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ORIGINAL ARTICLE

Life paths of patients with transthyretin-related familial amyloid polyneuropathy Val30Met: a descriptive study

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Abstract Transthyretin-related familial amyloid polyneuropathy Val30Met is a fatal progressive disease. It is a rare hereditary amyloidosis, manifesting as a sensorimotor neuropathy and autonomic dysfunction. It begins during adulthood and is a disabling disease, posing a great psychological burden to patients and their families. Our aim was to describe and characterize life events related to the disease and discuss its psychosocial implications. Social and demographic data and a questionnaire on history of family and personal disease, and biographic events, were applied to 209 subjects attending an outpatient specialized clinic. Descriptive and statistical analyses were performed. They were 84 men and 127 women belonging to three groups: pre-symptomatic carriers, patients, and subjects with no established diagnosis. Most subjects were married/lived with a partner and had children (mean of 4). Most (96.3%) had contact with the disease before having a diagnosis; the affected or at-risk parent was the mother in 53.8% and the father in 43.3%; 71.8% of these had deceased. At their parent's death, many subjects were aged under 10 (9.9%), 10–14 (15.5%), or 15–24 years (31.7%). Most were under age 14 (44.9%) at their parent's disease onset; 37.2% referred this brought life changes with psychological and familial impact; most had been parent's caregivers; 7.5% had not been raised by the parents. Some (8.4%) declined to know their genetic tests results for over 1 year. Parent's disease and death are very common early in these patient's lives. During childhood or youth, many subjects became caregivers, implying changes in family roles. This disease and its life implications pose a significant psychosocial burden since childhood. TTR-FAP patients and their relatives are highly vulnerable to emotional stress and psychopathology during their lifetime. Psychological and psychiatric support, implying a multidisciplinary group, must thus be available for all of them.

Keywords Transthyretin · TTR · Familial amyloid polyneuropathy · Amyloidosis · Psychosocial · Psychiatric · Life events

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Introduction

Transthyretin-related familial amyloid polyneuropathy Val30Met (TTR-FAP) is a progressive, life-threatening disease, which manifests as a mixed sensorimotor neuropathy and autonomic dysfunction (Coelho et al. 1994; Coutinho

et al. 1980). The disorder is due to a point mutation (Val30Met) in TTR, a transport protein for thyroid hormone and retinol that deposit as amyloid in endoneurial spaces and organs (Ando and Ueda 2012; Benson and Kincaid 2007; Merlini and Westermark 2004; Saraiva 1996). The mutant protein is mainly produced not only in the liver (95%) but also in the choroid plexus in the central nervous system (CNS) and the retina (Benson and Kincaid 2007; Sekijima et al. 2008).

It is a rare inherited autosomal dominant amyloidosis. TTR-FAP occurs worldwide, but has its most important clusters in Sweden, in Japan (Holmgren et al. 1994; Koike et al. 2002; Parman et al. 2016; Sousa et al. 1993), and in the north of Portugal (Sousa et al. 1995). More than 3700 patients have been registered at our central hospital, since Corino Andrade observed the first patient in 1939 (Andrade 1952). Age of onset of symptoms is highly variable and unpredictable among and even within families and the disease may have early or late onset (after fifties) (Conceição 2012; Koike et al. 2002; Koike et al. 2012; Sousa 1995, 2006). Onset occurs before age 40 years, and a mean age of 38 years was found in a Portuguese sample (Santos et al. 2016). In northern Portugal, where its prevalence is very high (90.3/100,000), mean age-at-onset is earlier (29 in men; 33.7 in women) (Coutinho et al. 1980; Hou et al. 2007; Sousa et al. 1990, 1995).

The disease has a variable clinical expression, the peripheral and autonomic neuropathy being one of the major problems, with sensory and motor, as well as gastrointestinal, bladder, and cardiac problems, until a cachectic bedridden stage (Adams et al. 2000; Conceição 2012). Amyloid deposits also occur in the eyes (vitreous opacities, iris irregularities, glaucoma), kidneys (microalbuminuria to end-stage renal failure), heart (conduction disturbances), and CNS (Beirao et al. 2011; Lobato and Rocha 2012; Maia et al. 2015). Symptoms provoke great incapacity and psychosocial burden, including sexual dysfunction, changes in body image, uncontrollable diarrhea, and loss of sphincter control. In advanced stages of disease, patients lose autonomy and become dependent for daily life activities (Jonsen et al. 1998) .

For a long time, there was no treatment for this disorder and patients died within a period of 11 years, on average, after appearance of the first symptoms (Coutinho et al. 1980). Since 1990, liver transplantation has been performed as a way to slow disease progression, by preventing liver production of mutant TTR (Adams 2013; Ericzon et al. 2015; Holmgren et al. 1991; Suhr et al. 1995). In recent years, tafamidis, a drug that decreases amyloid deposition by stabilizing TTR, became an additional possible treatment. Other drugs and forms of treatment are being studied or under clinical trials (Berk et al. 2013; Coelho et al. 2013; Ueda and Ando 2014). Current available treatments slow down the disease progression and modify its natural history (Adams 2013; Coelho et al. 2013).

The familial and hereditary characteristics of this disease, beyond its chronicity and devastating progression, pose a strong psychological impact upon the lives of these patients and their relatives (Lopes 2003). Patients have preserved fertile years (women more so, due to their slightly later onset and to sexual dysfunction in men as an early symptom), marry, and have children (Sousa 1995). Onset, more often in mid 20s to mid 30s, and its progression for over a decade, even when available treatments are delivered, impose a heavy presence of the disease in these families' lives. When it appears, it may change usual family patterns with economic, social and family losses as it is described for other chronic conditions (Breier et al. 1988). Thus, it is expected that during childhood, adolescence, and as young adults, members of these families may experience important life events related to the disease and its history in the family. Early parental loss and trauma have been studied as a cause of psychopathological distress early in life and later in adulthood (McLaughlin et al. 2012; Tyrka et al. 2008b). The impact of a chronic disease in one of the parents as a cause of family dysfunction and psychological problems in children has been reported (Bogosian et al. 2010; Steck et al. 2007). Vamos et al. (2007) assessed a group of adults who grew up in a household with a parent with Huntington's disease and concluded that adverse parenting were present in both parents, the HD positive and HD negative (Vamos et al. 2007). The aim of this study is to describe and characterize personal, social, and familial life events perceived as related to TTR-FAP along patients' lifetime and to discuss the psychosocial implications these may have.

Methods

Participants

The sample consisted of 209 adults (85 men and 124 women) with the Val30Met mutation. They were regularly followed at external consultation at the Corino de Andrade Unit of Centro Hospitalar do Porto: 109 participants had an established diagnosis of TTR-FAP in different evolution stages, 81 were proven asymptomatic carriers and 19 had no established diagnosis. This group either had symptoms but no amyloid deposits on biopsy or had amyloid on biopsy but no symptoms; although for this group there were no onset of symptoms, this group was also included because they suffer a psychosocial burden as diagnosed patients and asymptomatic carriers do. This was a non-probabilistic sequential convenience sample. All subjects aged 18 to 65 years were eligible to be included in the study. Participants were recruited between 2013 and 2015, at their routine consultation and agreed to answer the study questionnaires. A single investigator approached participants about taking part in the study and presented them the instruments. The institutional review board of Centro

Hospital do Porto approved the study, and written consent was obtained from all study participants.

Instruments

The study included two questionnaires: a social and demographical form and a questionnaire about the *Family and Personal History Disease*. Our research group developed this questionnaire specifically for this study. It was based on information provided by previous unpublished studies, where we had evaluated, by content analysis, results from a semi-structured interview addressing biographical facts perceived by patients with TTR-FAP, as relevant to their lives, and that they related to family and personal history of the disease. In this questionnaire, we considered the following as relevant: (1) the disease or death of parents; (2) the subject's age at parent's death or at parent's disease onset; (3) having cared for a sick parent; (4) the relation between knowledge and contact with disease and their own diagnosis, and how this happened; (5) life impact of the disease; (6) perceived life changes imposed by the disease, as having been moved to another caregiver family or other non-related persons; (7) having changed address; and (8) perceived psychological or emotional changes. In this *Family and Personal History*, (9) questions about seeking predictive test and time until disclosure of results were other relevant issues registered. (10) Moreover, the questionnaire had also questions addressing psychiatric issues, like attending or having attended psychiatric or clinical psychology appointments, previous or current use of any psychiatric drugs, and known psychiatric diagnoses the subject may have had. The questionnaire had multiple choice and *yes* or *no* questions. In three questions, participants were invited to elaborate on particular issues using free text. For these responses, a content analysis was conducted; however, the findings are not presented in this paper.

Statistical analysis

Quantitative variables were summarized as mean and standard deviation (SD). Categorical variables were reported as percentages. Proportions between subgroups were compared with chi-squared test. All statistical analyses were done with the SPSS software package, version 23.0 (Chicago, IL).

Results

Two hundred and nine subjects (59% female) completed the study protocol; 81 were asymptomatic carriers for TTR-FAP (mean age: 33.9±9.8 years); 109 were diagnosed as patients (mean age: 38.0±8.1 years); 19 had no established diagnosis, because they did not fulfill yet the necessary clinical criteria: they had some clinical symptoms, but no amyloid in biopsies, or biopsies with amyloid deposits, but no clinical findings (mean age, 40.9 ± 4.0 years). In the total sample, 15.8% were retired and 4.8% on sick leave. Most (59.3%) finished their basic education (9th year of schooling), but only 17.2% completed high school (12 years) and 21.5% had a university degree; four participants (1.9%) were illiterate. Considering only affected patients (n = 108), most (52.8%) were still actively working, 25.9% were retired, 13.0% were unemployed, and 8.3% were on a sick leave. In the total sample, most subjects were married or lived with a partner (68.4%) and 61.5% had children (mean children, 1.34±0.8, with a maximum of 4). Almost all of subjects (96.3%) had some contact with the disease before having their diagnosis, mainly through an affected parent (36.1%) or other family members (52.9%). The sick parent was the mother in 52.2% of the subjects, and the father in 45.0%. About 71.1% of sick parents were deceased, and, among those who were alive, most (76.0%) had symptoms of the disease.

Most subjects (57%) were under 24 years of age when their parents died due to TTR-FAP: 9.9% were 10 years of age or younger; 15.5% were between age 10 and 14 years; and 31.6% were aged 15 to 24 years; the remaining were older than 25 years (43%) when their affected parent died. The majority of the subjects were under 24 years of age at their parent's onset: 30.5% were under age 10 years, and the remaining were between age 10 and 14 years old (13.2%), between 15 and 24 (27.0%), and 18.4% were older than 25 years old age (Table 1).

When asked about whether and how the parent's disease had brought changes into their lives, 37.6% of the subjects answered yes, namely in terms of change in residence and familial and psychological modifications, which were felt as adverse. No significant differences were found when this was related to the sick progenitor (in 42.5%, the mother was the sick progenitor vs. 37.3%) (p = 0.455).

Fear of the future, changes in how life was seen, giving up school to help family needs, feelings of growing up faster, living with the parent's disease and thinking about that possibility for their own future, giving up playing, and feeling not having a normal childhood were some of the expressed perceptions of changes that the disease had brought.

Most subjects (53.9%) had been their parent's caregivers; of these, 54.7% were women and 52.5% were men (p = 0.778). A person other than their parents had cared for about 7.6% during their childhood and youth; the mother or the mother and another relative had cared for 36.3%, and the father or the father and another family member had cared for 2.4%.

When asked about pre-symptomatic testing and time of result disclosure, most subjects (79.5%) received their test results after completing genetic tests. Other at-risk subjects (8.4%) were genetically tested but declined to know their available results for more than 1 year (one of them only until

Table 1 Descriptive characteristics of the study sample

	N (%)
Study sample (n = 209)	
Asymptomatic carriers	81 (38.8)
TTR-FAP patients	109 (52.2)
No established diagnosis	19 (9.1)
Gender (female)	124 (59.3)
Age (> 35 years)	102 (48.8)
Marital status	
Married or living with a partner	143 (68.4)
Single	47 (22.5)
Divorced/separated	15 (17.2)
Widowed	4 (1.9)
With children	99 (47.4)
Professional situation	
Active	14 (67.0)
Retired	33 (15.8)
Sick leave	10 (4.8)
Unemployed	26 (12.4)
Age at parents' death	
≤ 14 years old	34 (24.5)
15 to 24 years old	44 (31.7)
≥ 25 years old	61 (43.9)
Age at parents' disease onset	
≤ 14 years old	76 (36.4)
15 to 24 years old	47 (22.5)
≥ 25 years old	32 (15.3)

8 years later). Only 1.4% of all subjects had known their genetic status when they were already symptomatic. When asked, 36.7% answered that the genetic test results had an impact on their lives. Changing plans about having children or concerns about them were among the most frequently reported; psychological impact and difficulties in coping with a *carrier* result were also reported, as well as changes in sentimental relationships. Some referred to inability to have a serious relationship and three respondents had divorced after the genetic test results.

Around 26.5% of all participants reported psychological or psychiatric problems in the past and 18.2% in the year before taking part in this study. There were no sex differences (p = 0.108), but affected patients were more likely to have had such problems than asymptomatic carriers were (p = 0.017); 21.2% were taking medication, namely anti-depressive drugs and/or tranquilizers. The most frequent diagnosis established by a psychiatrist or family doctor was depression and anxiety, and three patients were diagnosed as having an obsessive-compulsive disorder.

Discussion

A great number of subjects in our sample had a lifetime charged with distressful life events related to the presence of TTR-FAP in the family. Disease and death of a parent were frequent occurrences before young adulthood. Other consequences in that period of life, and possibly connected to it, included family disruption such as moving home, and being cared only by one parent or by another member of the family; a significant number of subjects reported psychological and emotional distress. Most of these subjects knew the disease well and its consequences from their sick parents and other relatives and had substantial previous contact with the disease. Moreover, they also knew its hereditary characteristics. We believe this knowledge and perception may possibly act as a permanent threat, in a subjective way, whether in the past, present, or future. Their parent's illness had already begun at a time when most participants were still under age 14 years; thus, most of them lived with a sick parent during their childhood or adolescence. Considering the severe incapacity imposed by the disease, this implies a great burden upon these families, with these children often having an actual parental loss because of death or at least, a parent that is not available due to disability. Adverse parenthood has been reported in families with other disabling, chronic diseases, namely Huntington disease, which shares some genetic and clinical characteristics with TTR-FAP (as late onset, physical incapacitation and having no cure) (Cerel et al. 2006). Additionally, more than half of the participants in our study reported having been a caregiver for their sick parent's. In our sample, although more daughters had this task, it was not significantly different from sons. Caring for these patients is a very demanding task and it seemed a very difficult challenge to face for a child, adolescent, or young adult; this reflects the perception that offspring, even as young children, have about the importance of their role as caring for their affected parent. Reports of feelings of "growing up fast" may also relate to the needs offspring had been obliged to fulfill, including becoming caregivers for a sick parent and/or giving up school to work and help financially at home.

More than half had lost their sick parent before the age of 24 years. Bereavement in childhood because of parental death is pointed as the most important stressor a child can live, and, although some say that its psychiatric effects are not yet fully understood, others have concluded that children that suffer depression in the context of parental depression and other stressors in the family are at the greatest risk for psychopathological distress and depression (Cerel et al. 2006; Tennant 1988). Beyond the effects in childhood, adolescence has been also the object of similar studies (Zajac and Kobak 2009). The effect of early parental loss and of parental depression has been related to future psychopathology during adulthood (Benjet et al. 2010; Hovens et al. 2010; Luecken 2000;

Stikkelbroek et al. 2012). Putative biological mechanisms for this have also been suggested: neuroendocrine effects of experiencing an early loss associate to decreased salivary cortisol responses to awakening and are believed to reflect an altered hypothalamic-pituitary-adrenal axis, which could explain the increased risk for stress-related disorders later in life (Meinlschmidt and Heim 2005; Nicolson 2004; Tyrka et al. 2008a). Depression and anxiety were referred by a significant number of participants. Also, a significant number of subjects reported psychological or psychiatric problems in the past, and approximately 20% were taking psychopharmacologic medication at the time, mostly antidepressants (with SSRI and mirtazapine being the most used). We may discuss if this increased vulnerability to psychological distress and psychopathology are related to early life events, namely parental loss or parental illness, to the continuous threat posed by a carrier status, or because of living with a chronic disabling disease and its consequences. In our study, we could not determine if the disease and death of a mother was more devastating than that of a father. A greater risk to psychopathological consequences in adulthood has been assigned to an early mother's loss, compared to that of a father (Agid et al. 1999; Brown et al. 1977). In this study, a small number of subjects reported that they had been cared by the father or by the father and another family member, when the sick parent was the mother, while a much more significant number of subjects stated they had been cared by the mother or the mother and another relative, when the sick parent was the father. This may mean that it is possible that when the affected parent is the mother, children may experience more life changes and eventually be more distressed. Nevertheless, the reduced number of offspring in our sample raised solely by a father or with the help of another relative made comparisons difficult. This hypothesis should be further investigated.

Anxiety and depression related to genetic testing have been reported in subjects at risk for hereditary, late-onset neurological disease, namely in Huntington and Machado-Joseph diseases (Gonzalez et al. 2004, 2012; Tibben 2007; Timman et al. 2004; van der Meer et al. 2015). Similar results were found in TTR-FAP at-risk subjects who looked for and did genetic testing (Ledo et al. 2016; Lêdo et al. 2016; Paneque et al. 2009; Rolim et al. 2006). In the present study, emotional distress around genetic testing was also referred. For some subjects, this created a major problem, and several of them have delayed receiving their pre-symptomatic test results for more than 1 year. For a small number of subjects, disclosure of their genetic status seemed very difficult challenge to face. That way, psychological denial of their genetic risk was maintained until the beginning of symptoms. In the case of these subjects, all admitted knowing they had the disease. In Portugal, specific legislation requires that persons at-risk seeking pre-symptomatic testing for these late-onset diseases receive pre- and post-test genetic counseling and psychosocial evaluation and follow-up, according to a national protocol for late-onset genetic diseases (Sequeiros et al. 2006); however, some chose not to be tested and a number of subjects gave up the counseling protocol before disclosure of results. Avoidance and denial may act in those subjects as the only coping mechanisms. These findings corroborate the need for psychosocial support during the process of genetic testing, included in established protocols. We also think that for several reasons, some of study respondent's may have not be included in the counseling protocol and did not have enough psychosocial support which possibly explains the difficulty to disclose results.

Concerns about procreation and future disease in offspring were some of the most important consequences of getting a pre-symptomatic or an affected diagnosis. Although prenatal diagnosis and preimplantation genetic diagnosis (PGD) are available, these procedures are not without constraints, particularly psychological and emotional ones (Carvalho et al. 2001; Dreesen et al. 2014; Land and Evers 2003; Sequeiros et al. 1998). One respondent claimed she made seven unsuccessful attempts at PGD. Some responded that they had decided not to have children, but we could not know if these subjects had already made any frustrated attempt to have children, if PGD posed some constraints to them or if other reasons were present.

In conclusion, TTR-FAP patients, persons at the pre-symptomatic stage and those still at genetic risk for the disease experience several stressful life events throughout their lives, which may begin as soon as their childhood. Loss and illness of a parent and psychological and effective changes in family life are among the most important, early in life. Occurrence of later life events is also relevant, though we cannot predict how significant they may be for future psychopathological problems. The decision about up taking pre-symptomatic testing once they reach adult life and seeking reproductive options are, nevertheless, other sources of psychosocial distress.

TTR-FAP patients and their relatives are, thus, a vulnerable group to emotional stress and psychopathology during their lifetime. Psychological and psychiatric support must be available for these patients and their families, including young children. This implies a multidisciplinary team, where genetic counselors, clinical psychologists, and psychiatrists should participate and should be organized for the best possible care of these patients and families.

Systematic follow-up for pre-symptomatic carriers and patients in reference centers is highly recommended. Studies on psychopathology in children and during adulthood, including family structure and functioning, still lacking, should be undertaken to clarify its possible relation with the potential life events in TTR-FAP families.

Compliance with ethical standards The institutional review board of Centro Hospital do Porto approved the study, and written consent was obtained from all study participants.

Conflict of interest Alice Lopes has received honoraria from Pfizer for presentations at courses of TTR-related FAP for physicians.

Alexandra Sousa has no conflicts to disclosure.

Isabel Fonseca has no conflicts to disclosure.

Margarida Branco has no conflicts to disclosure.

Carla Rodrigues has no conflicts to disclosure.

Jorge Sequeiros has received honoraria from Pfizer for presentations on genetic counseling of TTR-related FAP, at international meetings (ARiA) and courses for physicians, as well as for the preparation of leaflets and webminars on genetic counseling of TTR-related FAP.

Teresa Coelho received support from Pfizer, IONIS Pharmaceuticals, and Alnylam pharmaceuticals to attend scientific meetings and integrates the speakers' bureau of Pfizer and received honoraria.

Paula Freitas has no conflicts to disclosure.

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