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ORIGINAL ARTICLE

Frequency, entity and determinants of fatigue in Charcot–Marie–Tooth disease

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Abstract

Background and purpose: Fatigue, a disabling symptom in many neuromuscular disorders, has been reported also in Charcot–Marie–Tooth disease (CMT). The presence of fatigue and its correlations in CMT was investigated.

Methods: The Modified Fatigue Impact Scale (MFIS) was administered to CMT patients from the Italian Registry and a control group. An MFIS score >38 indicated abnormal fatigue. The correlation with disease severity and clinical characteristics, the Hospital Anxiety and Depression Scale and Epworth Sleepiness Scale scores, and drug use was analysed.

†Italian CMT Network; see Appendix S1 for other members.

Results: Data were collected from 251 CMT patients (136 women) and 57 controls. MFIS total (mean ± standard deviation 32 ± 18.3, median 33), physical (18.9 ± 9.7, 20) and psychosocial (2.9 ± 2.4, 3) scores in CMT patients were significantly higher than controls. Abnormal fatigue occurred in 36% of the patients who, compared to patients with normal scores, had more severe disease (median CMT Examination Score 9 vs. 7), more frequent use of foot orthotics (22% vs. 11%), need of support for walking (21% vs. 8%), hand disability (70% vs. 52%) and positive sensory symptoms (56% vs. 36%). Patients with abnormal fatigue had significantly increased frequency of anxiety/depression/general distress (Hospital Anxiety and Depression Scale), somnolence (Epworth Sleepiness Scale), obesity (body mass index ≥ 30) and use of anxiolytic/antidepressant or anti-inflammatory/analgesic drugs.

Conclusions: Fatigue is a relevant symptom in CMT as 36% of our series had scores indicating abnormal fatigue. It correlated with disease severity but also with anxiety, depression, sleepiness and obesity, indicating different components in the generation of fatigue. CMT patients' management must include treatment of fatigue and of its different generators, including general distress, sleepiness and obesity.

KEYWORDS
Charcot–Marie–Tooth disease, fatigue, hereditary motor and sensory neuropathies, sleep

INTRODUCTION

Charcot–Marie–Tooth disease (CMT) collects a heterogeneous group of hereditary peripheral neuropathies characterized by distal motor weakness and atrophy, variable distal sensory loss, foot deformities and decreased-to-absent deep tendon reflexes [1].

Fatigue is a common complaint in many neuromuscular disorders [2, 3], although it is difficult to define because of its subjective nature [4]. Definitions in clinical research include the following: an 'overwhelming and persistent feeling of tiredness and diminished ability to sustain voluntary mental and physical activities' and also a sensation of 'weakness, lethargy and lack of energy that interferes with daily activities' [5, 6].

Perceived or experienced fatigue, usually investigated through self-administered questionnaires, can be distinguished from performance fatigability, characterized by difficulty in maintaining a physical performance through time which is tested during physical tasks [5]. Fatigue has a multidimensional character and is determined by many factors, including health perceived status and participation in daily activities. Central fatigue is related to neuropsychiatric conditions and to disorders directly involving the central nervous system, whereas 'peripheral fatigue' is related to neuromuscular unit disorders [5–7].

Several questionnaires have been developed and employed to assess perceived fatigue, namely, the Checklist Individual Strength (CIS) scale [5, 6, 8], the Fatigue Severity Scale (FSS) [9, 10], the Visual Analogue Scale (VAS) [11], the Multidimensional Fatigue Inventory [12, 13] and the Modified Fatigue Impact Scale (MFIS) [14]. The MFIS is one of the most commonly used and has been validated in many neurological disorders, including multiple sclerosis and Parkinson disease [15, 16].

A few studies assessed experienced fatigue in CMT employing different questionnaires [5, 8, 10, 11, 13, 17] and found a remarkable proportion of patients reporting significant fatigue, ranging from 43.2% to 64% [8, 10, 13, 17]. Some researchers focused on performance fatigue by using physical measures (such as surface electromyography analysis and repeated strength measures with a dynamometer during sustained effort or electrical stimulation during rest and after muscle contraction) [5, 18, 19].

Perceived fatigue was assessed by using the MFIS in a large series of patients with CMT recruited through the Italian CMT Registry, and its correlations with disease severity and clinical characteristics, general distress, somnolence, body weight and use of drugs were examined.

METHODS

The Italian CMT Registry (www.registronmd.it) was developed thanks to a collaboration between Italian patients' associations, including ACMT-Rete, and Telethon-Italy Foundation, coordinated in the Associazione del Registro with clinical centres and Scientific Societies for the Study of Muscle and Peripheral Nerve [20]. In this dual registry, the patient first registers herself/himself and then selects the preferred reference centre amongst nine in Italy (Fondazione IRCCS Istituto Neurologico Carlo Besta of Milan, IRCCS Ospedale San Raffaele of Milan, Universities of Genoa, Verona, Parma, Rome, Naples, Catanzaro and Messina); here, the attending clinician visits the patient, collects a minimal dataset of information and administers the CMT Neuropathy Score/Examination Score (CMTNS/CMTES) clinical scale [21]. All data collected in the records of the Registry are reviewed and confirmed by the local physicians and validated by the Registry curator.

Friends and unaffected relatives of participating CMT patients, matched as much as possible for gender and age, were recruited as healthy controls. This study was approved by the Ethics Committees of the Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan (no. 52/2016, date 2 April 2014) and of the other participating centres. All participants to the Registry signed a written informed consent and those completing the questionnaires signed an online informed consent. Recruitment was conducted before the COVID-19 pandemic and lasted 3 years (2015–2017).

Both patients and controls were asked to complete online the validated Italian version of the MFIS questionnaire, a self-assessed questionnaire composed of 21 statements, nine exploring the presence of physical fatigue related symptoms (MFIS-PH scale), 10 exploring the presence of cognitive symptoms (MFIS-C scale) and two exploring the psychosocial domain (MFIS-PS scale), making up a total score (MFIS-T) indicative of fatigue level. Each statement is rated by a 5-point (0–4) system (range 0–84, where 0 is absence of fatigue and 84 the worst score). A total score >38 indicates abnormal fatigue, according to Flachenecker et al. [22].

Both patients and controls were asked to fill also questionnaires concerning the presence of anxiety, depression and general distress (Hospital Anxiety and Depression Scale, HADS, Italian version) [23] and the presence of diurnal somnolence (Epworth Sleepiness Scale, ESS, Italian version) [24] to explore the contribution of neuropsychiatric status and sleepiness to fatigue. Cut-off scores ≥11 were used for both the HADS-A and HADS-D to define the presence of anxiety/depression, ≥22 for the whole scale (HADS-T) to indicate the presence of general distress [25] and >10 for the ESS to indicate the presence of sleepiness [26].

Statistical analysis

Participant characteristics at baseline were described in terms of absolute numbers and percentages for categorical data and means with standard deviations (SDs) and medians for continuous data. The *t* test, Mann–Whitney *U* test, Fisher's exact test and Spearman's rank-order correlation were used to analyse associations between MFIS scores and type of participants (CMT patients vs. controls), gender, age, disease duration, disease severity (CMTES), walking ability and/or use of orthotics, hand disability, sensory symptoms, body mass index (BMI), HADS scores, ESS score and medication use (antidepressant/anxiolytic and analgesic/anti-inflammatory drugs). Throughout the statistical analysis, the significance level was set at 0.05 (significant <0.05).

RESULTS

The MFIS questionnaire was completed by 251 CMT patients and 57 controls (20 friends and 37 unaffected relatives). Demographic and clinical data and MFIS scores of CMT patients and healthy controls are summarized in Table 1.

The age of controls and CMT patients was similar, whereas there was a slight, although non-significant, predominance of females in the CMT group compared to controls. Amongst the 251 CMT patients, 116 (46.2%) had a diagnosis of CMT1A (*PMP22* duplication); the other most frequent CMT types were CMTX1 (*GJB1*: $n = 21$, 8.4%), CMT1B (*MPZ*: $n = 18$, 7.2%), CMT2I/CMT2J (*MPZ*: $n = 14$, 5.6%), CMT2A (*MFN2*: $n = 8$, 3.2%) and CMT4C (*SH3TC2*: $n = 5$, 2.0%).

The values of physical (MFIS-PH) and psychosocial (MFIS-PS) subscores and of the MFIS total (MFIS-T) score of CMT patients

TABLE 1 Demography, disease severity and MFIS scores of CMT patients and healthy controls

	CMT patients			Controls		
	Females ($n = 136$)	Males ($n = 115$)	Total ($n = 251$)	Females ($n = 25$)	Males ($n = 32$)	Total ($n = 57$)
Age (mean ± SD)	46.6 ± 12.2	47.7 ± 13.9	47.2 ± 13.0	46.5 ± 12.6	43.9 ± 12.6	45.0 ± 12.5
CMTES (mean ± SD, median)	7.9 ± 5.2, 7	8.4 ± 5.2, 8	8.2 ± 5.2, 8	–	–	–
Physical MFIS-PH score[a,b] (mean ± SD, median)	20.3 ± 8.9, 21[b]	17.4 ± 10.4, 17[b]	18.9 ± 9.7, 20[a]	9.2 ± 5.7, 9	6.5 ± 5.6, 4	7.7 ± 5.8, 7[a]
Cognitive MFIS-C score[b] (mean ± SD, median)	11.1 ± 8.7, 9.5[b]	9.1 ± 8.5, 7[b]	10.1 ± 8.6, 8	8.7 ± 7.4, 7	7.5 ± 5.9, 6	8.0 ± 6.6, 7
Psychosocial MFIS-PS score[a] (mean ± SD, median)	3.1 ± 2.4, 3	2.7 ± 2.8, 2	2.9 ± 2.4, 3[a]	2.0 ± 1.6, 2	1.1 ± 1.1, 1	1.5 ± 1.4, 2[a]
Total MFIS-T score[a,b] (mean ± SD, median)	34.5 ± 17.6, 35[b]	29.1 ± 18.8, 31[b]	32.0 ± 18.3, 33[a]	19.4 ± 11.4, 18	15.0 ± 10.8, 12.5	17.2 ± 11.3, 16[a]

Abbreviations: C, cognitive; CMT, Charcot–Marie–Tooth disease; CMTES, Charcot–Marie–Tooth Examination Score; MFIS, Modified Fatigue Impact Scale; PH, physical; PS, psychosocial; SD, standard deviation; T, total.

[a]MFIS-PH, MFIS-PS and MFIS-T scores were significantly higher in the CMT group ($p < 0.001$ for all comparisons) than in the control group (Mann–Whitney *U* test).

[b]MFIS-C, MFIS-PH and MFIS-T scores were significantly higher in CMT females than CMT males ($p = 0.039$, $p = 0.025$ and $p = 0.013$, respectively; Mann–Whitney *U* test).

were significantly higher than controls ($p < 0.001$ for all comparisons), whereas there was no difference for the cognitive subscore (MFIS-C, $p = 0.173$). The scores for the cognitive domain, physical domain and the MFIS total score were significantly higher in CMT females than in CMT males ($p = 0.039$, $p = 0.025$ and $p = 0.013$, respectively), but no significant difference between genders was evident in healthy controls (Table 1).

Amongst CMT patients, 36% (91/251) had abnormal levels of fatigue as assessed by MFIS (MFIS-T > 38), a rate significantly higher than controls (5%, 3/57, $p < 0.001$), with a slight although non-significant prevalence of females (Table 2).

Compared to CMT subjects with normal fatigue levels (MFIS-T ≤ 38), patients with abnormal general fatigue had more severe disease as assessed by CMTES (median 9 vs. 7), more frequent use of ankle foot orthotics (22% vs. 11%), need of support for walking (21% vs. 8%), hand disability (difficulties with buttons 70% vs. 52%), positive sensory symptoms (56% vs. 36%) and arthritic-like pain (21% vs. 11%). Patients with abnormal fatigue also had more frequently ESS scores indicative of sleepiness (36% vs. 16%), BMI above the threshold for obesity (BMI ≥ 30) (16% vs. 7%) and HADS scores suggestive of anxiety (51% vs. 10%), depression (22% vs. 3%) and general distress (33% vs. 3%). No difference was found in MFIS scores for age, disease duration, education level and CMT type.

Concerning the use of pharmacological drugs, 19.2% of CMT patients for whom the information was available ($n = 45/234$) took antidepressant/anxiolytic medications, with 11.5% ($n = 27$) taking them every day; 70.1% of CMT subjects ($n = 164/234$) made use of anti-inflammatory/analgesic drugs, 17% ($n = 40$) more than once per week. Notably, CMT patients with abnormal fatigue reported more frequent use of both anxiolytic/antidepressant drugs and analgesic/anti-inflammatory drugs. Conversely, MFIS scores (total score and physical/psychosocial/cognitive scores) were significantly higher in both categories of pharmacological drug users (Table 2, Table S1).

The correlations between fatigue scores and disease severity (CMTES), general distress, sleepiness and obesity were then examined (Table 3). Anxiety/depression/general distress (HADS-A, HADS-D, HADS-T) strongly correlated with general fatigue (MFIS-T) and with all MFIS subscores ($r = 0.55–0.76$; Table 3, Figures 1 and 2). No correlation was found with domains of MFIS for age and disease duration. Sleepiness correlated better with the cognitive domain of fatigue (Table 3, Figure 2), whilst obesity had a loose correlation with the physical domain (Table 3).

TABLE 2 MFIS scores by clinical characteristics of the CMT population

	Abnormal fatigue		
	MFIS-T score ≤ 38 ($n = 160$)	**MFIS-T score > 38 ($n = 91$)**	***p* value[a]**
Gender	Females 81/136 (60%)	Females 55/136 (40%)	
	Males 79/115 (69%)	Males 36/115 (31%)	0.148
Age (mean ± SD, median)	46.3 ± 13.4, 45	48.9 ± 12.2, 49	0.226
Disease duration (mean ± SD, median)	24.4 ± 14.4, 24	24.5 ± 14.5, 24	0.857
CMTES (mean ± SD, median)	7.2 ± 4.9, 7	**9.8 ± 5.2, 9**	**0.001**
Walking difficulties, *n* (%)	112 (70%)	74 (81%)	0.052
Ankle foot orthotics, *n* (%)	18 (11%)	**20 (22%)**	**0.028**
Walking support need, *n* (%)	13 (8%)	**19 (21%)**	**0.005**
Difficulties with buttons, *n* (%)	84 (52%)	**64 (70%)**	**0.005**
Arthritic-like pain, *n* (%)	17 (11%)	**19 (21%)**	**0.038**
Positive sensory symptoms, *n* (%)	57 (36%)	**51 (56%)**	**0.002**
Obesity BMI ≥ 30, *n* (%)	11/147 (7%)	**13/80 (16%)**	**0.045**
Anxiety HADS A score ≥ 11, *n* (%)	16/158 (10%)	**51/90 (51%)**	**<0.001**
Depression HADS D score ≥ 11, *n* (%)	5/158 (3%)	**20/90 (22%)**	**<0.001**
General distress HADS T score ≥ 22, *n* (%)	5/158 (3%)	**30/90 (33%)**	**<0.001**
Sleepiness ESS > 10, *n* (%)	26/158 (16%)	**33/91 (36%)**	**<0.001**
Anxiolytics/antidepressants, *n* (%)	18/152 (12%)	**27/82 (33%)**	**<0.001**
Analgesics/anti-inflammatories, *n* (%)	97/152 (64%)	**67/82 (82%)**	**0.004**

Note: *p* values for significant differences are reported in bold.

Abbreviations: A, anxiety; BMI, body mass index; CMT, Charcot–Marie–Tooth disease; CMTES, Charcot–Marie–Tooth Examination Score; D, depression; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; SD, standard deviation; T, total.

[a]*p* value calculated using the *t* test, Mann–Whitney *U* test or Fisher's exact test as appropriate.

TABLE 3 Correlations between MFIS scores and demographic and clinical characteristics of CMT, HADS and ESS scales, BMI

	Physical MFIS-PH score	Cognitive MFIS-C score	Psychosocial MFIS-PS score	Total MFIS-T score
Age	$r = 0.15$ $p = 0.066$	$r = -0.03$ $p = 0.631$	$r = 0.07$ $p = 0.113$	$r = 0.08$ $p = 0.215$
CMTES	**$r = 0.33$** **$p < 0.001$**	$r = 0.08$ $p = 0.147$	**$r = 0.22$** **$p < 0.001$**	**$r = 0.26$** **$p < 0.001$**
Disease duration	$r = 0.04$ $p = 0.544$	$r = -0.04$ $p = 0.587$	$r = 0.05$ $p = 0.549$	$r = 0.01$ $p = 0.946$
Anxiety HADS-A score	**$r = 0.57$** **$p < 0.001$**	**$r = 0.71$** **$p < 0.001$**	**$r = 0.55$** **$p < 0.001$**	**$r = 0.70$** **$p < 0.001$**
Depression HADS-D score	**$r = 0.58$** **$p < 0.001$**	**$r = 0.66$** **$p < 0.001$**	**$r = 0.60$** **$p < 0.001$**	**$r = 0.69$** **$p < 0.001$**
General distress HADS-T score	**$r = 0.63$** **$p < 0.001$**	**$r = 0.74$** **$p < 0.001$**	**$r = 0.62$** **$p < 0.001$**	**$r = 0.76$** **$p < 0.001$**
Sleepiness ESS	**$r = 0.40$** **$p < 0.001$**	**$r = 0.49$** **$p < 0.001$**	**$r = 0.35$** **$p < 0.001$**	**$r = 0.49$** **$p < 0.001$**
Obesity BMI ≥ 30	**$r = 0.14$** **$p = 0.036$**	$r = 0.02$ $p = 0.674$	$r = 0.03$ $p = 0.584$	$r = 0.10$ $p = 0.123$

Note: significant correlations are reported in bold.

Abbreviations: A, anxiety; BMI, body mass index; C, cognitive; CMT, Charcot–Marie–Tooth disease; CMTES, Charcot–Marie-Tooth Examination Score; D, depression; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; PH, physical; PS, psychosocial; *r*, Spearman correlation; SD, standard deviation; T, total.

DISCUSSION

Fatigue is a relevant symptom in many neurological and neuromuscular disorders. It is a multidimensional symptom, determined by several factors, including perceived health status, subject participation in daily activity, performance fatigability and subject's comorbidities [5–7].

This is the first study analysing the presence of fatigue by using the MFIS instrument in a large cohort of CMT patients ($n = 251$). It is found that more than one-third of the patients (36%) reported abnormal fatigue and that the MFIS scores in CMT subjects were significantly higher than controls, independently from CMT type. Correlation analyses were performed to assess the fatigue determinants and it was found that CMT severity is an important factor, but also mood disorders, assessed with the HADS, and sleepiness, evaluated with the ESS, are relevant contributing elements.

Although the MFIS has been used in many neurological disorders, such as multiple sclerosis and Parkinson disease [14–16], it has never been employed in neuromuscular disorders and in CMT subjects. This scale is easy to administer and allows the presence of fatigue to be explored in terms of different domains, such as physical, cognitive and psychosocial functioning. It was preferred to other scales used in previous studies as it better outlines the explored domains, is based on more objectively defined actions of daily life and embraces a longer period of time (4 weeks vs. the 2 and 1 of the CIS and FSS, respectively).

Until now, only a few studies have investigated the presence of experienced fatigue in CMT; two of them used the FSS [10,17], which is a very simple scale consisting of nine items [9], whilst three others employed the CIS [5, 8, 27], a self-reported multidimensional instrument which assesses four different aspects of fatigue (subjective fatigue severity, concentration problems, reduced motivation and reduced activity level) [6], and they found that fatigue was reported by a significant percentage of patients ranging from 43.2% to 64% [8, 10, 13, 17].

Schillings et al. [5] studied both experienced and performance fatigue in 73 CMT, 65 facioscapulohumeral dystrophy (FSHD) patients and 79 myotonic dystrophy (MD) patients by administering the four-item Abbreviated Fatigue Questionnaire to assess the level of experienced fatigue at baseline and the CIS scale to assess the level of fatigue in the 2 weeks following the baseline visit during which patients performed a dynamometer test and surface electromyography analysis to assess both peripheral and central fatigue, as well as fatigability. CMT patients were found to have levels of experienced fatigue higher than the 24 healthy controls, but similar to FSHD and MD subjects. The difference in amplitude of maximum voluntary muscular contraction before and after a voluntary sustained muscular activity, defined by the authors as central activation failure, was found to be higher than controls in all three groups of neuromuscular diseases, and in particular higher in CMT, indicating performance fatiguability [5].

In another series of 137 CMT patients, the mean CIS fatigue score was 36.5, with a cut-off of 35 used to define severe fatigue, whilst the percentage of severely fatigued patients was 64%, similar to patients with other neuromuscular disorders (74% for Duchenne muscular dystrophy and 61% for FSHD) [8]. The FSS revealed the presence of fatigue in 52% of 81 CMT patients in the

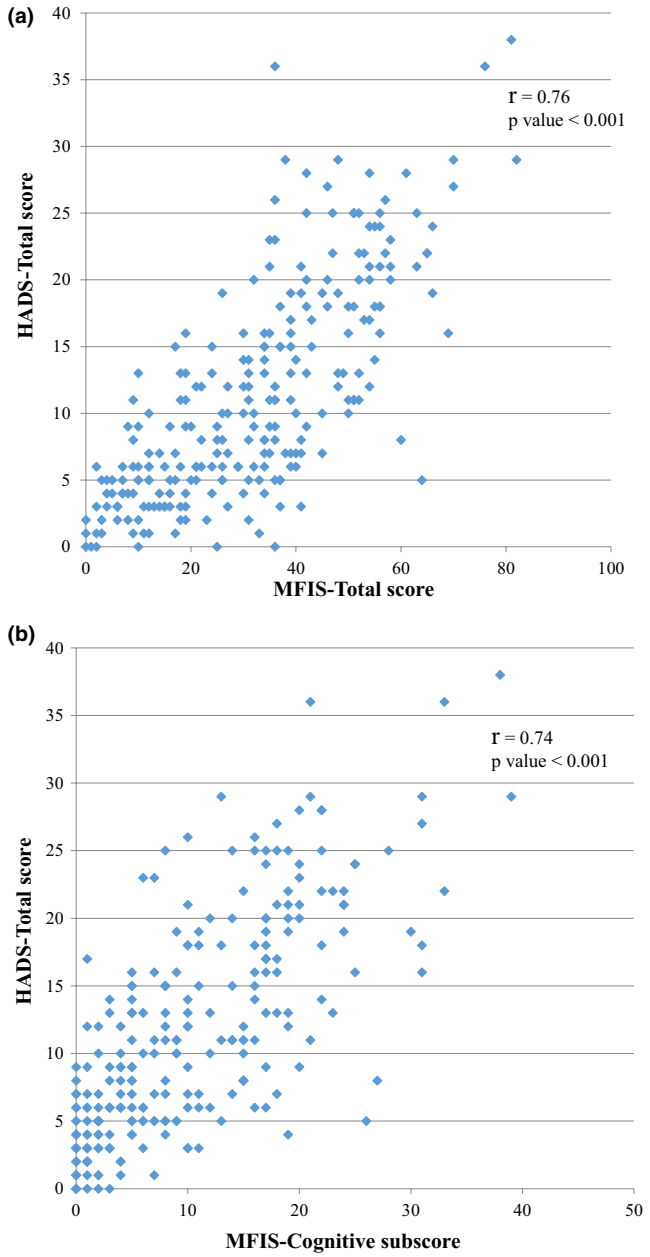

FIGURE 1 Correlation graphs between MFIS score (Modified Fatigue Impact Scale, Total score in (a) and Cognitive subscore in (b)) and HADS-T score (Hospital Anxiety and Depression Scale, Total). *r*, Spearman correlation

study by Anens et al. [10]. In a double-blind randomized trial with ascorbic acid, Pareyson et al. [11] assessed fatigue with the VAS in 277 CMT patients and obtained a mean score of 5 ± 2.7 at baseline assessment, consistent with a moderate fatigue level, with no change after ascorbic acid treatment and no difference with the placebo group. In another study, Boentert et al. [13] administered the Multidimensional Fatigue Inventory scale, a 20-item scale investigating five dimensions of fatigue (general, physical and mental fatigue, reduced activities and reduced motivation), to 227 CMT patients and found higher levels of fatigue, a higher prevalence of daytime sleepiness assessed by ESS and worse sleep quality as defined by the Pittsburgh Sleep Quality Index with respect to 34 healthy controls.

Our results confirm previous reports in that the MFIS score was significantly higher in CMT subjects compared to controls, and abnormal fatigue was present in 36% (91/251) of CMT subjects. The lower prevalence of fatigue compared to other studies (36% vs. the 43.2%–64% range) [8, 10, 13, 17] can be explained by the differences between scales.

The relationships between MFIS scores and several disease variables and other factors were analysed. Compared to patients without fatigue, those with abnormal fatigue (MFIS > 38) had more severe CMT assessed in several ways, that is, the composite measure of disability and impairment CMTES, the need for ankle foot orthoses and support for walking, the presence of positive sensory symptoms including pain, and the hand function disability. CMT patients with abnormal fatigue also had more frequent evidence of mood disorders as revealed by the HADS questionnaire (anxiety 51% vs. 10%, depression 22% vs. 3% and general distress 33% vs. 3%), sleepiness according to the ESS (36% vs. 16%) and obesity with BMI ≥ 30 (16% vs. 7%). Interestingly, HADS scores correlated well with all MFIS scores, ESS correlated mainly with the MFIS cognitive domain, CMTES and obesity with the physical domain.

Thus far, only a few studies have analysed the relationship between fatigue and mood disorders and showed conflicting results. In their study on 73 CMT patients, Kalkman et al. [27] found no correlation between fatigue (assessed with the CIS) and mood disorders on using the Beck Depression Inventory (BDI) scale, neither did they find any difference with other neuromuscular disorders (FSHD and MD). On the other hand, Ivanovic et al. [17] observed that 56% of a series of 45 CMT1A patients complained of abnormal fatigue (as assessed by the FSS scale) and 29% had symptoms of depression according to the BDI. Interestingly, both BDI and FSS scores significantly correlated with the Short Form Health Survey 36 scale, acting as predictors of a worse quality of life. Our study is the first to analyse the correlation between fatigue and mood disorders by using the HADS scale and indeed such a correlation was found between abnormal fatigue and anxiety, depression and general distress levels; mood disorders were related not only with general (total) fatigue but with all fatigue domains, particularly with the cognitive and physical domains. It was also found that patients with fatigue more frequently took antidepressant/anxiolytic drugs, confirming such a relationship.

The use of analgesic/anti-inflammatory drugs was also higher amongst patients with fatigue, suggesting a role for pain in fatigue; notably, fatigued patients complained more frequently of positive sensory symptoms and pain.

No correlation of perceived fatigue with age and disease duration was found, which may seem strange for a progressive disorder; however, previous studies did not find such a correlation either [5, 8, 10, 13, 17]. This suggests that several factors, beyond disease severity, which are independent of age and disease duration, contribute to the generation of fatigue. Interestingly, no progression of fatigue

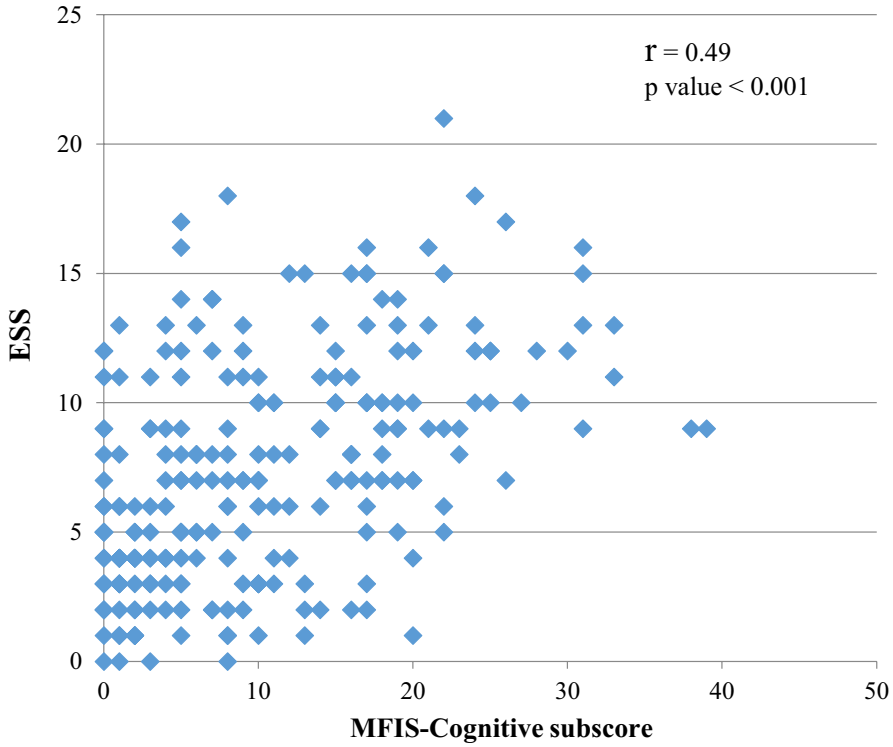

FIGURE 2 Correlation graph between MFIS-C score (Modified Fatigue Impact Scale, Cognitive subscore) and ESS score (Epworth Sleepiness Scale). *r*, Spearman correlation

was assessed with VAS over 2 years in the 107 CMT1A patients of the placebo arm of the ascorbic acid trial [11]. Further longitudinal studies may shed light on the matter.

Our research suggests that fatigue has a multidimensional origin and that, beyond the CMT disease itself, also neuropsychiatric changes, somnolence and obesity play an important role in its generation, and such results may carry important consequences on management of CMT. Longitudinal studies may reinforce these conclusions.

This study has some limitations. First, patients were those participating in the national Registry, more liable to participate in investigations and may not be fully representative of the whole CMT population. Secondly, the HADS and ESS are rapid scales for investigating the presence of general distress and somnolence but do not allow a definite diagnosis of depression or anxiety and of sleep disorders, including sleep apnoea. Thirdly, the number of controls (recruited in seven of the nine centres in a 17%–37% ratio with respect to patients) was limited, but the differences were so striking that it is thought that this is not a major issue. The study was conducted before the COVID-19 pandemic and therefore it is free of the biases generated by the dramatic psychological impact of the pandemic.

In conclusion, our findings confirm that fatigue is a relevant symptom for CMT patients. CMT severity is only one of the determinants of fatigue, as mood disorder, sleepiness, pain and obesity are contributing factors. Assessment and proper management of fatigue must become part of the evaluation and treatment of CMT patients, with the aim of alleviating disease burden. Treatment of fatigue should be multidimensional and addressed also to psychological status, sleepiness, pain and obesity management.

AUTHOR CONTRIBUTIONS

All authors reported in this manuscript had contributed to data collection and had revised the manuscript. DP had designed and conceptualized this study. IT and AB had provided statistical analyses and data management. MB and DP wrote the paper.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data relevant to the study are included in the article or uploaded as online supplemental information. Data supporting study results are deposited in an ad hoc repository and are available from the Principal Investigator (DP) to be shared anonymously on request from any qualified investigator.

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REFERENCES

1. Pisciotta C, Saveri P, Pareyson D. Updated review of therapeutic strategies for Charcot–Marie–Tooth disease and related neuropathies. *Expert Rev Neurother*. 2021;21:701-713. doi:10.1080/14737175.2021.1935242
2. Féasson L, Camdessanché JP, El Mandhi L, Calmels P, Millet GY. Fatigue and neuromuscular diseases. *Ann Readapt Med Phys*. 2006;49:289-300, 375-384. English, French. doi:10.1016/j.annrmp.2006.04.015
3. De Vries JM, Hagemans MLC, Bussman JBJ, et al. Fatigue in neuromuscular disorders: focus on Guillain–Barré syndrome and Pompe disease. *Cell Mol Life Sci*. 2010;67:701-713.
4. Ramdaharry GM, Thornhill A, Mein G, et al. Exploring the experience of fatigue in people with Charcot–Marie–Tooth disease. *Neuromuscul Disord*. 2012;22(Suppl 3):S208-S213. doi:10.1016/j.nmd.2012.10.016
5. Schillings ML, Kalkman JS, Janssen HM, van Engelen BG, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. *Clin Neurophysiol*. 2007;118:292-300. doi:10.1016/j.clinph.2006.10.018
6. Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: psychometric qualities and norms for the checklist individual strength. *J Psychosom Res*. 2017;98:40-46. doi:10.1016/j.jpsychores.2017.05.007
7. Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud*. 1996;33:519-529. doi:10.1016/0020-7489(96)00004-1
8. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry*. 2005;76:1406-1409. doi:10.1136/jnnp.2004.050005
9. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46:1121-1123. doi:10.1001/archneur.1989.00520460115022
10. Anens E, Emtner M, Hellström K. Exploratory study of physical activity in persons with Charcot–Marie–Tooth disease. *Arch Phys Med Rehabil*. 2015;96:260-268. doi:10.1016/j.apmr.2014.09.013
11. Pareyson D, Reilly MM, Schenone A, et al. Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. *Lancet Neurol*. 2011;10:320-328. doi:10.1016/S1474-4422(11)70025-4
12. Smets EM, Garssen B, Bonke B, De Haes JC. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39:315-325. doi:10.1016/0022-3999(94)00125-o
13. Boentert M, Dziewas R, Heidbreder A, et al. Fatigue, reduced sleep quality and restless legs syndrome in Charcot–Marie–Tooth disease: a web-based survey. *J Neurol*. 2010;257:646-652. doi:10.1007/s00415-009-5390-1
14. Larson RD. Psychometric properties of the Modified Fatigue Impact Scale. *Int J MS Care*. 2013;15:15-20. doi:10.7224/1537-2073.2012-019
15. Kos D, Kerckhofs E, Carrea I, Verza R, Ramos M, Jansa J. Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Mult Scler*. 2005;11:76-80. doi:10.1191/1352458505ms1117oa
16. Schiehser DM, Ayers CR, Liu L, Lessig S, Song DS, Filoteo JV. Validation of the modified fatigue impact scale in Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19:335-338. doi:10.1016/j.parkreldis.2012.11.013
17. Ivanovic V, Bjelica B, Palibrk A, et al. Physical and mental aspects of quality of life in patients with Charcot–Marie–Tooth disease type 1A. *Front Neurol*. 2022;13:852150. doi:10.3389/fneur.2022.852150
18. Menotti F, Bazzucchi I, Felici F, Damiani A, Gori MC, Macaluso A. Neuromuscular function after muscle fatigue in Charcot–Marie–Tooth type 1A patients. *Muscle Nerve*. 2012;46:434-439. doi:10.1002/mus.23366
19. Peterson DS, Moore A, Ofori E. Performance fatigability during gait in adults with Charcot–Marie–Tooth disease. *Gait Posture*. 2021;85:232-237. doi:10.1016/j.gaitpost.2021.02.002
20. Ambrosini A, Calabrese D, Avato FM, et al. The Italian neuromuscular registry: a coordinated platform where patient organizations and clinicians collaborate for data collection and multiple usage. *Orphanet J Rare Dis*. 2018;13:176. doi:10.1186/s13023-018-0918-z
21. Murphy SM, Herrmann DN, McDermott MP, et al. Reliability of the CMT neuropathy score (second version) in Charcot–Marie–Tooth disease. *J Peripher Nerv Syst*. 2011;16:191-198. doi:10.1111/j.1529-8027.2011.00350.x
22. Flachenecker P, Kümpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler*. 2002;8:523-526. doi:10.1191/1352458502ms839oa
23. Costantini M, Musso M, Viterbori P, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Cancer*. 1999;7:121-127. doi:10.1007/s005200050241
24. Vignatelli L, Plazzi G, Barbato A, et al. Italian version of the Epworth Sleepiness Scale: external validity. *Neurol Sci*. 2003;23:295-300. doi:10.1007/s100720300004
25. Singer S, Kuhnt S, Götze H, et al. Hospital Anxiety and Depression Scale cutoff scores for cancer patients in acute care. *Br J Cancer*. 2009;100:908-912. doi:10.1038/sj.bjc.6604952
26. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth Sleepiness Scale: failure of the MSLT as a gold standard. *J Sleep Res*. 2000;9:5-11. doi:10.1046/j.1365-2869.2000.00177.x

27. Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BG, Bleijenberg G. Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and hereditary motor and sensory neuropathy type I. *Acta Neurol Scand*. 2007;115:265-270. doi:10.1111/j.1600-0404.2006.00737.x

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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