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Patient-Reported Symptom Burden of Charcot–Marie–Tooth Disease Type 1A: Findings From an Observational Digital Lifestyle Study

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Abstract

Objectives:
This study aims to explore the impact of Charcot–Marie–Tooth disease type 1A (CMT1A) and its treatment on patients in European (France, Germany, Italy, Spain, and the United Kingdom) and US real-world practice.

Methods:
Adults with CMT1A (n = 937) were recruited to an ongoing observational study exploring the impact of CMT. Data were collected via CMT&Me, an app through which participants completed patient-reported outcome measures.

Results:
Symptoms ranked with highest importance were weakness in the extremities, difficulty in walking, and fatigue. Almost half of participants experienced a worsening of symptom severity since diagnosis. Anxiety and depression were each reported by over one-third of participants. Use of rehabilitative interventions, medications, and orthotics/walking aids was high.

Conclusions:
Patient-reported burden of CMT1A is high, influenced by difficulties in using limbs, fatigue, pain, and impaired quality of life. Burden severity appears to differ across the population, possibly driven by differences in rehabilitative and prescription-based interventions, and country-specific health care variability.

Key Words: burden of illness, Charcot–Marie–Tooth disease, international, observational, patient-reported outcomes

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INTRODUCTION

Charcot–Marie–Tooth disease type 1A (CMT1A) is a rare disease belonging to the group of inherited, chronic, progressive motor and sensory neuropathies referred to as Charcot–Marie–Tooth disease (CMT). CMT1A has an estimated prevalence of 1 in 5000 people.[1,2] It predominantly causes distal muscle weakness, atrophy, sensory loss, and progressive limb deformities.[3]

CMT compromises patient lifestyles, everyday activities, and career and family choices.[4] There is currently no pharmacologic treatment for CMT1A or CMT.[2] Treatment focuses on physical therapy to maintain movement, muscle strength, and flexibility, combined with occupational therapy, orthotics, pain management, and psychological and social support.[5] Surgical intervention may be required for more severe forms of the disease.

There is a lack of data about the patient experience of CMT1A to help make informed decisions to improve disease management and outcomes. The role of patient-reported outcome (PRO) data is becoming increasingly recognized as strengthening disease understanding and in the development, regulatory approval, reimbursement, and use of

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The authors report no conflicts of interest.

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treatments.[6–8] To date, much PRO evidence has been generated in randomized controlled trials (RCTs), with little data collected from patients managed in real-world clinical practice. Real-world evidence (RWE)—which can be gathered as part of decentralized/remote data capture (ie, away from hospitals and doctors' offices)—can provide more granular, longer-term data, from a broader patient population, than is typical in RCTs, so there is clear value in its collection and analysis.

The objective of this study is to provide a detailed view of the impact of CMT1A and its treatment on patients in the real-world setting (including factors such as epidemiology, natural history, and clinical and humanistic burden) and to define the economic impact of the disease on health care facilities and systems.

MATERIALS AND METHODS

Study Design

This is a prospective, longitudinal, observational, patient-reported lifestyle study. Adults with a self-reported diagnosis of CMT (CMT1A or other subtype) residing in one of the study countries (ie, France, Germany, Italy, Spain, the United Kingdom, or the United States) use a smartphone app, CMT&Me (Vitaccess, Oxford, United Kingdom), to both enroll and provide informed consent to participate in the study and enter regular data about CMT, its management, and its impact on their lives. Data collected between October 15, 2018, and June 1, 2021, from CMT1A patients—the most frequently reported CMT type[1,2]—are presented in this interim analysis.

Data Collection

Shortly after enrollment, participants are asked to complete a profile, which includes data on demographics, lifestyle characteristics, and diagnosis—many of which are expected to remain fairly stable over the duration of the study. For those data that may change over the duration of the study (eg, treatments, health care visits), participants are able—and encouraged—to make additions or updates.

Participants are also asked to complete a number of PRO instruments. Summary descriptions of the PRO instruments included in this study are provided below.

EQ-5D-5L

The EQ-5D-5L comprises 2 parts: the EQ-5D-5L descriptive system and the EQ visual analog scale.[9] The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems—ie, higher scores represent worse health). The scores for the 5 dimensions are combined in a 5-digit number describing the participant's health state.

The EQ visual analog scale records the participant's self-rated health on a vertical scale, with end points labelled "the best health you can imagine" and "the worst health you can imagine." Higher scores represent better self-perceived health.

Bespoke Instruments for this Study

Cramp is a common symptom among CMT1A patients.[10] Two cramp-specific items measuring frequency and intensity were developed for inclusion in the study. The cramp frequency item asks, "In the past 7 days, how many days did you experience any cramp?" and has 5 possible response options: had no cramp, 1–2 days, 3–4 days, 5–6 days, and every day. The cramp intensity item asks, "In the past 7 days, how intense was your cramp at its worst?" and has 5 possible response options: had no cramp, mild, moderate, severe, and very severe. Higher scores on both items represent greater cramp frequency and intensity, respectively.

QuickDASH

The Quick Disabilities of Arm, Shoulder and Hand (QuickDASH) measure uses 11 items to gauge physical function (eg, opening a tight or new jar) and symptoms

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(eg, hand, shoulder, or arm pain) in people with any or multiple musculoskeletal disorders of the upper limbs.[11] All questions are rated 1–5 (no difficulty/none/not at all to unable/extreme difficulty). Possible scores range from 11 to 55, where higher scores represent greater difficulties with physical function and symptoms.

BFI

The Brief Fatigue Inventory (BFI) assesses participants' fatigue severity.[12] The measure uses a 10-point numeric rating scale and a recall period of 24 hours. A global fatigue score is calculated by averaging all 9 items.

PROMIS Pain Intensity 3a and Interference 6b

The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a instrument includes 2 items that assess pain intensity over the past 7 days (average and worst pain) and one item that assesses pain intensity "right now," each score using a 5-point scale.[13] Possible scores range from 2 to 10, where higher scores represent worse pain. This measure is generic rather than disease specific.

The PROMIS Pain Interference 6b instrument assesses the extent to which pain hinders engagement with social, cognitive, physical, and recreational activities as well as enjoyment in life over the past 7 days using a 5-point scale.[14] Possible scores range from 6 to 30, where higher scores represent greater interference. This measure is generic rather than disease specific.

Statistical Analysis

Data analysis followed a predefined statistical analysis plan. All analyses were descriptive, and no hypotheses were tested. Aggregated, deidentified data were summarized as follows:

- For continuous variables, distributions: number, mean, SD, median, minimum, maximum, SE, first and third quartiles; and
- For categorical variables, summaries: n, frequency, proportion.

Descriptive distribution statistics for each PRO instrument score, or domain score, are presented for baseline (first data entry time point) and at each time point thereafter up until June 1, 2021.

Missing data were handled as set out in the scoring guidelines for the PRO instruments and according to best practice for profile questions. All missing data were assumed to be missing at random, and no adjustments were made to account for missing data.

RESULTS

Nine hundred and thirty-seven CMT1A participants responded to at least one item in any survey and were included in this interim analysis.

Demographic and Clinical Characteristics

Demographic and clinical characteristics of participants are provided in Table 1. The mean age of participants (n = 782) was 45 (SD 13.8) years, and the majority of participants (n = 781) were female (n = 553, 70.8%). The age and sex of participants were comparable across countries, although the percentage of female participants in Italy and Spain was closer to 60%. The majority of participants reported moderate or severe symptom severity at the time of survey completion. Just more than 40% of participants reported that they exercise (defined as at least 20 minutes, raising pulse and breathing rate) once per month or less. More than half of participants resided in either the United States or the United Kingdom.

Symptoms

The mean age at which study participants hit certain milestones is reported in Figure 1. Mean age at reported symptom onset was just more than 17 years, with the mean age at diagnosis almost 10 years later.

Symptom characteristics of participants are provided in Table 2. Participants reported that they had spent almost 30 years experiencing CMT1A symptoms and had been

TABLE 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	n (%)
Age, y (n = 937)	
Mean (SD)	44.8 (13.8)
Median (range)	45.0 (18–83)
Sex (n = 781)	
Female	553 (70.8)
Male	228 (29.2)
Symptom severity at the time of survey completion (n = 684)	
Mild	108 (15.8)
Moderate	400 (58.5)
Severe	167 (24.4)
None	9 (1.3)
Exercise frequency (n = 612)	
Daily	80 (13.1)
4–6 times per week	72 (11.8)
3 times per week	111 (18.1)
Once a week	95 (15.5)
Once a month	25 (4.1)
Seldom	112 (18.3)
Do not exercise	21 (3.4)
Cannot exercise	19 (3.1)
Cannot exercise because of disability	77 (12.6)
Country of residence (n = 937)	
United States	289 (30.8)
UK	241 (25.7)
Italy	133 (14.2)
France	119 (12.7)
Germany	89 (9.5)
Spain	66 (7.0)

receiving medical care for CMT1A for more than 20 years. Participants reported first seeking medical care approximately 8 years after symptom onset, whereas the time difference between symptom onset and diagnosis was a mean of approximately 11 years.

Almost half of participants reported that their symptom severity had worsened between diagnosis and the time of the survey response. The CMT1A symptoms ranked with highest importance by participants (Fig. 2) were weakness in hands and fingers (most important), difficulty walking, weakness in the feet, fatigue, weakness in the legs, and problems with balance (sixth most important). Pain was reported as the eighth most important symptom, and it is reflected in the fact that more than 70% (Table 3) of participants reported currently taking analgesics/painkillers. Results were similar across countries.

Comorbidities

The proportion of participants reporting comorbidities is presented in Figure 3. The most frequently reported comorbidities, in addition to CMT1A, were anxiety (most frequently reported), depression, gastrointestinal problems, respiratory problems, and thyroid problems.

Of those who reported depression, approximately 47% and 30% reported moderate or severe CMT1A symptom severity, respectively. Reported diagnosis of depression varied considerably by country. Highest rates were among participants in the United States and the United Kingdom, whereas

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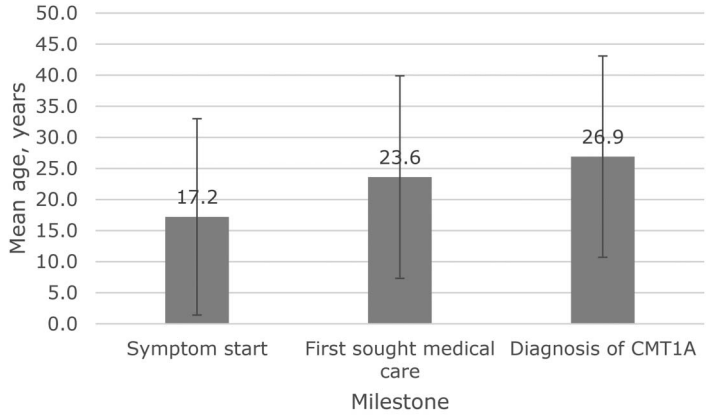

CMT1A = Charcot-Marie-Tooth disease type 1A.

FIGURE 1. Mean age at which study participants (n = 937) reported certain milestones.

lowest rates were among participants in France and Italy.

PRO Instrument Scores

EQ-5D-5L mobility domain scores are presented in Figure 4. Almost 60% of study participants reported at least moderate problems with mobility. This varied across countries, with the highest figures in France and lowest in the United States.

Of participants who reported the frequency by which they experienced cramp, just less than 75% experienced it on at least 1 day per week. This varied across countries —highest in the United Kingdom and lowest in Italy. More than half of participants rated the severity of the cramping they experienced as either moderate or severe.

QuickDASH scores are presented in Figure 5A, with the median score indicating some level of upper extremity disability and symptoms affecting the quality of life. BFI scores for worst level of fatigue during the past 24 hours are presented in Figure 5B, with the median score indicating high fatigue impact and severity.

PROMIS Pain Intensity 3a scores and PROMIS Pain Interference 6b scores are presented in Figure 5C and Figure 5D, respectively. The PROMIS Pain Intensity 3a median score is indicative of mild pain intensity, whereas the PROMIS Pain Interference

TABLE 2. Symptom Characteristics of Study Participants

Characteristic	n
Time spent with symptoms, y (n = 932)	
Mean (SD)	27.9 (16.0)
Median (range)	27.0 (0–79)
Time spent receiving medical care for CMT1A, y (n = 933)	
Mean (SD)	21.3 (14.9)
Median (range)	20.0 (0–79)
Time between symptom onset and first seeking medical care for CMT1A, y (n = 896)	
Mean (SD)	7.8 (11.0)
Median (range)	3.0 (0–71)
Time between symptom onset and CMT1A diagnosis, y (n = 882)	
Mean (SD)	11.3 (12.8)
Median (range)	6.0 (0–78)

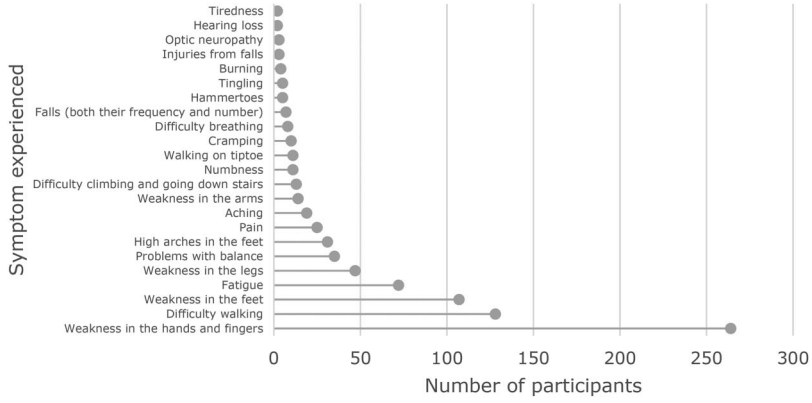

FIGURE 2. CMT1A symptom ranked as most important by participants (n = 826).

6b median score is indicative of moderate pain interference.

Treatments

Current treatment characteristics of participants are provided in Table 3. The rehabilitative interventions most frequently reported by participants were physical therapy, occupational therapy, and massage therapy. The medicines most frequently reported by participants were painkillers, antidepressants, and opioids/analgesics. The orthotics/walking aids most frequently reported by participants were off-the-shelf insoles, ankle or leg braces, and custom insoles.

DISCUSSION

According to interim findings from this prospective, observational, patient-reported lifestyle study, patients with CMT1A experience a high level of symptom burden. The long history of symptoms experienced by patients in the study (mean 27.9 years) may be reflective of the escalation of symptoms being the most rapid within the first 10 years[15] and patients likely being aware of them long before diagnosis.

Anxiety and depression were each reported by more than one-third of participants. This is similar to individuals with other neurological diseases, such as amyotrophic lateral sclerosis and multiple sclerosis,[16,17] but higher than the prevalence of anxiety and depression in the general global population (estimated at 4.4% and 3.6%, respectively),[18] although different quantification methodologies were used. The fact that diagnosis of anxiety and depression is higher in the study population than in the general population is not surprising for a disease with this symptom burden; however, anxiety or depression as comorbid conditions represent significant disease burden and can affect treatment and outcomes for CMT. Of those reporting depression, more than half of respondents categorized their CMT1A symptom severity as moderate, and more than one-third categorized their symptom severity as severe. Future research could examine the influence of these comorbidities on the condition of patients (similar to the GAMEDIS studies of chronic inflammatory demyelinating polyneuropathy[19]), as well as any potential links between reported anxiety/depression, use of medications to treat anxiety/depression, and EQ-5D-5L anxiety/depression domain scores. The prevalence of anxiety and depression among participants could also be reflective of the fact that the number of females—who, according to global estimates,[18] are more likely to suffer from both disorders—constitute more than 70% of the study population.

Our results show that the prevalence of anxiety and depression was highest for participants in the United States and in the United Kingdom and lowest for participants in France and Italy. The high incidence of both conditions in the United States when

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TABLE 3. Treatment Characteristics of Study Participants

Characteristic	n (%)
Rehabilitative interventions currently received (n = 445)	
Physical therapy	385 (86.5)
Occupational therapy	145 (32.6)
Massage therapy	93 (20.9)
Personal training	81 (18.2)
Yoga	59 (13.3)
Pilates	57 (13.3)
Other rehabilitative interventions	68 (15.3)
Medicines currently received (n = 404)	
Painkillers	293 (72.5)
Antidepressants	144 (35.6)
Opioids/analgesics	84 (20.8)
Antianxieties	72 (17.8)
Neuroleptic medications	70 (17.3)
Codeine	61 (15.1)
Cannabidiol oil	59 (14.6)
Natural homeopathic remedies	49 (12.1)
Benzodiazepines	21 (5.2)
Medicinal cannabis	19 (4.7)
Other medicines	92 (22.8)
Orthotics/walking aids currently used (n = 477)	
Off-the-shelf insoles	232 (48.6)
Ankle or leg braces	197 (41.3)
Custom insoles	192 (40.3)
Walking stick/cane	146 (30.6)
Walking aids	136 (28.5)
Crutches	61 (12.8)
Nonmotorized wheelchair	60 (12.6)
Thick handle tools	55 (11.5)
Walking frame/walker	49 (10.3)
Wrist splint	45 (9.4)
Motorized wheelchair	33 (6.9)
Thumb splints	30 (6.3)
Standing frame	4 (0.8)
Other orthotics/walking aids	93 (19.5)

compared with other countries is reflective of trends described in the literature. A study by Lim et al[20] investigated the prevalence of depression in 30 countries between 1994 and 2014 and found that among continents, South America had the highest aggregate prevalence at 20.6%, followed by North America at 13.4%, and Europe at 11.9%. The fact that the proportion of our study population who reside in the United Kingdom showed higher incidence of both conditions than those who reside in Italy or France, however, does not match recent statistics. According to the recent analysis of global depression[21] and anxiety rates,[22] the incidence of both conditions is higher in Italy and France than in the United Kingdom. Of course, medical comorbidity is an influencing factor, and further analysis of our results could reveal whether study participants in the United Kingdom collectively have a worse health status than those in Italy or France. However, understanding the impact of factors such as family history or social status—or even of the global COVID-19 pandemic, which coincided with the time period of our data cut, and its exacerbation of factors which determine poor mental health—is considerably more complicated, thus limiting our ability to speculate on these findings.

Almost one-third of participants reported that they experienced gastrointestinal problems. These problems are possibly sequelae of diet, lack of mobility, and medications taken to address CMT1A symptoms and warrant further analysis and exploration.

According to results from the PROMIS Pain Intensity 3a, pain intensity was mild or moderate for most participants. This is in line with prior literature; for instance, a study on pain assessment in CMT[23] found that more than 65% of participants reported some level of pain, usually with a moderate severity. Although pain intensity fell within normal limits for the majority of respondents in the present study, it should be noted that pain is still an interfering factor in participants' lives. This is reflected in the fact that more than half of participants reported moderate or severe interference of pain on engagement with social, cognitive, physical, and recreational activities via the PROMIS Pain Interference 6b and that pain was among the top 10 most frequently ranked symptoms of importance to participants. Whether there are any links between reported pain, PROMIS Pain Intensity 3a and PROMIS Pain Interference 6b scores, and use

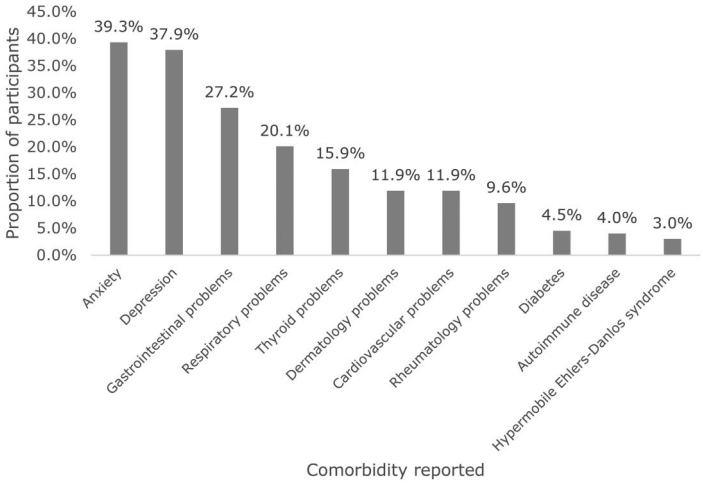

FIGURE 3. Proportion of study participants (n = 628) reporting different comorbidities. The remaining n = 198 study participants who responded to this survey question answered "no other medical condition."

of medications to treat pain is a subject to consider in prospective analyses.

Reported exercise levels were low, most likely due to symptoms of CMT1A; similar to individuals with other neurological diseases.[24,25] Almost two-fifths of participants reported that they do not or cannot exercise or that they exercise infrequently; this is higher than the quarter of the world's adult population who do not meet recommended levels of physical activity[26] (although it is difficult to compare these 2 figures due to the complexity of the World Health Organization's recommendations). Previous research has indicated a reduced life expectancy among patients with CMT, and it is unclear whether this finding is due to CMT itself or due to the accumulation of comorbidities.[27] The low activity levels described in this study may demonstrate some unmet need in terms of exercise that would be suitable to avoid further activity-related health problems. It would be interesting for future research to investigate a possible link between exercise levels, the impact of comorbidities, and thus changes in the mortality of CMT patients.

Reported symptom burden was mostly similar across countries, although there were some considerable differences. These are worth noting as symptoms ranked as higher importance could drive variation between countries in health-related quality of life, health care resource use, and costs. No participants in Spain ranked fatigue as the most important symptom they experienced, despite it being the fourth highest ranked symptom overall. Conversely, the highest impact of fatigue was reported by participants in Germany and the United Kingdom. Weakness in the feet, meanwhile, was ranked as the most important symptom by 9% of participants in the United States, but by 22% of participants in Spain. Methodological limitations of the study have been discussed

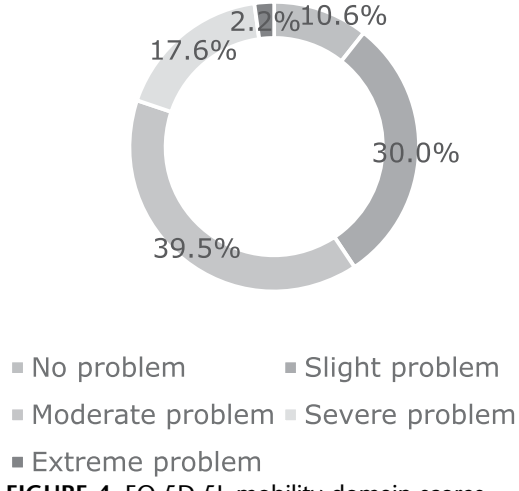

FIGURE 4. EQ-5D-5L mobility domain scores (n = 686).

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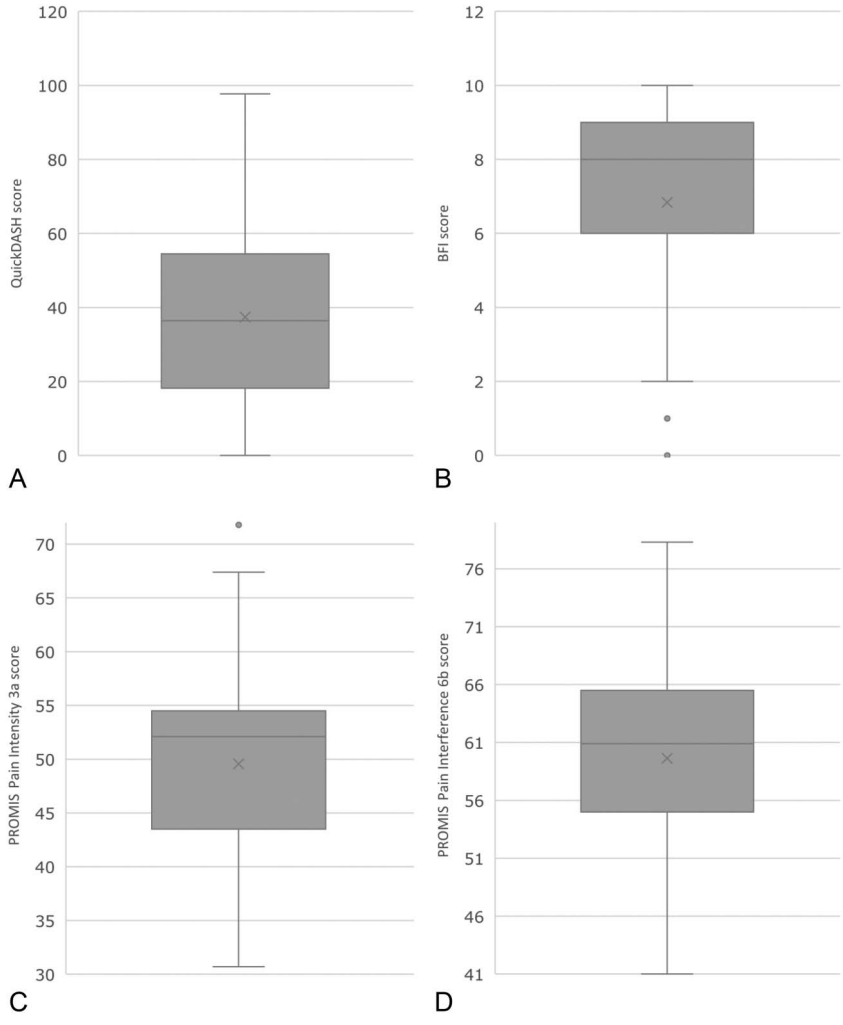

BFI = Brief Fatigue Inventory; PROMIS = Patient-Reported Outcomes Measurement Information System; QuickDASH = Quick Disabilities of Arm, Shoulder and Hand.

FIGURE 5. PRO instrument scores. (A), QuickDASH score (n = 642), (B) BFI score (n = 592), (C) PROMIS Pain Intensity 3a score (n = 628), (D) PROMIS Pain Interference 6b score (n = 584).

elsewhere.[28] The study was disproportionately women; this presents a risk of bias, but no information is available for the asymmetric participation and it is in line with literature indicating that women typically engage more with digital health apps than men.[29,30]

In the context of symptom burden, one limitation of these results is that they are reliant on patients' self-reported assessment. Subjective assessment of symptom severity, for example, may not match physician/objective assessment, as observed in spinocerebellar ataxia,[31] and could be driven by other factors (eg, comorbidities, concomitant medicines). However, the aim of this study was not to report severity according to clinical criteria but to understand how patients view the severity of their own symptoms, with the understanding that this severity assessment may be very subjective and differ greatly between participants; for this reason, participants were not asked to report their CMT neuropathy score, which is typically measured by physicians.

Although the results of the most frequently reported symptoms reveal those of greatest importance to participants, it should not be inferred that the less frequently reported symptoms do not affect

participants, and as such, any given result in isolation should be extrapolated with caution. Pain, for example, was only the eighth highest ranked symptom of importance, yet median PRO instrument scores indicate that patients experience both pain intensity and interference. Cramping, meanwhile, was only the 14th highest ranked symptom of importance, yet just under three-quarters of participants reported experiencing cramp at least one day per week.

CONCLUSION

Patient-reported burden of CMT1A is high, influenced by major difficulties using limbs, fatigue and pain symptoms, and impairment to quality of life. The level of burden appears to differ across the CMT1A population, possibly driven by differences in rehabilitative interventions and medicines received, orthotics/walking aids used, and country-specific differences in health care systems. Anxiety and depression, frequently reported comorbid conditions among the CMT1A population, represent significant additional disease burden. It is apparent that there remains a high unmet need in CMT1A caused by the burden on patients.

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