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Are novel outcome measures for Charcot–Marie–Tooth disease sensitive to change? The 6-minute walk test and StepWatch™ Activity Monitor in a 12-month longitudinal study

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Abstract

Charcot–Marie–Tooth (CMT) is the most common inherited neuropathy, yet has no available pharmacological therapy. Past pharmacotherapy trials failed to provide positive results, possibly due to a poor choice of outcome measures. We previously performed a study in which we validated the 6-minute walk test and StepWatch™ Activity Monitor in CMT. The aim of the current study was to determine if these outcome measures are sensitive to change over a 12-month period. In this longitudinal multicenter study, 149 out of 169 initially enrolled patients were re-evaluated after 12 months using the 6-minute walk test, StepWatch™ Activity Monitor and other outcome measures commonly adopted in CMT disease. Statistical analysis showed a worsening of the CMT-Neuropathy Score ($p < 0.05$), strength of distal muscles measured by myometry ($p < 0.05$) and StepWatch™ Activity Monitor outputs ($p < 0.05$). The 10 meter walking test ($p > 0.05$), muscular strength as detected by clinical evaluation ($p > 0.05$), 6-minute walk test ($p > 0.05$), pain ($p > 0.05$) and quality of life ($p > 0.05$) showed no change. In the current study, patients showed clinical worsening over 12 months, confirmed by a reduction of activity as detected by StepWatch™ Activity Monitor. The 6-minute walk test failed to detect change.

Keywords: Charcot–Marie–Tooth; Outcome measures; Rehabilitation; Sensitivity to changes.

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1. Introduction

Charcot–Marie–Tooth (CMT) is the most common inherited neuropathy, with an overall prevalence estimated at 10–28/100,000 [1]. It is characterized by sensorimotor impairment of the extremities, skeletal deformities and functional limitations [2]. Although it is considered a rare disease, it is more frequently diagnosed than in the past due to increased awareness and availability of genetic testing [3]. Unfortunately, improvements in diagnosis have been not followed by improvements in therapy. Rehabilitation and surgical treatment remain the only option and no pharmacologic disease modifying therapies are available. Confounding progress is the lack of consensus regarding which outcome measures (OMs) are best-suited for clinical trials [4–6].

In most prior trials, the second version of CMTNS (CMTNSv2) has been used as primary OM. This scale was modified from its initial version [7] in order to be more standardized and sensitive to change [8]. The first aim has been reached, but CMTNSv2 may not possess the sensitivity to detect changes due to interventions within clinical trials, although its items have been modified to avoid ceiling and floor effects [8,9]. Typical CMT worsens slowly, ranging from 0.17 to 0.68 point/year on the CMTNS [4,10,11]. This slow progression over time makes difficult to design appropriate OMs that can detect minimal change.

Past trials have investigated the possible therapeutical efficacy of ascorbic acid in CMT [12–15]. All failed to find an effect, and the authors hypothesized that suboptimal OMs may have led to negative results. A recent trial, in which the use of PXT3003 (a fixed-dose combination of baclofen, naltrexone, and sorbitol) was tested [16], demonstrated that the drug is safe and well tolerated, although its efficacy was reevaluated as "slight" improvement in the erratum [17].

A recent study conducted by Lencioni et al. [18] explored gait analysis as a sensitive-to-change outcome measure in CMT. Based upon their results, the authors concluded that biomechanical parameters of gait analysis could represent a useful OM for CMT patients showing moderate-to-high responsiveness.

To forward clinical research in CMT, it is necessary to examine novel OMs able to detect minimal changes. We previously published a study in which two OMs were validated in a large sample of CMT patients: the 6-minute walk test (6MWT) and StepWatch^{TM} Activity Monitor (SAM) [19].

In order to validate them in CMT patients, they were compared with all the other commonly used OMs in CMT trials. Both OMs correlated with commonly used OMs in CMT and, moreover SAM demonstrated capability to identify information on walking that was more related to quality of life (QoL) than the other OMs.

In the current study, we aim to collect longitudinal data of those OMs in order to establish their sensitivity to change in CMT over 12 months.

2. Material and methods

To determine the sensitivity to clinical change, this 12-month longitudinal, prospective multicenter study was conducted by repeat administration of the 6MWT and SAM to CMT patients evaluated in Italian CMT specialty centers. We repeated the evaluation performed at baseline (Ref. [19], see for details).

2.1. Patients

Local Ethics Committee approval was obtained from all involved centers. All patients provided written informed consent. All patients received routine, standard of care treatment in regards to orthotics and/or surgical interventions. Where applicable, details on the use of orthotics have been collected.

Inclusion criteria were as follows: (1) clinical diagnosis of CMT; (2) genetic confirmation of CMT1A (presence of the 17p11.2 duplication); CMT1B (presence of MPZ gene point mutation); CMTX (presence of GJB1/Cx32 gene mutation); (3) age 18–75 years; (4) unaided ambulation for at least 75 m at 6MWT, wearing orthoses if needed; (5) completion of the OMs; (6) absence of another significant illness at the time of assessment (assessments have been rescheduled for a later date in the event of any inter current illness that could have affect performance); (7) if on any treatment or supplements, the dose must have remained constant for the 60 days prior to entering the study; (8) signed informed patient consent.

Exclusion criteria were any of the following: (1) limb surgery in the six months prior to screening (or planned before final assessment); (2) presence of concomitant severe chronic illness that could significantly impair motor performance (e.g. severe cardiac impairment).

2.2. Outcome measures

The 6MWT was performed according to the guidelines provided by the American Thoracic Society [20].

The SAM is a small, lightweight, unobtrusive accelerometer, worn at the ankle and used to measure frequency, duration, and intensity of activity in adults and children [21]. The recording time was 5 days and patients were instructed remove it only for sleeping at night and showering.

SAM step data were analyzed using manufacturer's software according to proprietary algorithms. SAM monitoring was continuous for 5 days including non-wear-time, which registered as zero-step counts. Thus the "minutes none" output from the SAM included both inactivity and non-wear time.

The SAM calculates several outputs (Ref. [19], see for details) and in the previous study we excluded 5 outputs from the statistical analysis. *Step Total and Average Step Total* were excluded because these are influenced by lifestyle. *Step Included, Average Step Include and, Minutes Included* were not analyzed because they are utilized to check the recording

Table 1
StepWatch™ Activity Monitor outputs.

Variable	Description
Minutes none [min]	Total minutes of the time included for analysis in which no steps were recorded
Minutes low [min]	Total minutes of the time included for analysis in which the step count fell between and inclusive of 1 and the limit set in preference Low Activity
Minutes medium [min]	Total minutes of the time included for analysis in which the step count fell between and inclusive of the Low Activity limit +1 and the limit set in preference Medium Activity
Minutes high [min]	Total minutes of the time included for analysis in which the step count was greater than the Medium Activity limit set preferences
Average minutes at none, low, medium and high activity [%]	Percentage time spent at each activity level during the included time relative to the total included time. The percentages are calculated using the total minutes accumulated at each level divided by the total included minutes for all days
Steps low [step]	Total steps accumulated during the time included for analysis at step counts between and inclusive of 1 and the limit set in preferences for Low Activity
Steps medium [step]	Total steps accumulated during the time included for analysis at step counts between and inclusive of the Low Activity limit +1 and the limit set in preference for Medium Activity
Steps high [step]	Total steps accumulated during the time included for analysis at step counts greater than the Medium Activity limit set in preferences
Sustained activity measures: max 1, max 5, max 20, max 30, max 60 [step/min]	Each of these measures is derived by scanning the included time of a day with a "window" of the designated width (1, 5, 20, 30 or 60 min) and extracting the maximum number of steps achieved at any continuous interval of that duration. The maximum is then divided by the duration of the interval to give the average steps per minute of that best performance
Activity index [step/min]	The activity index represents the average step rate of the highest 30 min of the included time in a day, regardless of when they occurred. This differs from the Sustained Activity Measures that represent continuous blocks of time
Average steps at low, medium and high activity [step/min]	Average steps per day accumulated at each activity level for all included time

time. These 5 outputs were not taken into consideration for baseline or follow up analysis (see Table 1 for SAM outputs descriptions).

Those two tools were compared with the standard, commonly used OMs, specifically:

1. CMT-Neuropathy Score second version (CMTNSv2) [8];
2. 10-meter timed walking (10MWT) [5];
3. The maximal voluntary isometric contraction (MVIC) [5] of distal muscle groups by hand-held myometry (Cit Technics, Groningen, The Netherlands) for handgrip and three point pinch, foot dorsiflexion/plantar flexion;
4. Medical Research Council (MRC) [22] to measure strength of proximal and distal muscles of upper and lower limbs, as follows: arm abduction, elbow flexion, wrist extension, extensor digitorum, abductor pollicis brevis, first dorsal interosseous; hip flexion, knee flexion and extension, foot dorsiflexion and plantar flexion, extensor hallucis longus;
5. 36 item Short Form questionnaire (SF-36) [23,24] to assess Health-related QoL, and Visual Analogue Scale (VAS) [25] for pain.

2.3. Statistical analysis

Descriptive analysis was performed through calculation means and standard deviation (SD). Kolmogorov–Smirnov test with Lilliefors correction and Shapiro–Wilk test were used to assess distribution.

On the basis of data features and distribution, we have used parametric (*t*-test for dependent samples) or non-parametric (Wilcoxon matched paired test) tests. The type of test used is indicated in Tables 2–5. Furthermore, we have calculated the changes from baseline for 6MWT, SAM parameters, CMTNSv2 (total) and myometry parameters. The calculation was performed using the following formula: $\frac{T1\ value - T0\ value}{T0\ value} * 100$. We have correlated the results of the changes from baseline using the Spearman correlation test.

Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the STAT-SOFT (Oklahoma, USA) package and the Statistical Package for Social Science (SPSS) 12.0 (Chicago, USA).

Table 2
Responsiveness of Charcot–Marie–Tooth Neuropathy Score version 2 (CMTNSv2), 10 meter walking test (10MWT), Visual Analogue Scale (VAS) and 36 item Short Form questionnaire composite score (SF-36) in the whole sample at baseline and after 12 months of follow up. Wilcoxon matched paired test was used for the all variables. Statistical significance has been set at $p < 0.05$.

Scale	*N*	Mean (SD)			*P* level
		Baseline		12 months	
CMTNS	100	13.3 (5.2)		13.9 (5.2)	<0.001
10MWT	145	10.5 (4.6)	8.6	10.8 (4.6)	0.21
VAS	80	2.6 (3.0)		2.4 (2.8)	0.22
SF-36 physical composite score	138	41.5 (11.3)		40.4 (11.2)	0.28
SF-36 mental composite score	138	43.6 (9.9)		44.2 (9.8)	0.86

Abbreviations: Charcot–Marie–Tooth Neuropathy Score version 2: CMTNSv2, 10 meter walking test: 10MWT, Visual Analogue Scale: VAS and 36 item Short Form questionnaire composite score: SF-36.

Table 3
Responsiveness of StepWatch™ Activity Monitor outputs, 6 Minute Walking Test, hand and foot myometry in the whole sample at baseline and after 12 months of follow up. All participants who wore the SAM yielded 5 complete days of data and SAM data are therefore presented in minutes of activity or total step count per 5 days. Wilcoxon matched paired test was used for the all variables except for SAM Max 5 (Avg), which was assessed through *t*-test for dependent sample. Statistical significance has been set at $p < 0.05$.

	N	Mean (SD)			*P* level
		Baseline		12 months	
SAM minutes at low$^{(Avg\ min)}$	135	21.7 (11.4)		17.9 (6.7)	**<0.001**
SAM minutes at moderate$^{(Avg\ min)}$	135	8.1 (3.3)		7.4 (3.6)	**<0.01**
SAM minutes at high$^{(Avg\ min)}$	135	1.7 (1.4)	8.6	1.5 (1.4)	**<0.05**
SAM step low$^{(Avg\ step)}$	135	1837.0 (598.2)		1674.7 (704.0)	**<0.01**
SAM step moderate$^{(Avg\ step)}$	135	2741.9 (1129.7)		2501.6 (1216.7)	**<0.05**
SAM step high$^{(Avg\ step)}$	135	1203.3 (1003.6)		1059.1 (1012.1)	**<0.05**
SAM peak activity index$^{(Avg\ step/min)}$	135	42.4 (8.7)		40.2 (11.7)	**<0.01**
SAM max 60$^{(Avg\ step/min)}$	133	19.6 (8.4)		19.2 (9.2)	0.40
SAM max 30 $^{(Avg\ step/min)}$	134	27.6 (9.8)		27.9 (9.7)	0.39
SAM max 20$^{(Avg\ step/min)}$	134	29.3 (10.2)		28.1 (11.0)	0.09
SAM max 5$^{(Avg\ step/min)}$	135	43.7 (9.9)		41.1 (12.0)	**<0.001**
SAM max 1$^{(Avg\ step/min)}$	135	55.8 (8.4)		53.5 (13.1)	**<0.05**
6MWT	149	393.1 (93.0)		393.0 (98.1)	0.71
Myometry measure	*N*	Mean (SD)			*P* level
		Baseline		12 months	
Handgrip preferred side	140	74.1 (33.2)		66.1 (31.5)	**<0.001**
Handgrip other side	138	71.4 (32.9)	8.6	64.0 (30.1)	**<0.001**
Large three-point pinch preferred side	140	60.9 (29.9)		56.4 (31.0)	**<0.05**
Large three-point pinch other side	136	58.3 (29.2)		54.9 (29.1)	**<0.01**
Foot plantar flexion preferred side	136	103.7 (71.1)		99.2 (71.0)	**<0.001**
Foot plantar flexion other side	120	103.4 (71.8)		101.6 (71.7)	**<0.01**
Foot dorsiflexion preferred side	130	63.3 (47.3)		60.8 (45.1)	**<0.05**
Foot dorsiflexion other side	115	65.0 (54.3)		61.9 (48.5)	**<0.05**

Abbreviations: SAM: StepWatchTM Activity Monitor; 6MWT: 6 Minute Walking Test; Avg: average; SD: standard deviation; *N*: number; Avg min: average of minutes; Avg step: average of steps; Avg step/min: average of steps/minutes.

We have performed a power calculation for dependent samples and Alpha was set at 0.05. Concerning the SAM parameters, a priori sample calculation was performed considering the value of the current study.

3. Results

One-hundred-forty-nine out of 169 initially enrolled patients ($n = 89$ with CMT1A, $n = 25$ with CMT1B, $n = 35$ with X-linked CMT) were re-evaluated 12 months after baseline testing. The mean age of the cohort, at follow up evaluation, was 42.5 years (range: 18–70, SD: 12.5; 51% female, 49% male) with normal distribution.

One output of SAM, "Minutes None" represents time in which no steps were recorded (see Table 1). This includes sleeping and waking hours. It has been analyzed in order to compare if the minutes included in analysis were similar between baseline and 12 month measurements. We found that the mean percentage of "Minutes None" were similar between baseline and follow up (respectively, 69% and 70%).

Statistical analysis showed a worsening of clinical function as detected by CMT-NS ($p < 0.05$) (Table 2) and of motor function as detected by MVIC of distal muscle groups by hand-held myometry both in the upper and lower limbs (see Table 3). Conversely, the 10MWT, SF-36 and VAS were unchanged over 12 months ($p > 0.05$) (Table 2). Concerning the novel OMs, we found that 6MWT showed no worsening ($p > 0.05$) (Table 3), while several SAM outputs demonstrated worsening ($p < 0.05$) (Table 3).

Moreover, we divided the whole sample into the three differing genetic patterns and we observed a lower number of OMs with significant changes between baseline and follow up but interesting SAM outputs remain the only parameter able to detect the worsening (Tables 4 and 5). The severity of clinical picture of sample, recruited in the different centers, was similar.

The performed correlation shows few significant results, summarized in Table 6.

The sample size calculation was based on the change score of SAM Minutes at Low (showing $p < 0.001$), yielding 90% power for future studies including 56 participants.

4. Discussion

In conditions like CMT, where disease progression is very slow, it is essential to adopt OMs that are highly sensitive to small changes. The results of the current study confirm that CMT patients worsen over a 12-month period, as demonstrated by change in the CMTNSv2 and MVIC of upper and lower limbs. This worsening, due to the natural

Table 4
Responsiveness of Charcot–Marie–Tooth Neuropathy Score version 2 (CMTNSv2), 10 meter walking test (10MWT), Visual Analogue Scale (VAS) and 36 item Short Form questionnaire composite score (SF-36) in the CMT1A, 1B and X subgroup at baseline and after 12 months of follow up. Wilcoxon matched paired test was used for the all variables. Statistical significance has been set at $p < 0.05$.

CMT1A subgroup

Scale	Mean (SD)		*P* level
	Baseline	12 months	
CMTNSv2	14.2 (4.89)	14.3 (5.0)	0.14
10MWT	10.0 (4.0)	10.6 (4.1)	0.12
VAS	2.7 (3.0)	2.4 (2.8)	0.59
SF-36 physical composite score	40.8 (10.9)	40.4 (11.2)	0.26
SF-36 mental composite score	42.5 (10.1)	44.2 (9.8)	0.58

CMT1B subgroup

Scale	Mean (SD)		*P* level
	Baseline	12 months	
CMTNSv2	13.1 (5.7)	13.92 (5.7)	0.07
10MWT	12.6 (6.8)	12.7 (6.7)	0.49
VAS	3.7 (3.5)	2.5 (3.1)	0.80
SF-36 physical composite score	39.88 (13.8)	39.0 (12.1)	0.14
SF-36 mental composite score	44.6 (9.5)	43.3 (10.2)	0.17

CMTX subgroup

Scale	Mean (SD)		*P* level
	Baseline	12 months	
CMTNSv2	13.0 (6)	13.6 (6)	0.10
10MWT	11.4 (5.0)	11.1 (5.1)	0.36
VAS	2.7 (3.3)	2.1 (2.7)	0.08
SF-36 physical composite score	38.5 (12.2)	38.9 (10.9)	0.46
SF-36 mental composite score	44.0 (10.0)	42.5 (10.3)	0.50

Abbreviations: Charcot–Marie–Tooth Neuropathy Score version 2: CMTNSv2, 10 meter walking test: 10MWT, Visual Analogue Scale: VAS and 36 item short form questionnaire composite score: SF-36.

Table 5
Responsiveness of StepWatch™ Activity Monitor outputs, 6 Minute Walking Test and myometer in the CMT 1 A, 1 B and CMT X subgroups at baseline and after 12 months of follow up. Wilcoxon matched paired test was used for the all variables except for SAM Max 5 $^{(Avg)}$, which was assessed through *t*-test for dependent sample. Statistical significance has been set at $p < 0.05$.

CMT1A

	P level
SAM minutes at low$^{(Avg\ min)}$	**<0.001**
SAM minutes at moderate$^{(Avg\ min)}$	**<0.01**
SAM minutes at high$^{(Avg\ min)}$	**<0.01**
SAM step low$^{(Avg\ step)}$	0.42
SAM step moderate$^{(Avg\ step)}$	**<0.05**
SAM step high$^{(Avg\ step)}$	**<0.05**
SAM peak activity index$^{(Avg\ step/min)}$	**<0.01**
SAM max 60$^{(Avg\ step/min)}$	0.65
SAM max 30$^{(Avg\ step/min)}$	0.52
SAM max 20$^{(Avg\ step/min)}$	0.12
SAM max 5$^{(Avg\ step/min)}$	**<0.01**
SAM max 1$^{(Avg\ step/min)}$	**<0.05**
6MWT	0.48

Table 5 (*continued*)

Myometry measure	***P level***
Handgrip preferred side	**<0.001**
Handgrip other side	**<0.001**
Large three-point pinch preferred side	**<0.001**
Large Three-point pinch other side	**<0.01**
Foot plantar flexion preferred side	**<0.001**
Foot plantar flexion other side	**<0.01**
Foot dorsiflexion preferred side	**<0.01**
Foot dorsiflexion other side	**<0.05**

CMT1B

	P level
SAM minutes at low$^{(Avg\ min)}$	**<0.01**
SAM minutes at moderate$^{(Avg\ min)}$	**<0.01**
SAM minutes at high$^{(Avg\ min)}$	0.64
SAM step low$^{(Avg\ step)}$	**<0.01**
SAM step moderate$^{(Avg\ tep)}$	0.24
SAM step high$^{(Avg\ step)}$	0.58
SAM peak activity index$^{(Avg)}$	0.96
SAM max 60$^{(Avg\ step/min)}$	0.36
SAM max 30$^{(Avg\ step/min)}$	0.27
SAM max 20$^{(Avg\ step/min)}$	0.69
SAM max 5$^{(Avg\ step/min)}$	0.32
SAM max 1$^{(Avg\ step/min)}$	0.68
6MWT	0.63

Myometry measure	*P* level
Handgrip preferred side	0.18
Handgrip other side	0.59
Large three-point pinch preferred side	0.48
Large three-point pinch other side	0.42
Foot plantar flexion preferred side	0.99
Foot plantar flexion other side	0.57
Foot dorsiflexion preferred side	0.43
Foot dorsiflexion other side	0.10

CMTX

	P level
SAM minutes at low$^{(Avg\ min)}$	**<0.001**
SAM minutes at moderate$^{(Avg\ min)}$	0.40
SAM minutes at high$^{(Avg\ min)}$	0.07
SAM step low$^{(Avg\ step)}$	**<0.01**
SAM step moderate$^{(Avg\ step)}$	0.64
SAM step high$^{(Avg\ step)}$	0.09
SAM peak activity index$^{(Avg\ step/min)}$	0.08
SAM max 60$^{(Avg\ step/min)}$	0.18
SAM max 30$^{(Avg\ step/min)}$	0.20
SAM max 20$^{(Avg\ step/min)}$	0.16
SAM max 5$^{(Avg\ step/min)}$	**<0.05**
SAM max 1$^{(Avg\ step/min)}$	0.08
6MWT	0.34

Myometry measure	*P* level
Handgrip preferred side	**<0.001**
Handgrip other side	**<0.01**
Large three-point pinch preferred side	0.13
Large Three-point pinch other side	0.07
Foot plantar flexion preferred side	0.12
Foot plantar flexion other side	0.39
Foot dorsiflexion preferred side	0.37
Foot dorsiflexion other side	0.53

Abbreviations: SAM: StepWatchTM Activity Monitor; 6MWT: 6 Minute Walking Test; Avg: average; SD: standard deviation; *N*: number; Avg min: average of minutes; Avg step: average of steps; Avg step/min: average of steps/minutes.

Table 6
Significant correlation (Spearman *R* test) between changes from baseline of the used outcome measures.

Correlations	*r*	*p*
CMTNSv2/6MWT	−0.23	0.02
Handgrip preferred side/6MWT	0.21	0.01
Foot plantar flexion preferred side/SAM max $1^{(Avg)}$	0.22	0.02
Foot plantar flexion other side/SAM max $1^{(Avg)}$	0.24	0.01
Foot plantar flexion other side/SAM minutes at $high^{(Avg)}$	0.25	0.01
Foot dorsiflexion other side/6MWT	0.22	0.02

Abbreviation: Charcot–Marie–Tooth Neuropathy Score version 2: CMTNSv2; 6MWT: 6 Minute Walking Test; SAM: StepWatchTM Activity Monitor; Avg: average.

course of disease and detected by CMTNSv2 has been already described [11,26], and it seems that this OM is more useful in detecting changes due to natural history instead of those due to a presumed therapeutic effect, so that it is recommended as a functional outcome measure in phase 3 trials [6].

Concerning the evaluation of muscular strength, MVIC detected changes over time better than MRC [4]. A similar finding was observed in a study examining the effect of physical therapy on balance [27]. This capability could depend on the fact that MVIC measures the strength by using a dynamometer that could be more sensitive with respect to MRC to detect clinical changes, although also MVIC could be influenced by floor effect especially for those patients with a high level of weakness, or for those who underwent surgery. However, results from pharmacological trials are conflicting. In a study conducted by Micalleef et al. [10], muscular strength measured by myometer did no show a significant change, as the other principal OMs used. In another pharmacological study, this measure seemed to show a trend toward improvement despite evidence of a training effect [16]. Nevertheless, we recommend its use as OM in trials. The previous results confirm existing data, but the continuous need to look at other OMs is due to the fact that the previous used in this pathology failed to show changes when used in pharmacological/rehabilitation trials. Before starting a new therapeutical trial we aimed to test new OMs possibly able to detect changes over time. SAM was previously shown be valid, reliable and correlated Quality of Life scores. This data can guide the physician in designing a tailored rehabilitative approach [19]. The current study now shows that SAM is also able to detect clinical changes in a "natural course" study. In the current sample, SAM demonstrated objective worsening independent of physician and patient impression. This capability may be the result of the multiple numerical outputs generated based upon activity levels in patients' daily lives, reflecting true function in an organic setting. In fact, because of its intrinsic characteristics, SAM can be considered a "dynamic" OM. It is useful in recording the physical activity of the patient throughout a typical day and provides a more accurate representation of function in CMT. An added advantage is that it can be used outside of clinical or research centers. This capability could have a great impact in designing future trials. In an article, de Visser wrote that, "clinical trials are only as credible as their outcomes" [6,28]. This is a crucial point, especially for disorders like CMT, where there is very slow progression and no pharmacological therapy. The capability to detect clinical changes over time was maintained also when the sample has been divided into the three main subgroup while the other OMs failed to do this.

Another result, carried out after performing statistical correlation between changes from baseline of the different OMs, showed that only few of them where significant. Interestingly, the low number of significant correlation findings, although always consistent, showed that each measure is able to assess a specific pattern, hence there is no redundancy among the OMs we used and several OMs are needed to provide a comprehensive evaluation of the patience. This result can make us speculate on the fact that probably it is not possible to find the "perfect" OM for this pathology as different OMs are necessary.

SAM is inexpensive (about 400 euros) is probably affordable for most clinical trials conducted on rare diseases. Importantly, a sample size of 56 subjects is sufficient to reach results in future trials. This number, quite low, is essential for use in a rare disease trial.

Not all of our tested OMs performed well. The 6MWT, whose validity and reliability was already verified [19], failed to show changes over 12 months. This test does not reflect typical daily activity and patients could try to perform the test at their best as they are in presence of an examiner. In a recent trial [16], the 6MWT was used as secondary OM and authors found an improvement of this test, although only in the higher dosage of this drug compared to placebo. Because this OM has been recently introduced in the evaluation of CMT, its meaning needs to be clarified further. What emerges from the literature is that 6MWT is preferable respect to 10MWT [4] to evaluate the deambulation, and, where SAM is not available, we recommend the use of 6MWT to assess walking.

The results of this study also confirm a well-known behavior of CMT patients that is that QoL remains quite stable in spite of a clinical worsening. This has already proved in several studies [26,29] and the evoked mechanism is the capability of CMT patients to adapt to a slow worsening of the clinical condition [30,31]. For these reason a more sensible QoL tool should be used for CMT patients.

Based upon the results of the current study and the previous one [19], SAM should be added as an OM in pharmacological/rehabilitative trials, to evaluate if its "sensitivity to changes" is able also to detect modifications due to therapeutical interventions.

5. Conclusions

In conclusion, the current study confirmed clinical worsening of CMT over 12 months detected by the CMTNSv2, SAM and myometry measures. In spite of this worsening the QoL remained stable, probably because of compensatory strategies. SAM, a novel OM, was sensitive

for detecting worsening in the natural course of CMT, but now requires testing in a clinical therapeutic trial.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.01.009.

References

[1] Pareyson D, Saveri P, Pisciotta C. New developments in Charcot–Marie–Tooth neuropathy and related diseases. Curr Opin Neurol 2017;30:471–80.
[2] Padua L, Coraci D, Lucchetta M, Paolasso I, Pazzaglia C, Granata G, et al. Different nerve ultrasound patterns in Charcot–Marie–Tooth types and hereditary neuropathy with liability to pressure palsies. Muscle Nerve 2018;57:E18–23.
[3] Pareyson D, Scaioli V, Laurà M. Clinical and electrophysiological aspects of Charcot–Marie–Tooth disease. Neuromolecular Med 2006;8:3–22.
[4] Piscosquito G, Reilly MM, Schenone A, Bovi G, Di Sipio E, Diverio M, et al. Responsiveness of clinical outcome measures in Charcot–Marie–Tooth disease. Eur J Neurol 2015;22:1556–63.
[5] Solari A, Laurà M, Salsano E, Radice D, Pareyson D. Reliability of clinical outcome measures in Charcot–Marie–Tooth disease. Neuromuscul Disord 2008;18:19–26.
[6] de Visser M, Verhamme C. Ascorbic acid for treatment in CMT1A: what's next? Lancet Neurol 2011;10:291–3.
[7] Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, et al. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 2005;64:209–14.
[8] Murphy SM, Herrmann DN, McDermott MP, Scherer SS, Shy ME, Reilly MM, et al. Reliability of the CMT neuropathy score (second version) in Charcot–Marie–Tooth disease. J Peripher Nerv Syst 2011;16:191–8.
[9] Reilly MM, Shy ME, Muntoni F, Pareyson D. 168th ENMC international workshop: outcome measures and clinical trials in Charcot–Marie–Tooth disease (CMT). Neuromuscul Disord 2010;20:839–46.
[10] Micallef J, Attarian S, Dubourg O, Gonnaud PM, Hogrel JY, Stojkovic T, et al. Effect of ascorbic acid in patients with Charcot–Marie–Tooth disease type 1A: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2009;8:1103–10.
[11] Verhamme C, van Schaik IN, Koelman JHTM, de Haan RJ, de Visser M. The natural history of Charcot–Marie–Tooth type 1A in adults: a 5-year follow-up study. Brain 2009;132:3252–62.
[12] Verhamme C, de Haan RJ, Vermeulen M, Baas F, de Visser M, van Schaik IN. Oral high dose ascorbic acid treatment for one year in young CMT1A patients: a randomised, double-blind, placebo-controlled phase II trial. BMC Med 2009;7:70.
[13] Burns J, Ouvrier RA, Yiu EM, Joseph PD, Kornberg AJ, Fahey MC, et al. Ascorbic acid for Charcot–Marie–Tooth disease type 1A in children: a randomised, double-blind, placebo-controlled, safety and efficacy trial. Lancet Neurol 2009;8:537–44.
[14] Toth C. Poor tolerability of high dose ascorbic acid in a population of genetically confirmed adult Charcot–Marie–Tooth 1A patients. Acta Neurol Scand 2009;120:134–8.
[15] Pareyson D, Reilly MM, Schenone A, Fabrizi GM, Cavallaro T, Santoro L, et al. Ascorbic acid in Charcot–Marie–Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. Lancet Neurol 2011;10:320–8.
[16] Attarian S, Vallat J-M, Magy L, Funalot B, Gonnaud PM, Lacour A, et al. An exploratory randomised double-blind and placebo controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot–Marie–Tooth disease type 1A. Orphanet J Rare Dis 2014;9:199.
[17] Attarian S, Vallat J-M, Magy L, Funalot B, Gonnaud PM, Lacour A, et al. Erratum to: an exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot–Marie–Tooth disease type 1A. Orphanet J Rare Dis 2016;11:92.
[18] Lencioni T, Piscosquito G, Rabuffetti M, Bovi G, Di Sipio E, Diverio M, et al. Responsiveness of gait analysis parameters in a cohort of 71 CMT subjects. Neuromuscul Disord 2017;27:1029–37.
[19] Padua L, Pazzaglia C, Pareyson D, Schenone A, Aiello A, Fabrizi GM, et al. Novel outcome measures for Charcot–Marie–Tooth disease: validation and reliability of the 6-min walk test and StepWatch(TM) Activity Monitor and identification of the walking features related to higher quality of life. Eur J Neurol 2016;23:1343–50.
[20] ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–17.
[21] Coleman KL, Smith DG, Boone DA, Joseph AW, del Aguila MA. Step activity monitor: long term, continuous recording of ambulatory function. J Rehabil Res Dev 1999;36:8–18.
[22] McCluskey D. Aids to the examination of the peripheral nervous system. In: London: her Majesty's Stationary Office, editor. Ulster Med J 1989;55:201 Memorandum.
[23] Apolone G, Mosconi P. The Italian SF-36 health survey: translation, validation and norming. J Clin Epidemiol 1998;51:1025–36.
[24] Padua L, Shy ME, Aprile I, Cavallaro T, Pareyson D, Quattrone A, et al. Correlation between clinical/neurophysiological findings and quality of life in Charcot–Marie–Tooth type 1A. J Peripher Nerv Syst 2008;13:64–70.
[25] Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983;16:87–101.
[26] Shy ME, Rose MR. Charcot–Marie–Tooth disease impairs quality of life: why? And how do we improve it? Neurology 2005;65:790–1.
[27] Pazzaglia C, Camerota F, Germanotta M, Di Sipio E, Celletti C, Padua L. Efficacy of focal mechanic vibration treatment on balance in Charcot—Marie–Tooth 1A disease: a pilot study. J Neurol 2016;263:1434–41.
[28] Boers M, Tugwell P. OMERACT conference questionnaire results. OMERACT Committee. J Rheumatol 1993;20:552–4.
[29] Padua L, Pareyson D, Aprile I, Cavallaro T, Quattrone A, Rizzuto N, et al. Natural history of CMT1A including QoL: a 2-year prospective study. Neuromuscul Disord 2008;18:199–203.
[30] Padua L, Pareyson D, Aprile I, Cavallaro T, Quattrone DA, Rizzuto N, et al. Natural history of Charcot–Marie–Tooth 2: 2-year follow-up of muscle strength, walking ability and quality of life. Neurol Sci 2010;31:175–8.
[31] Vinci P, Serrao M, Millul A, Deidda A, De Santis F, Capici S, et al. Quality of life in patients with Charcot–Marie–Tooth disease. Neurology 2005;65:922–4.