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Factors that influence health-related quality of life in Australian adults with Charcot-Marie-Tooth disease

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Abstract

Health-related, quality of life (HRQoL) is an important outcome in clinical trials of patients with Charcot-Marie-Tooth disease (CMT). In a cross-sectional survey of 295 Australian adults with CMT, HRQoL was measured using the Short Form-36 (SF-36) and predictors of reduced HRQoL were identified with a CMT-specific health status questionnaire. People with CMT demonstrated lower HRQoL scores than the general Australian population in all SF-36 dimensions. The disparity between people with CMT and normative data was greater for physical dimensions than for mental health dimensions. SF-36 scores were generally lower in older vs younger people, but not between men and women, or between CMT types. HRQoL in CMT was predicted strongly by lower limb weakness and to a lessor extent by leg cramps, suggesting clinical trials targeting weakness and cramps are a priority for improving HRQoL in patients with CMT.

Key words: Peripheral neuropathy; Charcot-Marie-Tooth disease; Hereditary Motor and Sensory Neuropathy; Neuromuscular disease; Quality of life; Health Status; Predictive models; Questionnaire; Disability; Muscle weakness; Muscle cramp

1. Introduction

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), is the most common type of inherited nerve disorder, with an estimated incidence of one in 2,500 individuals [1]. Affected patients demonstrate distal muscle weakness, atrophy, foot deformity and sensory loss due to a length-dependant degeneration of the peripheral nervous system [2]. The severity of symptoms associated with CMT is highly variable, even within kinships with the same type of CMT. The impact on sufferers can range from the sub-clinical to considerable disability requiring use of a wheelchair and other marked activity limitations and participation restrictions.

While the clinical features of CMT are widely recognised by neurologists, good data on the impact of the disease on health status and quality of life, also known as health-related, quality of life (HRQoL), are scarce. Barriers to the collation of broad epidemiological data about secondary manifestations include the relatively low prevalence of CMT in the general population, combined with the heterogeneity of secondary presentations. It has thus proved difficult historically, to assemble a large enough sample of people with CMT to collate comprehensive epidemiological data in face-to-face situations. Vinci *et al* (2005) reported lower HRQoL in 121 patients with CMT compared to the Italian population as a whole [3]. Scores were lower in nonworking vs working patients, women vs men, and older vs younger patients, but not between patients with demyelinating vs axonal forms or between patients who had undergone orthopaedic foot surgery vs those who had not. In a subsequent study of HRQoL in 211 Italian patients, scores were influenced by disability, gender and CMT type [4]. However these studies did not investigate other important factors that may contribute to a reduction of HRQoL in CMT such as muscle weakness and wasting, tremor, foot type, sensory deficit, bladder/bowel/sexual function, pain, leg cramps, restless legs and balance.

There is a need to understand what really influences HRQoL in CMT to help interpret natural history data and investigate alternate strategies to improve HRQoL and disability in these patients [5]. Therefore, the aims of this study were to evaluate the impact of CMT on HRQoL in a large Australian sample, identify those factors that most influence HRQoL, and to describe the place of CMT in the broader context of chronic disease.

2. Materials and Methods

Between 2001 and 2003 the CMT Association of Australia (CMTAA) worked with the authors to conduct a comprehensive health status survey of all CMTAA members. The study was approved by the Human Ethics Committee of The University of Sydney, Australia.

Survey construction

A postal survey was conducted to maximize sample size in this relatively small population with a wide geographical spread. The survey consisted of the Australian version of the Medical Outcomes Survey Short Form-36 (SF-36) [6], plus a bespoke disease survey with questions targeting symptoms in CMT (Australian CMT Health Survey, see supplementary appendix) [7]. The SF-36 consists of 36 individual questions (items) aggregated into eight dimensions which yield a scoring profile highlighting aspects of physical status (physical functioning, impact of physical health on role performance, bodily pain, general health) and mental status (vitality, social functioning, impact of emotional health on role performance, general mental health) [6]. The eight scores are each expressed on a scale of 0-100, where a higher score equates with greater well-being. The validity of the SF-36 has been established in a wide range of populations in the USA, UK, and specifically Australia [8], and the Australian Bureau of Statistics has published a set of population norms established in a survey of 18,800 people [9]. Reproducibility

(test-retest), acceptability and internal consistency of the SF-36 has also been reported as being good to excellent in people with hereditary neuromuscular disorders [10].

The Australian CMT Health Survey (see supplementary appendix) covered a range of areas of clinical interest. An initial consultation process to identify potential areas for inclusion consisted of verbal interviews with all representative health disciplines (two neurologists, two physiotherapists, one occupational therapist and three podiatrists) and an open consultation session at a CMTAA meeting. Where possible the questions were designed to elicit closed responses, and where appropriate the closed response was combined with an option for a further open response to provide more detail. All questions relating to participants' perceptions and their rating of experience were based on the well recognised five-point Likert scale, similar to the SF-36 [11]. The scales were consistently ordered with no change, or the minimal change in perception acting as the left anchor, and the maximal change acting as the right anchor. The draft survey was piloted by the CMTAA at a local meeting for internal validity. A number of minor amendments were made to produce the final survey which covered: CMT type, age at diagnosis/onset of symptoms, family history, impact of pregnancy, musculoskeletal complaints (pain, foot deformity, muscle weakness, tremor, cramps, restless legs), sensory manifestations, bladder/bowel/sexual function, balance, aids/assistive devices, therapies (conservative, alternative, surgical) and co-morbidities [7].

Survey delivery

The CMTAA database contained contact information for 375 members including 57 members who are health professionals, or non-CMT sufferers with a secondary interest. The active sample was therefore 318 members, themselves CMT sufferers, who each received by mail a copy of the SF-36 and Australian CMT Health Survey. Survey forms were fully anonymized

and follow-up to the initial mail-out was therefore aimed at the CMT community at large (newsletter, local state events and at the CMTAA Annual General Meeting), rather than direct contact.

Data processing and statistical analysis

Responses were entered into a Microsoft Access database (Microsoft Corp, Redmond, Washington) in which all closed responses were codified and entry was by mouse click on 'radio buttons' to minimize data entry errors. Open responses were recorded in text fields. All data were subjected to an error checking protocol including random sampling, dual entry and cross checking, exploration for mutually exclusive responses and cross referencing of similar questions. The error rate was four errors in the 1,296 observations examined (0.38%) and there was no evidence of systematic error or mismatch of cases in data entry. Data were exported into SPSS v15.0 (SPSS Inc, Chicago, Illinois) for statistical analysis. The SF-36 data were norm-adjusted to the Australian Bureau of Statistics data, using the recommended gender tables and the age standardization formula to enable comparison of estimates between populations which have different characteristics [9]. All SF-36 and Australian CMT Health Survey data were first evaluated descriptively, along with exploratory graphing and inferential analyses as appropriate [12].

A multiple logistic regression model was constructed to determine predictor variables associated with HRQoL (SF-36) as the outcome. Using the 50^{th} centile cut-off values, each of the eight dimensions of the SF-36 were converted to a binomial outcome variable (poor/good health) and subsequently modelled [13]. On the basis on an empiric assessment of clinical importance and relevance to overall HRQoL, a range of factors were included in an initial exploratory analysis, namely: gender, age, marital status, CMT type, leg/foot weakness, high-arched foot deformity,

hearing loss, vision impairment, shooting pains in legs/feet, pins and needles in legs/feet and leg cramps. In order to meet the assumptions for modelling, the variables chosen were those that appeared related to HRQoL, in the exploratory analyses, while demonstrating no interaction or correlative relationship to each other (collinearity) [14]. Leg/foot weakness was significantly correlated with several of the intended factors (age, high-arched foot deformity, hearing loss, vision loss, shooting pains and pins and needles). Age was also highly correlated with hearing and vision loss. Shooting pains, leg cramps and pins and needles were highly correlated. Highly co-dependent variables are inappropriate for inclusion in regression modelling and so the independent variables entered in the final multivariate logistic regression model were reduced to: gender, age, marital status, CMT type, leg/foot weakness and leg cramps. All independent variables in the model were coded to enable cross-tabulation and robust logistic regression analyses as follows: severity of weakness and cramps were dichotomised so that the most severe two levels were collapsed into a single category designated ‘more severe’ and the lower three levels collapsed into a single category designated ‘less severe’; respondents with CMT1A were separated out for comparison with responses from the rest of the sample; age was stratified into 20 year strata as recommended by the Australian Bureau of Statistics (Table 1). Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated and models were considered statistically significant if $P < 0.05$.

3. Results

Response rate

A total of 330 people with CMT were mailed survey forms, the sample comprised of 318 people on the CMTAA database and a further 12 who requested copies of forms after hearing of the survey from relatives or from the CMT press. Completed surveys were received from 324 respondents, an empirical response rate of 98.2%. This rate is artificially inflated however,

because 74 responses were received as multiple returns coordinated by CMTAA members representing a family or group (250 single returns, 25 double returns and eight triple returns). Thus the response rate adjusted for multiple respondents per CMTAA member was 85.8%.

Respondent demographics

The SF-36 has only been validated in adult populations, therefore responses from those less than 18 years of age were excluded (N=29) and analysis is based only on the responses from adults (N=295). There were no other reasons for exclusion. The mean age of this group was 49.5 (SD, 16.8; range, 18-87) years, with a gender distribution of 124 (42%) men and 171 (58%) women. Fifty-eight (20%) had never married, 196 (66%) were currently married or living in a de facto relationship, 27 (9%) were separated or divorced and currently single, and 14 (5%) reported their marital status as widowed. One-hundred and ninety nine (68%) respondents reported having had genetic testing to aid diagnosis, with genetic confirmation of CMT in 169 (57%) people. As might be expected, the self-reported classification of CMT type was incomplete. One-hundred and thirty-two of respondents (45%) were not sure of their CMT type, 96 (33%) reported CMT type 1A, six (2%) CMT type 1 - other demyelinating form, 21 (7%) CMT type 2 axonal form, 3 (1%) Dejerine-Sottas Syndrome, 27 (9%) CMT *X*-linked, and 10 (3%) 'other' forms. The mean age at onset of symptoms was 22.7 (SD, 18.0; range, birth to 70) years. The mean age at diagnosis was 34.0 (SD, 17.2; range, 2 to 74 years), and 86 (29%) reported having had a misleading initial diagnosis.

HRQoL in CMT

People with CMT demonstrated lower SF-36 scores than the general population in all SF-36 dimensions (*One-Sample T Test, P*<0.01) (Table 1). The disparity between people with CMT and the normal population is generally greater for the physical dimensions (lower in the CMT

sample by 14% to 31%) than for the mental health dimensions (lower in the CMT sample by 5% to 21%). The effect of age standardization is more apparent in the physical dimensions as the slightly older CMT group deflates the physical dimension scores (Table 1).

Gender and HRQoL in CMT

The gender profiles for SF-36 scores in people with CMT are remarkably similar for the two genders (Table 1). Men reported slightly lower scores in most dimensions but the differences were not substantial (*Independent Samples T-Test, P*>0.498).

Age and HRQoL in CMT

Age had a significant impact on SF-36 scores with substantial lowering of scores in older people with CMT (Table 1). In particular, advancing age significantly affected two of the HRQoL dimensions: physical functioning and impact of physical health on role performance *(One-way analysis of variance, P*<0.05).

CMT type and HRQoL

CMT type 1A and CMT type 2 produced comparable scores suggesting little difference in the impact of the two disease processes on HRQoL (*One-way analysis of variance, P*>0.05). There were also no significant differences between any other type of CMT on any dimension of HRQoL (*One-way analysis of variance, P*>0.05). CMT *X*-linked was generally the most benign of the clearly defined CMT types, and further analysis between males (N=14) and females (N=13) revealed no significant differences for any dimension of HRQoL (*Independent Samples T-Test, P*>0.1). There are obvious limitations associated with data derived entirely from self-reported disease status, with genetic defects unable to be checked. Therefore, a comparative analysis was undertaken for a subset of respondents with a diagnosis of CMT type 1A confirmed

by either a personal diagnosis following a positive test for Chromosome 17p11-p12 duplication or a clinical diagnosis of demyelinating peripheral neuropathy plus a positive test for Chromosome 17p11-p12 duplication in a first degree relative. The data for the confirmed cases of CMT type 1A (N=79) did not differ from other cases of CMT type 1A (N=13) (*Independent Samples T-Test, P*>0.05) and differed only from the general CMT sample for the bodily pain dimension, for which respondents with confirmed CMT type 1A reported worse bodily pain (*One-way analysis of variance, F*=4.501, *P*=0.035).

Comparison of HRQoL in CMT with a range of chronic conditions

SF-36 scores for the CMT sample were compared with scores from population-based studies describing HRQoL in a range of common chronic diseases (Figure 1). Overall, the CMT scores lie in the mid-range of scores for the conditions being compared.

Australian CMT Health Survey

Data from the range of responses are reported in detail elsewhere [7], but of importance to subsequent modelling is that more than 80% of respondents reported moderate or worse weakness in their legs/feet and only 7% reported no leg/foot weakness. More than half of respondents (51%) considered the weakness in their legs/feet to affect them ‘quite a lot’ or ‘severely’. Leg camps were reported to occur in more than three-quarters (79%) of the sample and for 20% of CMT sufferers the cramps occur “very often” or “constantly”.

Predictors of HRQOL

Logistic regression models predicting HRQoL in CMT are presented in Table 2. Leg/foot weakness and cramps were both related to SF-36 scores in a number of physical dimensions. Leg/foot weakness was a highly significant predictor of impaired physical functioning, with a six-fold enhanced risk for those reporting weakness (*OR*=6.68, *P* =0.001). Leg/foot weakness

was significant in all of the physical dimensions except bodily pain where leg cramps were highly significant. The risk of those with more frequent leg cramps reporting bodily pain scores below the 50th centile (more pain) was increased nearly four-fold (*OR*=3.65, *P* =0.001). Age was a significant factor in two of the physical dimensions: physical functioning (*OR*=1.82, *P* <0.001); impact of physical health on role performance (*OR*=1.38, *P* =0.013), with advancing age increasing the risk of reporting physical impairment. Gender, marital status and CMT type did not appear to affect significantly the scores in the physical dimensions of the SF-36 (*P*>0.05).

Leg/foot weakness and cramps were linked to SF-36 scores in a number of mental dimensions (Table 2). More severe leg/foot weakness was associated with a substantial lowering in the mental health dimension (depression/anxiety) (*OR*=2.23, *P*=0.001). The presence of more frequent cramps was associated with an approximately two-fold increased risk of scores below the 50th centile (i.e. scores indicating poorer mental health) in vitality (*OR*=2.00, *P*=0.005), social function (*OR*=1.76, *P*=0.023) and emotional role (*OR*=1.86, *P*=0.013). Age was not significant in any of the SF-36 mental dimension models although it was close to significance in all four. Marital status was significant in the emotional role and social function dimensions and the responses were associated with opposite spectra of risk. In the emotional dimension respondents without partners reported approximately half the risk of significant impairment than those with partners, while singles were at twice the risk of severe impairment to social function.

4. Discussion

The intention of this study was to improve our understanding of what, to-date, has been an incomplete clinical picture, to evaluate the impact of CMT on HRQoL and identify those clinical features that most influence HRQoL. The survey used an industry standard measure (SF-36), as well as a CMT-specific component, providing comprehensive data describing the position of

CMT in the spectrum of other chronic diseases. The response rate of 85.8% was good for a survey of this kind. Male respondents were marginally under-represented although the spread of ages and CMT types was acceptable. Patient self-reporting of CMT type is problematic, even in this relatively well-informed community, and although some 45% were honest enough to report being unsure of the precise type of CMT, others will have erroneously reported their disease type. Data relating specifically to CMT type must be viewed therefore as a broad indicator only.

People with CMT scored lower than the general population on all dimensions of the SF-36 indicating significantly poorer HRQoL and confirming the data from the 'Sickness Impact Profile' scoring in 50 German patients with CMT type 1A [15]. The trend was particularly marked for the physical dimensions of the SF-36. The SF-36 scores for the CMT community showed much greater differentiation with age than is seen in the general population [9], indicating some cumulative effect of the disease on HRQoL over the lifespan. This finding was consistent with a HRQoL report of 121 Italian CMT patients [3]. Our gender profiles for SF-36 scores in people with CMT were remarkably similar for the two genders. Men reported slightly lower scores in most dimensions compared to women, but the differences were not substantial. This does contrast with lower female scores in the Italian population of CMT sufferers for reasons possibly relating to different cultural conditions at work and home between countries [3, 4]. These results suggest culturally-validated HRQoL measures and norms should be considered for clinical trials of patients with CMT.

The type of CMT did not appear to be highly influential on reported HRQoL, with the exception of the small group of people with Dejerine-Sottas Syndrome. Dejerine-Sottas Syndrome is the most severe form of CMT, with some debate about the exact underlying genetic mutation (Online Mendelian Inheritance in Man #145900), and not surprisingly resulted in substantial

reduction in the physical dimensions of the SF-36. While previous studies have also found little difference between CMT types and HRQoL [3, 4], this should be explored further in an Australian sample in which the CMT type is confirmed by neurological assessment before such an assertion can be made with any confidence.

Examination of the SF-36 scores for CMT and a range of other chronic conditions reveal useful information about the impact of the disease on sufferers. CMT does not impact substantially on lifespan and its impact is often trivialised as consequence [16]. However, people with CMT report lower (worse) physical function scores than people with epilepsy (N= 336) [17], diabetes mellitus (N=11,247) [18], angina pectoris (N=732) [17] and stroke patients at six months post cerebrovascular accident (N=434) [19]. Similarly, more bodily pain was reported by people with CMT compared to people with diabetes mellitus and stroke. Vitality and mental health scores in CMT were comparable between conditions, although all were lower than the population norms. Clearly, as a long term degenerative condition, CMT does not have as severe an impact on HRQoL as the pain associated with advanced osteoarthritis of the knee (N=1,848) [20], or the significant impact of physical health on role performance as angina pectoris [17], but it is comparable to other chronic conditions such as diabetes mellitus and cerebrovascular disease. These data suggest that in the absence of quantification, the impact of CMT on the HRQoL of sufferers has been underestimated previously.

The patient's own estimate of the severity of disability has been suggested previously to be a good marker of disease severity [2] and was thus of great interest in this study. Self-reported muscle weakness was profound in the lower limbs with only 7% of our CMT sample reporting no leg/foot weakness, a figure in accordance with both manual and dynamometric muscle testing in the literature [2, 21]. Our survey also confirmed a high prevalence of leg muscle cramps in

people with CMT. Painful leg cramps are a clinical symptom widely reported in the CMT literature [15, 22] and we found 20% of CMT sufferers report cramping “very often” or “constantly”. While the mechanism underpinning muscle cramps is unknown, in this sample, the relationship between weakness and prevalence of cramps is again of note. Cramping may result directly from the primary neurogenic factors also causing the progressive weakness, or the cramps may be secondary features, perhaps reflecting underlying histological or functional changes in the muscle. This warrants further research as the presence and severity of leg cramps proved a significant factor in the models predicting HRQoL. There is a suggestion that addressing cramping in the CMT population may improve the health status of these patients.

The overall predictors of HRQoL in people with CMT were interesting. Of the physical health dimensions, leg/foot weakness was the single most influential factor in the analysis, appearing as a significant factor in three of the four SF-36 physical dimensions. Age was also implicated in reducing the reported physical HRQoL, as it is in the general population [9], although age standardized figures point to a significant disease specific effect. The bodily pain dimension appeared to be affected more by the presence of cramps than features secondary to other physical factors such as foot deformity. In the mental health dimensions, the merit of leg/foot weakness as a marker for overall disease severity is again substantiated. Leg/foot weakness and cramps were both, perhaps surprisingly, significant factors in the predictive model for three of the four mental health dimensions. This indicates that CMT-related weakness may be mentally debilitating as well as producing the more obvious physical effects.

A postal survey of this type has some limitations. First, there is always a trade-off between postal surveys (incorporating self-reported measures of health and disability) and direct interview (either by telephone or in person). However to maximise the response rate (thus increasing

power for the study) and reduce data collection costs, postal surveys are significantly more effective [23]. Second, self-reported data on CMT type, symptoms (foot deformity, muscle weakness) and sensory manifestations are liable to errors and misinterpretation. However, self-reporting of age at diagnosis/onset of symptoms, family history, impact of pregnancy, musculoskeletal complaints (pain, tremor, cramps, restless legs), bladder/bowel/sexual function and balance are invaluable as they provide more meaningful patient-orientated markers of disease severity. Third, people belonging to the CMTAA might not be representative of the entire CMT population of Australia and therefore the sample may be biased with more severe cases that require the support of the CMTAA. However, to ensure collection of a large enough sample of people with CMT from across Australia in order to conduct robust statistical analysis, we recruited from the largest organisation supporting CMT in Australia.

The addition of HRQoL outcome measures in clinical trials of therapies for patients with CMT are considered essential to obtain trial participants' views as to the effectiveness of a treatment [5]. This is especially important in trials where the primary endpoint may be one that lacks obvious relevance to patients' day-to-day experiences such as nerve conduction studies, muscle weakness scores or sensory deficit.

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Figure Legend

Figure 1 Health-related quality of life in people with CMT compared to Australian norms and a range of common chronic diseases.

Table Legend

Table 1 SF-36 scores for adults with CMT and comparative Australian norms, and sub-grouped for gender and age.

Table 2 Logistic regression modelling for predictors of SF-36 dimensions in CMT.

Supplementary Data

Appendix 1: Australian CMT Health Survey