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Quality-of-Life in Charcot Marie Tooth Disease: The Patient's Perspective

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Abstract

This study determines the impact of symptoms associated with Charcot-Marie-Tooth disease on quality-of-life. Charcot-Marie-Tooth patients in the Inherited Neuropathies Consortium Rare Diseases Clinical Research Network Contact Registry were surveyed. The survey inquired about 214 symptoms and 20 themes previously identified as important to Charcot-Marie-Tooth patients through patient interviews. Symptom population impact was calculated as the prevalence multiplied by the relative importance of each symptom identified. Prevalence and symptom impact were analyzed by age, symptom duration, gender, Charcot-Marie-Tooth type, and employment status. 407 respondents identified foot and ankle weakness (99.7%) and impaired balance (98.6%)

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as the most prevalent themes. Foot and ankle weakness and limitations with mobility were the themes with the highest impact. Both symptom prevalence and impact gradually increased with age and symptom duration. Several themes were more prevalent in women with Charcot-Marie-Tooth, including activity limitations, pain, fatigue, hip-thigh weakness, and gastrointestinal issues. All of the themes, except emotional or body image issues, were more prevalent among unemployed individuals. There were minimal differences in symptom prevalence between Charcot-Marie-Tooth types. There are multiple symptoms that impact Charcot-Marie-Tooth quality-of-life in adults. These symptoms have different levels of importance, are readily recognized by patients, and represent critical areas of Charcot-Marie-Tooth health.

Keywords

Charcot Marie Tooth disease; quality of life; patient reported outcomes; peripheral neuropathy

1. Introduction

Charcot Marie Tooth Neuropathy (CMT) is the most common form of inherited neuropathy [1]. The classification of CMT is based on clinical and electrodiagnostic features, the inheritance pattern, and genetic cause [1]. Most types of CMT share similar symptoms, including progressive distal weakness, atrophy, numbness, and associated functional limitations. These functional limitations may affect quality-of-life (QOL) and should be considered in upcoming clinical trials of therapeutic agents.

Prior studies have investigated aspects of QOL in several forms of CMT. One study compared a generic QOL measure, the Short Form-36 (SF-36), with patients' self report of disability in 295 adults with CMT. In these patients, lower limb weakness and leg cramps correlated with QOL on the SF-36 [2]. Another study of Italian patients compared clinical and electrophysiological measures with the SF-36 in a series of 89 patients with CMT1A. In this population, the ability to ambulate independently and toe-heel walk correlated with QOL on the SF-36 [3]. In children with CMT1A, the most common form of CMT, muscle cramps, tremor, and distal weakness were all shown to adversely impact QOL [5]. Fatigue and restless leg syndrome also play a key role in CMT QOL, using generic QOL measures [6]. More recently, qualitative interviews with patients identified difficulty with mobility and ambulation and activity impairment as the life altering themes that are most frequently mentioned by CMT patients [7].

In order to further define CMT QOL, we used a large international contact registry of patients with CMT to determine the prevalence and impact of symptoms that affect QOL in adult CMT.

2. Methods

2.1 Study participants

This study utilized the web-based Inherited Neuropathies Consortium Rare Diseases Clinical Research Network (RDCRN (1U54NS0657)) Contact Registry. This is a patient-based

registry that allows patients with all forms of CMT to self-register. All registry participants over the age of 18 were asked to participate.

2.2 Survey construction

The survey instrument was constructed based on qualitative interviews with 16 CMT1A participants. As previously reported, these patient interviews reached saturation, demonstrating appropriate coverage of relevant symptoms [7]. The survey was constructed to be inclusive of all potential areas of importance to the CMT population identified through the above qualitative interviews as well as other neuromuscular populations [15]. The survey consisted of 20 themes representing 214 symptoms. Participants were asked to rate each symptom using a 6-point Likert scale. Likert options included: 1) I don't experience this; 2) I experience this but it does not affect my life; 3) It affects my life a little; 4) It affects my life moderately; 5) It affects my life very much; 6) It affects my life severely.

Registry members were sent an initial invitation to complete the survey and, if they did not respond, were sent an additional two reminders over a period of three months.

2.3 Statistical analysis

The prevalence of each theme and symptom was calculated. Likert responses were scored: 0= I don't experience this or I experience this but it does not affect my life; 1= It affects my life a little; 2=It affects my life moderately; 3=It affects my life very much; 4=It affects my life severely. The mean impact score was calculated by averaging all participant Likert responses. The population impact score (0-4) was calculated by multiplying the prevalence by the mean Likert response of those participants endorsing symptoms, as previously reported [15].

Responses were categorized by age, gender, symptom duration, and level of education. Fisher exact tests were employed to compare the prevalence of each theme across different subgroups. Kruskal-Wallis tests were used to compare the distributions of mean Likert scores across different subgroups. A two-tailed p value < 0.05 was considered significant for these exploratory analyses.

3. Results

Of the 800 registry members surveyed, 407 members (50.9%) responded. Details of the participant demographic information are provided in Table 1. The prevalence and impact of each theme is provided in Supplemental Table 1.

3.1 Prevalence of Themes and Symptoms

The most prevalent themes were: foot and ankle weakness (99.7%), impaired balance (98.6%), limitations with mobility (97.5%), and hand and finger weakness (97.0%). Each theme's prevalence by age, symptom duration, CMT type, and gender is provided in Supplemental Table 2. The prevalence of shoulders or arm problems increased until age 60 and then declined in prevalence ($p=0.0018$) (Figure 1). Emotional issues were less prevalent with advancing age ($p=0.035$) (Figure 1). Similarly, problems with shoulders or arms

($p=0.012$), activity limitations ($p<0.0001$), mobility limitations ($p<0.0001$), and proximal leg weakness ($p=0.0082$), among others, all increased in prevalence with symptom duration (Figure 2). Proximal leg weakness ($p=0.04$), activity limitations ($p=0.035$), fatigue ($p=0.044$), pain ($p=0.009$), numbness ($p=0.017$), and gastrointestinal issues ($p=0.002$) were all more prevalent in women than in men (Figure 3). Difficulties with reproduction were reported more frequently by men ($p=0.0013$).

Differences were also present based on employment (Figure 4, supplemental table 2). Fourteen of the 20 identified themes were more prevalent in the unemployed category ($p<0.05$) (Figure 4). Many of the differences in prevalence based on employment status were larger than those associated with age or gender (supplemental table 2). Mobility limitations were more prevalent in CMT1A and non-categorized CMT types compared to CMT 1B, 2A, 4, and X ($p=0.021$) (Supplemental table 2).

Among individual symptoms, 10 symptoms had a prevalence of greater than 95%: balance problems (98.0%), difficulty with rough ground (96.9%), foot weakness (96.4%), loss of foot muscle (96.2%), need for railing on stairs (96.1%), difficulty running (96.1%), tripping (96.1%), need to be cautious when walking (96.1%), difficulty with slippery surfaces (95.8%), and awareness of disease progression (95.0%).

3.2 Impact of Themes and Symptoms

Themes with the highest individual impact scores were: foot and ankle weakness (2.93; SD 1.06), impaired balance (2.79; SD 1.15), and limitations with mobility (2.69; SD 1.14). Each theme's mean Likert response by age, symptom duration, CMT type, gender, and employment is provided in Supplemental Table 2. Hand and finger weakness ($p=0.049$), difficulty thinking ($p=0.038$), decreased social satisfaction ($p=0.016$), fatigue ($p=0.011$), and pain ($p=0.004$) were all more impactful with increasing age (Figure 1). Problems with shoulders or arms, hand and finger weakness, foot and ankle weakness, mobility limitations, and balance problems ($p<0.05$) were also more impactful with increasing symptom duration (Figure 2). Both proximal leg weakness and pain ($p<0.05$) were more impactful in women (Figure 3). Only proximal leg weakness varied in impact between CMT groups, being more common in respondents with CMT2A ($p=0.038$). Similar to the prevalence data, 14 of the 20 themes were more impactful in the unemployed group ($p<0.05$) (Figure 4). In both the prevalence and impact data, employment status generated significant differences in QOL themes more frequently than age, symptom duration, CMT type, or gender.

Among individual symptoms, responses that had an average impact greater than 3 (on a 0-4 scale) included: difficulty running (3.20; SD 1.18), inability to run (3.17; SD 1.20), trouble getting around when slippery (3.06; SD 1.17), difficulty walking distances (3.04; SD 1.21), and difficulty with rough ground (3.01; SD 1.18).

3.3 Population Impact

Among the 20 themes, Foot and ankle weakness (2.92) and impaired balance (2.75) had the highest population impact scores within the population. Among the 214 symptoms, difficulty running had the highest population impact score (3.07). The population impact score for the majority of themes increased with age and symptom duration (Figure 1 and 2).

4. Discussion

This study demonstrates that several themes related to CMT significantly affect patients' quality-of-life. Not surprisingly, many of the issues identified as most impactful include those related to mobility, balance and distal motor and sensory limitations (e.g. foot and ankle weakness, and hand-finger weakness). However, themes related to fatigue, pain, and body image also factored into how patients' perceive their disease related QOL. This diverse set of themes underscores the importance of a multidisciplinary approach and offers opportunities for a range of therapeutic interventions to improve quality-of-life and function in adult CMT, and provides several targets for experimental therapeutics. Given the important patients' place on mobility issues in particular, future therapeutic trials should consider this emphasis.

This patient-directed approach to identifying symptomatic impact of CMT is largely distinct from previous research. Prior efforts have utilized pre-existing instruments or categories to describe the impact of CMT on patient QOL. By allowing patients to qualitatively identify symptoms in this study, which are then validated in a large cross-sectional population, we have been able to specifically prioritize concerns as patients identify them. This approach also fulfills a portion of regulatory agencies' directives requesting direct patient input prior to the development of adult disease-specific patient reported outcome measures [8, 13].

Analysis of symptom duration discloses that many of the symptoms have the greatest increase in prevalence and impact in the first decade of symptoms followed by a less rapid escalation over 40 years of symptom duration. There is a more predictable progression of disease based on duration of symptoms than there is by age. Therefore, symptom onset may be more meaningful when designing therapeutic trials than age alone. Specifically, future therapeutic trials may consider early intervention as optimal given the apparent rapidity of progression in the first decade after first symptom occurrence. The severity of symptoms decreased after 50 years of symptom duration in this study. This may be related to survivor bias or improved coping strategies with increased age [15]. As expected, employment status discriminated between symptom impact as well, with those individuals who were not employed experiencing more severe symptoms. This may be related to the age of participants (e.g., reaching retirement age) or to functional disability that prevents employment. The mean age of the unemployed was 56 (SD 15.4) and the employed was 46.2 (SD 12.1). This modest difference would suggest that functional disability may be the predominant factor accounting for the differences between the two groups. It is also possible that affective symptoms might contribute to higher rates of unemployment, however affect related themes did not differ according to employment status in this survey.

Examination of symptoms by CMT type did not disclose substantial variation in the impact of symptoms. Therefore, while several symptoms, including impaired balance and mobility limitations were more prevalent in certain subtypes, there was not a significant difference in the overall impact. The one apparent exception was proximal leg weakness, the impact of which was more significant in CMT2A than other forms of CMT. Less common forms of CMT (e.g., CMT1B and CMT4) have small sample sizes and therefore comparisons between CMT types are limited. There were few significant differences by gender.

There are some potential limitations of this study. First, this study utilizes a patient-based registry. However, the contact registry is affiliated with the Inherited Neuropathies Consortium of the Rare Diseases Clinical Research Network (INC RDCRN). In this network, patients with different inherited neuropathies are evaluated in detail across 12 sites in the USA and sites in the UK, Australia, and Italy. The distribution of CMT genetic subtypes in the patient contact registry, largely mirrors that of enrollees in the INC RDCRN studies (53.45% vs 39% for CMT1A, 3.8% vs 3.5% for CMT1B, 9.7% vs 3.6%, for CMT2A, and 4.9% vs 5.6% CMTX, respectively). Second, as this was an anonymous survey, there was not validation of participant responses. Finally, as is the case in all survey research, it is possible that the respondents did not ideally represent the larger study population. This potential ascertainment bias may have influenced the results by selecting for participants who were more symptomatic.

This study is the largest cross sectional study to date examining the impact of CMT on patient QOL. Issues related to ambulation and distal motor function were the most impactful, though under-recognized symptoms such as pain, fatigue, and body image issues also impacted quality-of-life. The study emphasizes the patient viewpoint, as recommended by regulatory agencies and provides a patient-centered perspective into the symptomatic challenges of this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

The Impact of CMT by Age. A. Prevalence of physical health themes by age; B. Prevalence of social and cognitive health by age; C. Mean Likert response of physical health by age; D. Mean Likert response of social and cognitive health by age; E. Physical health impact score by age; F. Social and cognitive health impact score by age. (*) indicates a p-value <0.05.

Figure 2.

The Impact of CMT by Symptom Duration. A. Prevalence of physical health themes by symptom duration; B. Prevalence of social and cognitive health by symptom duration; C. Mean Likert response of physical health by symptom duration; D. Mean Likert response of social and cognitive health by symptom duration; E. Physical health impact score by symptom duration; F. Social and cognitive health impact score by symptom duration. (*) indicates a p-value <0.05.

Figure 3.

The Impact of CMT by Gender. A. Prevalence of themes by gender; B. Mean Likert response by gender. (*) indicates a p-value <0.05.

Figure 4. The Impact of CMT by Employment Status. A. Prevalence of themes by employment status; B. Mean Likert response by employment status. (*) indicates a p-value < 0.05.

Table 1

Demographic and Clinical Characteristics of Survey Respondents (n=407)

Age (years)	52.3 (SD 15.1)
Duration of CMT symptoms (years)	30.7 (SD 17.7)
Female (%)	63.9
Employed (%)	39.1
Highest Level of Education (%)	
None	0.7
Grade School	1.2
High School	22.4
Technical Degree	9.6
College	41.0
Master's or Doctorate	25.1
Type of CMT (%)	
CMT1A	36.1
CMT1B	3.4
CMT2A	7.1
CMT4	1.5
CMTX	3.2
Unknown	48.7