows through with Testing

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Abstract Diagnostic tests are available to detect several mutations related to adult-onset, autosomal dominant, neurodegenerative diseases. We aimed to describe our experience in a presymptomatic testing program run by the Brazilian Public Health System from 1999 to 2009. A total of 184 individuals were eligible for presymptomatic testing due to a risk for spinocerebellar ataxia (SCA) - SCA3 (80%), Huntington's disease (11.9%), familial amyloidotic neuropathy (4.3%), SCA1, SCA2, SCA6, or SCA7. Most were women (70%), married (54%), and had children prior to presymptomatic testing (67%). Their mean age at entrance was 34 (SD = 11 years). Educational level was above the average Brazilian standard. After receipt of genetic counseling, 100 individuals (54%) decided to undergo testing; of these, 51 were carriers. Since no individual returned for post-test psychological evaluation, we conducted a subsequent survey, unrelated to test disclosures. We contacted 57 individuals of whom 31 agreed to participate (24 had been tested, 7 had not). Several ascertainment concerns relating to these numerous losses prevented us from generalizing our results from this second survey. We concluded that: decision-making regarding presymptomatic testing seems to be genuinely autonomous, since after genetic counseling half the individuals who asked for presymptomatic testing decided in favor and half decided against it; general characteristics of Brazilians who sought presymptomatic testing were similar to many European samples studied previously; and individuals at risk for SCA3 may be at greater risk of depression. Although no clear-cut reason emerged for rejection of follow-up psychological sessions after presymptomatic testing, this finding suggests adjustments to our presymptomatic testing program are necessary.

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Introduction

Diagnostic genetic tests are available to detect several mutations related to adult-onset, autosomal dominant, neurodegenerative diseases, by highly accurate laboratory methods. Successful prevention or treatment is usually not possible, and genetic counseling usually focuses on presymptomatic testing of at risk relatives. Among these conditions are Huntington's disease (HD) and spinocerebellar ataxias (SCAs) 1, 2, 3, 6, 7, 17 and DRPLA; all of these are caused by a CAG repeat expansion within the coding region, producing an extended polyglutamine (polyQ) tract in the mutant protein. Presence of polyQ induces neuronal intranuclear inclusions (NII) and neurodegeneration (Rudnicki and Margolis 2003). Familial amyloid polyneuropathy (FAP) is another neurogenetic, autosomal dominant disorder characterized by a progressive peripheral and autonomic neuropathy with extracellular deposition of fibrillar transthyretin (TTR) amyloid. In this polyneuropathic form of disease, ATTR Val30Met is the most commonly found mutation (Ando et al. 2005).

Presymptomatic testing (PT) identifies individuals who will develop a genetic disorder if they live long enough. Presymptomatic testing for late-onset neurological diseases became available in 1983 for HD (European Community Huntington's Disease Collaborative Study Group 1993), first by linkage analysis and subsequently by direct molecular test. The counseling procedure developed for PT in HD has become a model of how to proceed (Broadstock et al. 2000; Decruyenaere et al. 1995; Duisterhof et al. 2001; Tibben et al. 1992; Wiggins et al. 1992).

For ethical reasons, PT involves adult subjects and should be performed according to specific programs and guidelines (Wertz et al. 2003). Early reports pointed out the necessity of using safe programs to avoid so-called catastrophic events (Almqvist et al. 1999). Presymptomatic testing results may affect life plans, depending upon "the perceived severity of the disorder, the availability of support systems for people with the disorder..; and the personal and cultural values and perceptions of disability" (Wertz et al. 2003). Widely studied in the case of HD, the impact of PT on SCAs in general and on FAP has received less attention. Although some studies have been published on the testing uptake and on the potential effects of PT on SCAs in countries outside Europe or United States (Alonso et al. 2009; Gonzalez et al. 2004; Lima et al. 2001; Paneque et al. 2007a, b and 2009), there is still a need for more knowledge about the influence of cultural background and about the acceptance of PT in diverse societies.

Purpose of the Present Study

The present study aimed to describe the experience of a PT program, run in accordance with the international guidelines for HD, SCAs and FAP (Wertz et al. 2003) and offered in the context of Brazilian Public Health System from 1999 to 2009. Major research questions investigated were: (1) what epidemiological characteristics and rates of acceptance our population presents in each step of our PT program?; (2) are these rates different from those reported elsewhere?; and (3) why none of the individuals that received their test results returned for follow-up visits? Since we had detected an absolute rejection of post-test (post-PT) psychological evaluation, we aimed to conduct a subsequent survey of the psychological characteristics of all individuals who sought PT in the last 10 years, in order to detect differences between those who decided for and against PT, and between carriers and non-carriers.

Methods

Sample and Procedures

Presymptomatic Testing Program Description

The present PT program has been implemented in a university hospital located in south Brazil. The program was approved by the local Bioethics Committee. To take part in the PT program, individuals must belong to families carrying HD, FAP or SCA mutations. They apply themselves and must be asymptomatic. If minor signs are noted on examination but the individual is unaware of them, or if the individual is in doubt about his/her own clinical status, the PT program is carried out exactly as for those who are asymptomatic. During the time under study, symptomatic individuals belonging to 2 SCA1, 7 SCA2, 146 SCA3, 2 SCA6, 1 SCA7, 46 HD, and 5 FAP families were registered at our institute. The most prevalent was SCA3 and, at the end of the present survey, there were 760 individuals who were at 50% risk for SCA3, and older than 18 years of age, in our region.

Our PT program is carried out over at least five sessions. The first of these is a genetic counseling session conducted by a medical geneticist. After discussing topics related to diagnosis, prognosis, risk and other aspects, the physician presents the program, reassuring the individual that he/she is free to drop out at any time without any loss of confidentiality. Sessions two and three are conducted by a psychologist, and consist of an undirected interview followed by the administration of three tests: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and the Rorschach projective tests. The purpose of

the psychological assessment is to detect possible psychological risks, and resolve them. In the fourth session, the main results of the psychological tests are discussed and, if the patient agrees, a blood sample is collected. The disclosure session (session five) is carried out by the same clinical geneticist who conducted the initial genetic counseling session.

We ask each participant to ensure they are accompanied by another person, at least in this fifth session, but disclosure of the test results themselves may be made privately to the patient. Follow-up evaluations are offered and scheduled by the psychologist, at three-week, six-month and 12-month intervals. In cases where the individual drops out at any of these stages, we make no further efforts to contact the person, in order to respect his/her decision. The person's data are maintained in protected files, in case the individual changes his/her mind in the future. Neurological assessment and further genetic counseling sessions may be available upon their request, but are not a routine part of this program.

Participant Recruitment for the New Survey

At least 1 year after entry into the PT program, a new survey was performed, after approval by the local Bioethics Committee. A psychologist, unaware of the former PT results, attempted to contact individuals who came for PT in our hospital, independently of their decision for or against PT and invite them to participate in the present study. Telephone calls were made, in order to explain to these individuals the nature of the interview being offered. Patients were reassured that the interviewer: did not know any of their test results, would respect personal opinions about PT, and did not intend to invite the individual to return to PT. The interviewer explained the aim of the present research was to find out the opinion of the participants about PT, and to offer a psychological evaluation, unrelated to any collection of blood samples.

Instrumentation for the Presymptomatic Testing Program

Demographic Data

Socio-demographic data were collected by anamnesis, during the first session. These data included: age, gender, education level, marital status, number of children, and the disease for which the participant was at risk.

Psychosocial Functioning

The self-report Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Beck Hopelessness Scale (BHS), were used in pre- and post-genetic testing interviews, in their Brazilian versions (Beck and Steer 1993a, b and c; Gorenstein et al. 1996). The BAI is a 21-item scale assessing the respondent's last week; scores range from zero to 63. Final scores relate to no anxiety (0–10), mild to moderate (11–19), moderate to severe (20–30), or serious anxiety (31–63). The BDI is a 21-item inventory, assessing how the participant has been feeling in the last week, and scores range from zero to 63. Final scores correspond to no depression (5–9), mild to moderate (10–18), moderate to severe (19–29), or serious depression (30–63). Average ± sd BDI scores, in control populations from Brazil, range from 6.47±5.6 to 9.98±7.8 (Gorenstein et al. 1995 and 1996). The BHS is a dichotomous 20-item scale, with scores ranging from zero to 20. Final scores are related to no hopelessness (0–4), mild to moderate (5–8), moderate to severe (9–13), or serious hopelessness (14–20). In the present study additional psychological intervention was offered to individuals with a BDI and BAI score of 19 or higher and also for individuals who were felt to be at psychological risk during clinical evaluation.

The Coping Strategies Inventory by Lazarus and Folkman (1984), and personality traits measured by Rorschach projective tests were also performed in pre-and post-genetic testing interviews. Data from these measures are not reported herein since they will be presented elsewhere.

Procedures for the New Survey

Individuals interested in participating in this study were interviewed in our institution by the same psychologist that recruited them. Interviews were transcribed. The participants also completed new BAI, BDI and BHS.

Instrumentation for the New Survey

Interview Questions

A 50 min long, semi-structured interview was performed, covering five main interview questions: whether or not participants had completed the PT program; what their motivations were for taking or not taking the test; how they recalled the relationship with the genetic counselor; how they perceived changes in their lifestyle and future plans after knowing the results; and what they considered to be the advantages and disadvantages of being tested.

Data Analysis

For each sub-group obtained in the presymptomatic testing program (defined either by drop-outs at each possible step, according to Fig. 1, and by the disease at risk) , relationships between psychological scores (BDI, BAI, BHS) and the independent variables of disease at risk, age, gender, education level, marital status, and molecular results were

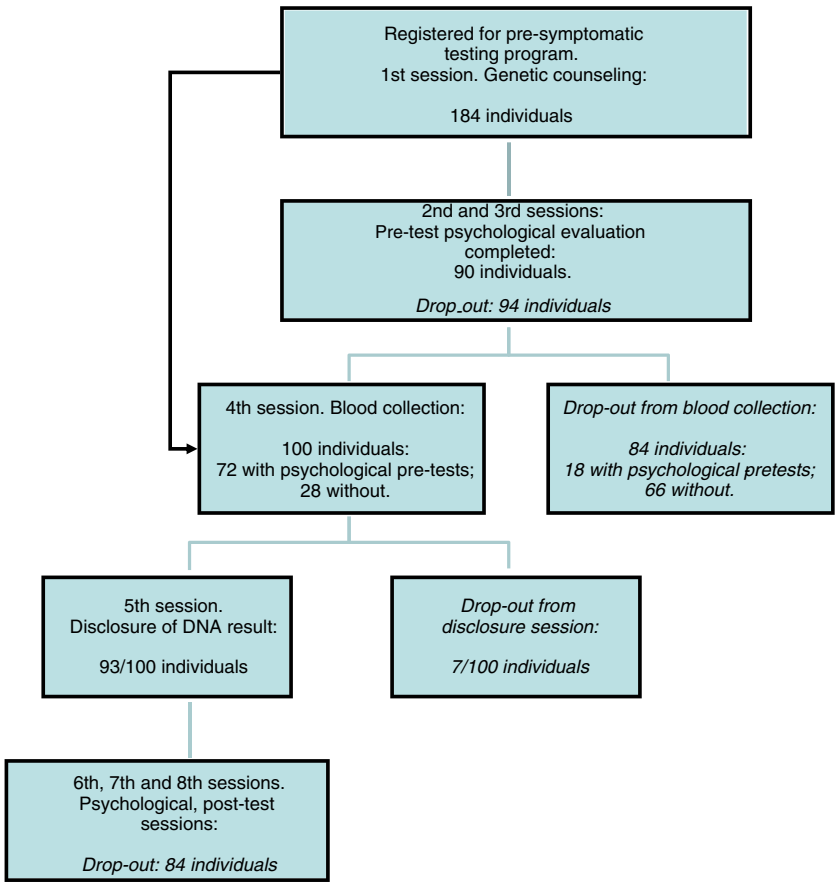

Fig. 1 Outcome of 184 pre-symptomatic test requesters for spinocerebellar ataxias (n=154), Huntington's disease (n=22) and familial amyloidotic neuropathy (n=8)

assessed. The BDI and BAI scores obtained in the new survey were also compared to those obtained at pre-genetic testing sessions, when available, and to the independent variables under study.

Comparisons of quantitative variables between subgroups of patients were performed by using Student's t-test for unrelated samples or One-Way ANOVA. Univariate General Linear Model was utilized to control for confounding factors that were significantly correlated with the variables. Differences related to categorical variables such as gender or molecular diagnoses were analyzed with Chi-Square test. Correlations between simultaneous psychometric variables were assessed by the Spearman correlation test followed by the linear regression model. Comparisons of psychometric variables before and after molecular tests were performed by paired Student's t-test. Statistical significance was defined as $p<.05$.

Results

Sample Characteristics

Between 1999 and 2009, 184 individuals at risk for an autosomal dominant, adult-onset neurogenetic disease sought PT in our institute. They were at 50% risk for HD, SCA or FAP. Most of them had an affected parent or sibling; only one was at 25% risk: a grand-daughter of a SCA3 symptomatic person. Their characteristics are shown in Table 1. Of the total sample, there were 123 women and 61 men. Women comprised 66% of the sample, $X^2(1)=11.3$, $p\leq.05$. Education level was higher than in the general population: that is, illiterate comprised 0% whereas those with more than 15 years of schooling comprised 36% of the total sample, $X^2(3)=57.3$, $p<.001$.

Mean ages at PT registration were higher in those individuals at risk for HD and FAP than for those at risk for SCA3 – the three groups of disorders with a sufficiently large sample size to be included in this comparison (p=.011, ANOVA). However, where they could be compared, the ages at PT registration were very similar to the mean age at disease onset in SCA3 and in HD (Table 2).

One hundred subjects (51.5%) decided to provide a blood sample, and 93/100 (93%) of these decided to receive their results (Fig. 1). Quite surprisingly, not one of these individuals returned for post-test evaluation. It appears that PT acceptance or access was lower in SCA2 and FAP families than in the other families (Table 2), although the small n's preclude statistical analysis.

Table 1 General characteristics of individuals who sought presymptomatic testing in South Brazil

		Observed	Expected*	*p*
Male/female		61/123	92/92	<.05
Age	m ± sd	34±11	–	
Marital status	Single Married	69 (38%) 99 (54%)	41% 52%	ns
	Separated	15 (8%)	6.6%	
Schooling	Illiterate Less than 8 years	0 41	9 97	<.001
	8 years	97	51	
	15 years or more	36	7	
With children	Yes No	86/129 (67%) 43/129	97/129 (75%) 32/129	ns
At risk for	SCA1 SCA2	1 1	– –	-
	SCA3	147	–	
	SCA6	3	–	
	SCA7	1	–	
	HD	22	–	
	FAP	8	–	

* According to the Brazilian Institute of Geography and Statistics (IBGE) data

Individuals who Completed Psychological Testing

After genetic counseling not all 184 individuals adhered to the PT program (Fig. 1). Individuals dropped out of the program after either the first or second session, citing, as the most important reason, the absence of effective therapies.

Forty-eight percent of individuals (90/184) who asked for PT completed the pre-genetic testing psychological evaluation. Other independent factors such as age, marital status, education level, previous children and disease at risk did not seem to have significantly influenced this decision (Table 3).

Individuals who Completed Blood Sampling

Fifty-four percent of the initial sample (100/184) decided to undergo blood sampling. As can be seen in Fig. 1, not all of

Table 2 Differences and similarities between individuals registered in PT, according to the disease at risk

	Individuals registered in PT	Families in general care	Families with individuals registered in PT	Age at PT m ± sd (*n*)	Age at disease onset, in our population m ± sd (*n*)	BDI scores at PT registration	BAI scores at PT registration
SCA1	1	2	1 (50%)	19	–		
SCA2	1	7	1 (14%)	26	–		
SCA3	147	146	59 (40%)	32.7±10.7 (114) ns ***	32.1±12* (62)	9.69±9.1 (74)	11±10.6 (74)
SCA6	3	2	2 (100%)	–			
SCA7	1	1	1 (100%)	39			
HD	22	46	12 (26%)	39.7±10.7 (21) ns ***	36.7±13 (54)	9.83±6.4 (6)	11.5±6 (6)
FAP	8	5	1 (20%)	39.5±12.4 (7)	–	6±7.2 (3)	7.3±5.7 (3)
Total	185	209 *p*<.001 **	77 (37%)	–		9.45±8.8 (83) ns ****	10±10 (83) ns ****

* from Jardim et al. (2001), Acta Neurol Scand

** chi-square

*** t test and **** ANOVA

Table 3 Subgroups defined by drop-outs at each possible step, and their comparisons according to their general characteristics

			Genetic counseling for PT session	PT Psychological evaluation completed	Blood collected	Picked up test result	Came to scheduled follow-up visits	Accepted invitation to second survey
n			184	90	100	93	0	31/57 contacted
Female			123/184 (67%)	69/90 (76%)	67/100 (67%)	63/93 (72%)		22/31 (70%)
Age	m ± sd		34±11	33.2±10.4	33.9±10.4	33.2±10.4		32.3 10
Marital status	Single		69/183 (38%)	28/90 (31%)	31/99 (31%)	25/87 (30%)		7/31 (22%)
	Married		99/183 (54%)	54/90 (60%)	60/99 (61%)	53/87 (63%)		22/31 (71%)
	Separated		15/183 (8%)	8/90 (9%)	8/99 (8%)	6/87 (7%)		2/31 (6%)
Schooling	m ± sd		9.9±3.8	9.7±3.9	9.8±4.1	9.9±4.2		9.9 4.4
With children	Yes		86/129 (67%)	48/76 (63%)	50/76 (65%)	43/65 (66%)		18/24 (75%) (3 after GC)
Number of children	m ± sd		1.37±1.6					
At risk for *n* (%)	SCA1	Overall	1 (0.5%)	0	1 (1%)	1 (1%)		
		Positive results			0	0		
	SCA2	Overall	1 (0.5%)	1 (1%)	1 (1%)	1 (1%)		
		Positive results			0	0		
	SCA3	Overall	147 (80%)	78 (87%)	82 (82%)	71 (82%)		27 (87%)
		Positive results			44	38		14/16
	SCA6	Overall	3 (1.6%)	0	1 (1%)	1 (1%)		
		Positive results			0	0		
	SCA7	Overall	1 (0.5%)	0	0			
		Positive results						
	HD	Overall	22 (11.9%)	8 (9%)	12 (12%)	10 (12%)		4 (13%)
		Positive results			6			2/4
	FAP	Overall	8 (4.3%)	3 (3%)	3 (3%)	3 (3%)		
		Positive results			1	1		
Positive results			51/100	36/71	51/100	47/93		16/24

* Significant association; $p<.05$ or less

them agreed to be psychologically tested (n=28). The main reason given for not accepting psychological testing was that they were already engaged in some form of psychotherapy. These individuals included 16 persons at risk for SCA3, eight at risk for HD and four at risk for FAP. Subsequent molecular results for those tested for HD and FAP were random. In contrast, 11 out of 16 tested for SCA3 were actually carriers (ns).

None of the independent factors under study were significantly associated with the decision to provide a blood sample – gender, age, marital status, education level, previous children and disease at risk (Table 3). As expected, the decision to collect DNA was more prevalent among those individuals undergoing psychological testing (72/90 or 80%) than among those who did not (28/94 or 29%), $X^2(1)=42.3$, $p<.001$. Finally, no temporal trend in favor of or against blood collection was detected during the 10 years' observation (data not shown).

As previously noted among the cohort that sought PT, individuals at risk for HD and FAP who underwent blood sampling were significantly older than the rest, at 40.8±8.8 and 49 years of age, respectively, versus 34±11 (p=.006).

Individuals who Picked up their Test Results

Ninety-three individuals (93% of those who collected their samples) decided to receive their test results, while seven decided against receiving them.

Molecular Results

Fifty-one (51%) individuals were carriers of dominant mutations. These rates were due to the results seen in diseases with a large enough sample size, namely, SCA3 and HD (Table 3). There were no significant differences between carriers and non-carriers, with respect to their ages, gender proportions, education level, marital status and number of children.

Pre-test Psychological Evaluation

Mean ± sd BAI scores were 10.8±10.2 (n=84); scores ranged from zero to 60. Mean scores were not significantly related to the existence of children, to marital status, to the further decision to provide a blood sample, to the disease at risk, or to the final test result (Fig. 2).

Mean ± SD BDI scores were 9.45±8.8 (n=84); scores ranged from zero to 40. Nine individuals (10% of the total) had moderate to severe scores and were referred for psychotherapeutic evaluation. Again, the BDI scores were not significantly related to the existence of children, to marital status, to the further decision to provide a blood sample, to the disease for which at risk, or to the final test result (Fig. 2). As expected, BDI scores were significantly correlated showed with BAI scores (r=0.61, $p<.001$, Spearman correlation test), such that more depressed individuals tended to also report greater anxiety.

Although there were no significant differences between BDI scores according to the disease at risk, all nine individuals with moderate to severe scores belonged to SCA3 families.

Response to the New Survey

In 2009 and 2010, several attempts to recontact 169 of the former patients were made by telephone and letters. Since 15 individuals had only entered the PT program in 2009, they were not contacted for this second survey.

There were 112 (66.3%) true losses: including 106 individuals that could not be found, five were unable to come to a follow-up visit (one of whom was already symptomatic), and one that was deceased for unknown reasons. Another 26 individuals (14%) declined to participate in the survey, including: 11 that refused directly and 15 that avoided contact – postponed their decision, did not answer the telephone, etc. Finally, 31 individuals (17%) accepted the invitation to participate in this second survey.

In order to check for any possible bias that these losses and refusals to answer the survey would produce, we compared the three groups of respondents (losses, refusals and acceptances) on several characteristics. A greater percentage of individuals in the losses group were at risk for SCA3 (69%) than for HD (21%), $X^2(7)=14.6$, $p<.04$. More acceptances were obtained among individuals who had formerly provided DNA samples (72%) than those that had not done so (28%), $X^2(1)=11.4$, $p<.001$.A trend towards greater acceptance among carriers than among non-carriers was observed. Gender, marital status, education level, previous and further children were not related to the acceptance of the invitation. Since only 34 of 57 individuals found by phone gave information about their clinical status, this variable could not be compared among the three responder groups.

Therefore, the data obtained in this second round are not representative of the overall group of at-risk individuals who sought the PT program.

Individuals' Evaluation of the PT Program

Twenty-three of the 31 respondents evaluated the present PT program favorably. The other eight reported they had not been satisfied with the services received. The time interval between blood collection and receipt of test results was the main complaint, made by three individuals. Other complaints included: a poor support system during the

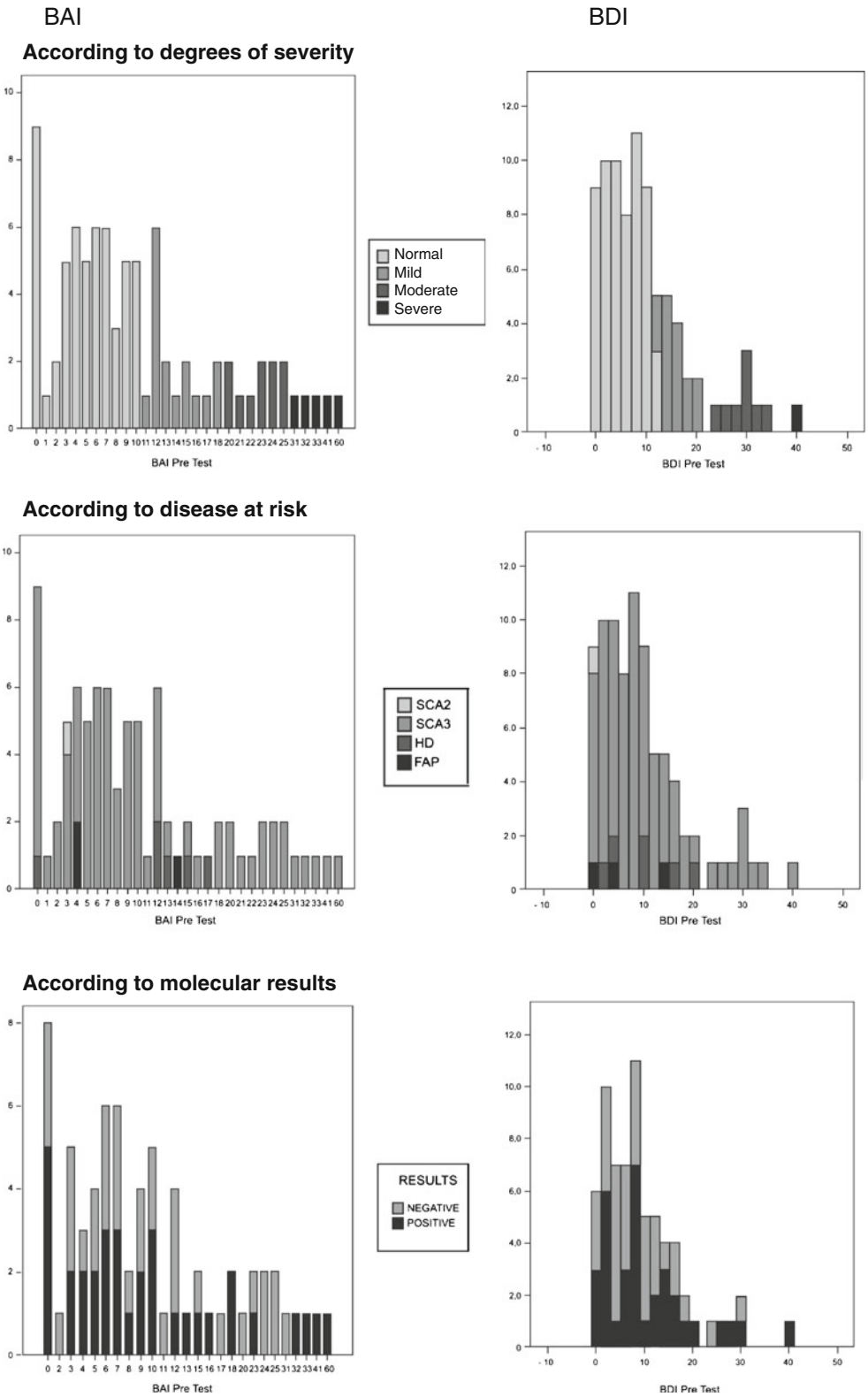

Fig. 2 BAI and BDI pre-test scores, according to (**a**) severity, (**b**) disease at risk, and (**c**) molecular results according to degrees of severity

delivery of test results (n=2); poor quality of information given during genetic counseling, leading to the decision against PT; inconsistent and unnecessary psychological tests before blood collection; and lack of PT programs in other centers, leading to the need for long-distance trips (one person each).

Impact of Presymptomatic Testing on the Individuals Tested

Among the 31 participants in the second survey, 24 had been tested previously. Data about children born after PT were obtained for 22 previously tested persons. Four of the seven non-carriers and two of the 15 carriers had children after PT.

Fifteen individuals at risk for SCA3 had two BDI scores: the first one, collected during pre-test evaluations, and the second, collected during the second survey. Time interval between the two evaluations was quite variable (range: 1 to 10 years). There were 10 carriers and five non-carriers. Their BDI scores either decreased or regressed toward the mean (ns, GLM).

The second BDI scores for those individuals who were molecularly tested were 9.8±9 (n=24), whereas from those did not were 13±9 (n=7).

Of the 31 participants, 18 were asymptomatic, and 13 were already symptomatic. The difference between their BDI scores (9±7.7 and 13±12.5) was not significant (p=.3, t test).

Similar trajectories for BAI scores were obtained in the 15 individuals at risk for SCA3 who completed pre- and post-test (during the second survey) evaluations. The BAI scores for the 24 individuals formerly tested were 13.2±10, whereas those for the seven non-tested persons were 9±4.5. Among carriers, asymptomatic individuals had significantly lower BAI scores (8.8±5) than the symptomatic individuals (16.9±12.3) (p=.04, t test).

BHS scores obtained in the second survey among those individuals who underwent PT were 4.5±4.3 (n=24), whereas from those who did not were 3.14±2.6 (n=7). In the previously tested individuals, the BHS scores of carriers (4.9±4.8) and of non-carriers (3.7±3.2) were similar. Finally, among carriers, those who were symptomatic had significantly higher hopelessness scores (6.2±5.4) than those who were asymptomatic (2.2±1.3) (p=.04).

Discussion

The present study yielded six major findings: (1) around half of the individuals who sought presymptomatic testing decided to follow through with testing; (2) women, and people with a higher than average education level were more likely to seek PT; (3) the sample had fewer children than the general population; (4) the ages at which individuals sought testing were very similar to the respective ages at onset of the disease for which they were at risk; (5) at the time of the request for PT, 10% of individuals showed moderate to severe depression (all belonged to SCA3 families), and (6) none of the individuals that received their test results returned for follow-up visits.

Our region is characterized by a relatively high frequency of SCA3 (Trott et al. 2006), and therefore more demographic data about this disease are available than for other diseases. These data indicate that there were 760 individuals at 50% risk for SCA3 in our population, at the time of the present study. Taking this number as the reference point, those 71 individuals at risk for SCA3 who completed PT would represent 9% of the total population potentially eligible for a PT program. These numbers may be comparable to those described mostly for HD, in Europe, where between 5 and 18% of the at-risk population opts for PT (Tibben et al 1993; Goizet et al. 2002)."

The finding of around 50% follow through after genetic counseling acceptance among those who asked for a PT test, seems to reflect a good parity of opinions in favor of and against PT tests, in our society. Most withdrawals occurred between the genetic counseling session and the end of psychological testing (49% of cases): the most important reason given was the absence of effective therapies. But withdrawals also occurred after the blood sample was collected (13% of cases). Similar acceptance proportions have been described in other societies and among groups of individuals at risk, such as Italians at risk for HD (36 to 50% of acceptance); (Cannella et al. 2001; Mandich et al. 1998), French at risk for HD and SCAs (47 to 58%) (Gargiulo et al. 2009; Goizet et al. 2002), and south-eastern Brazilians at risk for HD and SCAs (34%) (Paiva 2006). These proportions differ considerably from other reports, however, where a vast majority decided in favor of testing – such as Cuban individuals at risk for SCA2 (87% of acceptance) (Paneque et al. 2007b), Mexican persons at risk for HD (88%) (Alonso et al. 2009), and Portuguese at risk for HD (85%) (Sequeiros, personal comm.).

Presymptomatic testing programs are designed to help persons gain sufficient insight about their subjective perception of risk and their motivation for testing. The multi-step nature of such programs allows the delay necessary for individuals to choose the best path for themselves. Comparisons among reports from different countries may reflect the diverse nature of each PT program, or differences in the information level of the candidates. However, some interesting changes in rates are appearing in the literature, showing that the culture, environment and personal experiences themselves may explain the acceptance rates to a greater extent. For instance, Bernhardt et al. (2008) described a decreasing uptake of predictive testing for Huntington's disease in Germany: in 12 years, acceptance declined from 71 to 38%. In any case, these results underline the importance of giving the person at risk enough time to decide and the importance of the right to not know.

We failed to identify any underlying factors related to the decision to follow through with PT: neither gender, marital status, education level, existence of children, disease at risk, nor pre-test BDI and BAI scores were significantly, related to this decision. Rates of pros and cons have fluctuated during the years, without any temporal trend.

The observed rates of heterozygotes (51%) were almost exactly those expected by Mendelian segregation, arguing against a role of genetic status in the decision-making process. However, this finding deserves further reflection. Other studies with similar mean ages at PT observed higher ratios of non-carriers to carriers (Goizet et al. 2002). For those studies, these results were expected because a proportion of gene carriers will already have manifested illness and therefore no longer be likely to seek PT. If that is true, than we have in fact seen a higher than expected proportion of carriers. These would be in accordance with the hypothesis of a preferential transmission of expanded over normal alleles, already raised for SCA3 (Ikeuchi et al. 1996; Iughetti et al. 1998; Jardim et al. 2001; Riess et al. 1997).

Similar to results of previous studies on HD (Goizet et al. 2002; Tibben et al. 1993), more women than men requested and received PT in the present study. Besides this, several other socio-demographic characteristics of the present sample of Brazilian candidates for PT corroborate previous findings, such as mean age over 30, the proportion who were parents, a predominance of individuals living in a couple, and an over-representation of those in the higher socio-economic brackets (Tibben et al. 1993; Decruyenaere et al. 1995; Binedell et al. 1998; Goizet et al. 2002). The candidates' ages may be viewed as a sign of the maturity needed for the test. However, we wonder whether this would also reflect an identification with the transmitting parent or with other symptomatic relatives, since those ages were very similar to the respective ages at onset of HD and SCA3.

A particularly unwelcome result was the apparently low acceptance of PT by FAP and SCA2 families. Familial amyloidotic neuropathy is a treatable disease, if a liver transplant is performed early in the disease's course. Familial amyloidotic neuropathy has a low prevalence among the population of Brazil. An active search for these families in our State gave no more than the present five lines of descent. Perhaps the PT program was more likely to be accepted by those who were more knowledgeable: by those with at-risk diseases for which community networks already exist, such as SCA3 and HD.

At the time of PT request, mean ± sd BDI scores were of 9.45±8.8 in the general group, and of 9,69±9.1 in the SCA3 subgroup. These scores may be comparable to those found in the Brazilian population, which vary from 6.47± 5.6 to 9.98±7.8 (Gorenstein et al. 1995; Gorenstein and Andrade 1996). In a previous survey, we measured BDI scores from symptomatic SCA3 patients, their caregivers and their children at risk, outside the setting of a PT program (Cecchin et al. 2007). The BDI scores obtained in that survey from 80 persons at risk for SCA3, aged 30.5± 9.7, who were not considering PT, were of 5.6±6.9 – lower than the present findings. Moreover, 10% of the present individuals showed moderate to severe depression scores at the time of PT: all belonged to SCA3 families. It is worthwhile to remember the relationship already observed between SCA3 and depression, both in symptomatic individuals and in their caregivers, not only in our cultural area but also elsewhere (Cecchin et al. 2007; Klinke et al. 2010; Saute et al. 2010).

None of the tested individuals returned for programmed follow-up visits, after receiving their test results. The lack of return visits after disclosure may leave many issues unresolved. In order to understand the reasons for this wholesale rejection, we carried out the second survey, asking the original candidates for PT to participate in interviews, years after their visits. Our recruitment approach was similar to with those used by other investigators (cf. Gargiulo et al. 2009), except that we tried to contact even those persons who had decided to withdraw from PT, years before. Our aim was to measure whether there was some impact of PT over an individual's life, by comparing them to those who did not undergo PT.

The number of losses (66%) were very similar to those obtained by Gargiulo et al. (2009), and prevented us from generalizing our conclusions. In spite of the several ascertainment concerns relating to these numerous losses, we decided to present the results of the re-contact study, provided that no generalized conclusions were extracted. We were motivated by two main reasons: first, the most possible explanation for the low uptake of follow-up sessions was some inherent problem in our local PT program, and we needed to identify it; and second, because some of the answers we obtained could give us clues about the thought processes that surround a genetic test. Some individuals who refused to talk said they "didn't want to see our Hospital again." Some others repeatedly postponed the interviews. Both were interpreted as avoidance behaviors.

Among all the individuals we have encountered, no major adverse event was detected. Moreover, 75% of the 31 individuals who agreed to be interviewed evaluated our PT program favorably. Only two individuals described a poor doctor-patient relationship during their PT process. Among the 31 responders, we were able to detect some clues about how PT might have influenced their lives. We observed a trend to a lower rate of subsequent children among carriers than among non-carriers. We were also able to obtain new psychological test data for 15 individuals who were formerly evaluated. Their anxiety and depressive scores had decreased, as has been observed by others (Decruyenaere et al. 2003). Contemporary BDI, BAI and BHS

obtained from previously tested individuals were all similar to those obtained from non-tested ones.

So many years after considering PT, some carriers were already symptomatic. The BAI and BHS were significantly higher only in these symptomatic cases, all of them SCA3 individuals, when compared to asymptomatic carriers, suggesting that the disease status per se, and not its anticipation, was the agent of psychological distress. By disease status, we mean some impairment or dysfunction. We have already presented some evidence that neurological disability per se, and not mutation or atrophy of brain stem structure, was related to BDI scores in this disease (Cecchin et al. 2007; Saute et al. 2010). Therefore, in SCA3, severity of neurological symptoms seems to be the main agent of psychological distress.

Clinical Implications

Presymptomatic testing should be the patient's decision. For some individuals at risk, ending the uncertainty is paramount. For others, the existentialist dilemma that Nancy Wexler (1992) called "Tiresias complex", predominates – or in other words, the possibility that the knowledge that one is destined to develop a fatal disease for which there is no prevention or cure is useless and may even acts like a curse ("do you want to know how you are going to die, if you have no power to change the outcome?"). Potential adverse effects for those found to be affected are various. Depression, loss of personal relationships, concerns about entering long-term commitments, fear of passing the condition on to future generations, and job discrimination are some examples (McPherson 2006). However, these adverse events are almost the same as those one may expect among at-risk people who do not seek testing.

In conclusion, we have found several patterns in common with the literature about PT acceptance in European and North American countries. The main difference found in our population, when compared to others, rested in a general rejection by Brazilians of the follow-up psychological sessions after PT. This finding deserves attention, since it points to the necessity of further adjustments to our PT program, although no clear-cut reason has emerged from respondents to the second survey.

Study Limitations and Research Recommendations

The main limitations of this study are those related to its small sample size and to ascertainment. We can not determine whether people who agree to participate in the PT program and in the new survey differed in important ways from those who did not. Moreover, the small sample size means low statistical power. Given the exploratory nature of this study, we set a liberal alpha level for significance in order to identify information that might assist us in program development and maintenance. We are aware that, by doing so, however, there is a likelihood of some family-wise error rates due to multiple univariate tests.

However, this study gave valuable information about our PT program, in special by pointing to the total lack of follow ups in the post-test (post-PT) psychological evaluation. In our opinion, this rejection may reflect the fact that the PT program does not offer a good support system after the delivery of test results, nor actively offer psychotherapeutic support to the post-test period. We agree that "much of the stress associated with the test and many of the most vexing questions are not necessarily ethical, but clinical" (Wexler 1992). Therefore we decided to incorporate to our PT program the explicit offering of psychotherapy after the test result, and we suggest that other PT programs consider to do the same. We also recommend the creation of new community networks on FAP and SCA2, in our population, so that more individuals be knowledgeable about PT tests addressed to those diseases.

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