Performance of activities of daily living in patients with myotonic dystrophy type 1

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Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

ABSTRACT

Objectives: The objective of this cross-sectional, observational study was to investigate performance of activities of daily living in patients with myotonic dystrophy type 1 (DM1).

Materials & Methods: Adults with genetically confirmed late- or adult-onset DM1 were recruited from Newcastle University (Newcastle upon Tyne, UK) and University College London Hospitals NHS Foundation Trust (London, UK) as part of the PhenoDM1 study. Data on activities of daily living was recorded through the DM1-Activ^C (scale scores range between 0 and 100, where a higher/lower score indicates a higher/lower ability).

Results: Our sample comprised 192 patients with DM1 (mean age: 46 years; 51% female). Patients reported most difficulties with running, carrying and putting down heavy objects, and standing on one leg, and least difficulties with eating soup, washing upper body, and taking a shower. Irrespective of the disease duration (mean: 20 years), most patients were able to perform examined basic and instrumental activities of daily living, with the exception of functional mobility/transfer tasks (e.g., walking uphill and running). The mean DM1-Activ^C total score was estimated at 71 (95% CI: 68–74). Estimated progenitor cytosine-thymine-guanine repeat length and age explained 27% of the variance in DM1-Activ^C total scores ($p < 0.001$).

Conclusions: We show that DM1 impairs performance of activities of daily living, in particular those requiring a high degree of muscle strength, stability, and coordination. Yet, across the lifetime of the disease, the majority of patients will still be able to independently perform most basic and instrumental activities of daily living.

Introduction

Myotonic dystrophy type 1 (DM1) is a rare, disabling neuromuscular disorder of varying severity caused by the expansion of the cytosine-thymine-guanine (CTG) triplet repeat in the *DMPK* gene.[1] Longer CTG triplets expansion has been shown to be related to greater disease severity and earlier age at onset. DM1 is the most common muscular dystrophy with an estimated prevalence of 8 per 100,000.[2] Typical manifestations of DM1 include muscle weakness, myotonia, and fatigue, but symptoms are heterogeneous and may also involve other organs and systems, such as the heart and eyes, and the endocrine, gastrointestinal, and central nervous system.

In recent decades, the increased understanding of the underlying molecular pathology of DM1 has enabled the design of new targeted treatments, including antisense oligonucleotides, GSK3β inhibitors, and other pharmacological and genetic treatments.[3] This acceleration in therapy development has resulted in a pressing need to map out the natural history of the disease to inform the design of clinical trial programs, including the selection of appropriate clinical endpoints and tools that are fit for purpose to measure drug benefits.[4,5]

The DM1 activity and participation scale for clinical use (DM1-Activ[C]) is a rating-scale designed to measure self-reported performance of activities of daily living (e.g., brushing teeth, preparing meals, and walking up a flight of stairs) in patients with DM1. The tool was initially developed in 2010,[6] but re-constructed in 2015,[7] and the current version encompasses a total of 25 items, each described in three levels. The DM1-Activ[C] has been tested using modern psychometric analysis (i.e., Rasch analysis[8]) and has been shown to adhere to the epistemological requirements for stable measures.

Since its development, the DM1-Activ[C] has been employed as part of a few studies,[11,12] and the instrument was also included in a recently completed multi-national trial in DM1 (i.e., the OPTIMISTIC trial).[13] However, to date, no study has reported results from the DM1-Activ[C] beyond summary point estimates of mean instrument scores. Accordingly, the objective of this study was to investigate the impact of DM1 on activities of daily living as recorded using the DM1-Activ[C] in patients with DM1 from the UK. A specific aim was to examine if the disease burden varies by sex, disease duration, and several clinical measures and biomarkers of the disease, including estimated progenitor and modal allele CTG repeat length, respectively.

Materials & Methods

Study design and patient sample

This study was based on a sample of patients with DM1 recruited from two sites in the UK (Newcastle University, Newcastle upon Tyne, and University College London Hospitals NHS Foundation Trust, London) as part of the Myotonic Dystrophy Type 1 Deep Phenotyping to Improve Delivery of Personalized Medicine and Assist in the Planning, Design and Recruitment of Clinical Trials (PhenoDM1) study (ClinicalTrials.gov identifier: NCT02831504). To be eligible to participate, all patients were required to meet the following inclusion criteria: (i) ≥18 years of age, (ii) genetically confirmed diagnosis of late- or adult-onset DM1, and (iii) ability to perform the 10 meters walking test at selected pace without any assistance (walking devices allowed). All participants provided informed consent to participate in the study and ethical approval was granted by the Newcastle and North Tyneside Ethics Committee (reference: NE/15/0178).

Study procedures and outcome measures

Eligible patients were asked to complete the DM1-Activ[C] as part of the study visits. We also recorded data from patients concerning their basic demographic and clinical characteristics as shown in Table 1. As outcome measure of functional ability, the 6MWT was included for comparison. The test was performed in a 25-meter long corridor in Newcastle and 20-meter long corridor in London with input every minute per currently agreed procedures.[4]

Genetic analysis

Recent studies have shown that the length of the repeat expansion at birth as expressed by the progenitor allele is the most relevant predictor of disease onset and severity later in life, while

disease progression is closely related to the rate of somatic expansion over time within different tissues (approximated as the difference between modal length at the time of DNA sampling and the progenitor allele, where the modal allele length is the most common repeat length in that tissue at time of sampling). For our analysis, we included both CTG repeat counts from blood DNA (i.e., the estimated progenitor and modal allele length) to allow comparison of data. The genetic analysis was completed using the CTG repeat-flanking primers DM-C and DM-DR.[15,16] Replicate reactions were separated by gel electrophoresis, Southern blotted and hybridised using a ^{32}P-labelled 56 x CTG repeat probe. Bands were detected by autoradiography and sized by comparison against the DNA molecular weight marker, using CLIQS software (TotalLab UK Ltd.). The bottom edge of the expanded allele bands was used to determine the ePAL[16] The densest part of the expanded allele bands was used to estimate the modal allele length at the time of DNA sampling (i.e. CTG modal alleles).

Statistical analysis

We calculated the distribution of replies across all items and levels within the DM1-Activ[C] and the corresponding mean item scores, ranging from 0 ("Not possible to perform") to 2 ("Possible, without any difficulty"), as well as the mean transformed total instrument score (ranging between 0 and 100, where a higher/lower score indicates a higher/lower ability to perform activities of daily living). We related the total score to two previously derived[7] threshold values (amended for the transformed scale): ≤30 (indicating severe limitations in activities of daily living), and >70 (indicating relativity few limitations). We summarized the three most difficult activities (i.e., the items with the lowest mean scores), as well as the three easies activities (i.e., the items with the highest mean scores), in the pooled sample and by patient age (i.e., <30 years vs. ≥30 years, as limitations in activities of daily living, as well as

the DM1-Activ^C scoring algorithm, have been shown to be different for these strata[7]]), respectively. We also calculated the proportion of patients able to perform (with or without help) included activities of daily living (i.e., "Possible, without any difficulty" or "Possible, but with some difficulty" vs. "Not possible to perform"). Moreover, to examine the predictive properties of individual item levels with respect to the mean DM1-Activ^C total score, we derived and presented the mean DM1-Activ^C total score by item levels. We derived the proportion of patients able to perform (with or without help) included activities of daily living by four categories of disease duration (<10 years, 10–20 years, 20–30 years, and ≥30 years, measured from onset) and compared total DM1-Activ^C scores by sex using Welch's t-test. We also estimated Pearson's correlation coefficients to investigate the crude relationship between DM1-Activ^C total scores and disease duration, CTG repeat length, the Muscular Impairment Rating Scale (MIRS) score, and 6MWT result, respectively, and also derived linear trends using the ordinary least squares method. Finally, to further explore the relationship between estimated progenitor CTG repeat length and performance of activities of daily living, we fitted an ordinary least squares regression model to the study data, with the mean DM1-Activ^C total score as the dependent variable and estimated progenitor CTG repeat length and age, as well as an interaction variable between estimated progenitor CTG repeat length and age, as independent variables (with estimated progenitor CTG repeat length normalised by log transformation). All analyses were conducted in Stata 14.

Results

A total of n = 192 adult patients with DM1 met the study inclusion criteria and completed the DM1-Activ^C in accordance with the instructions. Summary descriptive statistics of the sample are presented in Table 1. Mean estimated progenitor and modal allele length, available for n = 104 and n = 102 patients, respectively, was 245 CTG repeats (SD: 178, range: 54–916) and 479 CTG repeats (SD: 346, range: 57–1,441).

The distribution of replies to the DM1-Activ^C are presented in Figure 1, sorted by mean item score (ranging between 0 to 2). Patients were able, although with some difficulty, to perform most activities of daily living captured by the scale. The three most difficult activities (i.e., the items with the lowest mean scores) were "Run" (mean item score: 1.0), "Carry and put down heavy object (10 kg)" (1.1), and "Stand on one leg" (1.2). The three easiest activities were "Eat soup" (1.9), followed by "Wash your upper body" (1.9) and "Take a shower" (1.8). In patients <30 years of age (n = 19), the three most difficult activities were "Carry and put down heavy object (10 kg)" (0.8), "Vacuum clean" (1.3), and "Stand up from squatting position" (1.3), and the three easiest "Eat soup" (1.9) and "Dress your lower body" (1.8), and "Take a shower" (1.8). Results for patients ≥30 years of age (n = 173) were identical to estimates for the total sample.

The mean DM1-Activ^C total score was estimated at 71 (SD: 21, range: 28–100, 95% CI: 68–74). Approximately 1% (2 of 192) scored ≤30 (indicating severe limitations in activities of daily living), and 47% (91 of 192) >70 (indicating relativity few limitations). There were no significant differences between women and men in estimated mean DM1-ActivC total scores (70 vs. 72, p = 0.530).

We found disease duration to be significantly associated with the mean DM1-Activ^C total score (ρ = -0.29, p < 0.001). Specifically, the mean score in patients with a duration of <10 years was estimated at 79 (SD: 22, 95% CI: 71–86, n = 40), between 10 and 20 years at 75 (SD: 19, 95% CI: 70–80, n = 57), between 20 and 30 years at 67 (SD: 21, 95% CI: 60–73, n = 46), and ≥30 years at 62 (SD: 20, 95% CI: 56–69, n = 39). Figure 2 presents the proportion of patients able (with or without difficulties) to perform the activities of daily living exhibiting the largest change across categories of disease duration (i.e., <10 years vs. ≥30 years). Results for additional tasks covered by the scale, exhibiting a mean change across categories of disease duration of <2.10 percentage units, are presented as supplemental material online.

Results from our correlation analysis showed that DM1-Activ^C total score was significantly associated with estimated progenitor CTG repeat length (i.e., the length of the repeat expansion at birth) (ρ = -0.36, p < 0.001), modal allele CTG repeat length (i.e., the length of the repeat expansion at DNA sampling) (ρ = -0.42, p < 0.001), MIRS score (ρ = -0.61, p < 0.001), and 6MWT result (ρ = 0.66, p < 0.001). Scatter plots for these variable-pairs, as well as crude linear trends, are presented in Figure 3. Outcomes from our regression analysis also showed that the estimated progenitor CTG repeat length and age were able to explain 27% of the variance in DM1-Activ^C total scores (R^2 = 0.27, p < 0.001). In total, five patients had CTG repeat interruptions, and their mean DM1-Activ^C total score was 62 (SD: 15, range 48–84, 95% CI: 43–81).

Discussion

The objective of this study was to investigate the impact of DM1 on activities of daily living as recorded using the DM1-Activ^{C}, and investigate the association between impairment and disease duration, genotype, and phenotype. Taken together, our results show that most men and women with DM1 experience some limitations in performance of many common household and leisure tasks (Figure 1). However, our examination of specific activities revealed that only a few were impaired in a progressive pattern from onset. In particular, irrespective of the duration of the disease, the vast majority of patients in our sample were still able to perform examined *basic* activities of daily living (e.g., personal hygiene and grooming, showering, and eating), with the exception of functional mobility/transfers (e.g., walking uphill and running). Most patients (>80% per task) were also able to perform included *instrumental* activities of daily living (e.g., cleaning and shopping), as well as visiting family or friends. In general, across the lifetime of the disease, the activities affected the most were those recognized with major demands of muscle strength, stability, and coordination, for example standing on one leg, carrying and putting down heavy objects, and running. Yet, even after 30 years of onset of symptoms, almost half of our cohort were still able, although with some problems, to perform the most difficult tasks studied (Figure 2).

We found that the easiest tasks included in the DM1-Activ^{C} were "Eat soup", "Wash your upper body", and "Take a shower" ("Wash your upper body" replaced by "Dress your lower body" in patients <30 years of age). These findings are comparable to the ranking of instrument items based on the psychometric Rasch analysis of the tool,[7] which identified "Eat soup", "Visit family or friends", and "Care for your hair and body" as the easiest tasks ("Wash your upper body" and "Take a shower" were ranked the fifth and sixth easiest,

respectively). The ordering of items in terms of difficulty was also similar to the Rasch analysis output, with some exceptions. Specifically, in patients <30 years of age, the most difficult items were "Carry and put down heavy object (10 kg)", "Vacuum clean", and "Stand up from squatting position" in our study, and "Run", "Carry and put down heavy object (10 kg)", and "Walk 3 flights of stairs" in the Rasch analysis. Corresponding results for those ≥30 years of age were "Run", "Carry and put down heavy object (10 kg)", and "Stand on one leg", and "Carry and put down heavy object (10 kg)", "Walk 3 flights of stairs", and "Walk uphill", respectively. It is not possible, based on the data at hand, to further analyze potential reasons for these inconsistencies. However, when comparing our results with the Rasch study, it is important to keep in mind that we only included patients that were able to walk a minimum of 10 meters without the assistance of somebody else and who had the capacity to understand the study information and consent to participating in the study, which means that the most functionally and cognitively impaired patients were not included. Future research should aim to include also patients with lower levels of ability, and also explore changes over time, to further broaden the understanding of the impact of DM1 across the evolution of the disease. In particular, to help inform the design of trials with endpoints defined in terms of the DM1-Activ[C], it would be of interest to examine variability in annual changes in the total score across categories of baseline ability (which may serve as a meaningful criterion for trial inclusion), as well as clinical and genetic measures. Further translation and validation of the DM1-Activ[C] to other cultural settings should also constitute a prioritized topic for future studies of the scale.

The CTG repeat length in the PhenoDM1 patient cohort was found to correlate with DM1-Activ[c] total score, MIRS and the 6MWT. The estimated inherited, or progenitor, allele length was previously shown to be the single largest factor accounting for variation in age at disease

onset, with a further contribution from somatic instability (Morales, 2012). This suggests that repeat length is the most important determinant of the underlying biology of the disease. Since DM1-Activ^c total score, MIRS and the 6MWT correlate with estimated CTG repeat length, they may also capture some aspect of disease mechanism, which suggests they could represent useful outcome measures for clinical trials. These three measures were also found to correlate with estimated progenitor allele length in the baseline data collected from the OPTIMISTIC patient cohort (Cumming, 2019).

Five of the PhenoDM1 cohort tested were found to have AciI-sensitive variant repeat interruptions. These have previously been shown to result in reduced somatic instability and delayed disease onset (Overend, 2019, Cumming 2019). Further, in several different phenotypic measures, individuals with variant repeats scored better (Overend, 2019, Cumming, 2019). This does not appear to be the case in the current study for DM1-Activ^c total score, however the number of identified individuals bearing variant repeats is relatively small. In any future natural history studies or clinical trials, it will be very important to identify any individuals with variant repeat interruptions, as they can profoundly alter symptoms and, potentially, response to therapies.

Comparing our results with previous research based on the DM1-Activ^C, selected outcomes of the scale have been described as part of three recently published studies. DiPaolo et al.[11] reported correlation coefficients between the scale for the assessment and rating of ataxia (SARA) and DM1-Activ^C total scores in a subset of 54 patients (mean age: 48 years; 39% female) from the same sample population as our study. Similar to our findings with respect to the 6MWT, the authors identified a significant relationship between the two measures ($\rho = -0.75$, $p < 0.001$). Moreover, in a study investigating body composition in DM1, Sedehizadeh

et al.[12] estimated the mean DM1-Activ^C total score at 28 (using the first version of the scale[6])

in a sample of 38 patients with DM1 from the UK (mean age: 42 years; 47% female).

However, due to differences in instrument versions, this point estimate is not easily

comparable to our data. Finally, the DM1-Activ^C was the primary outcome measure in the

OPTIMISTIC clinical trial,[13] but no scale data were published except for differences in total

scores between examined interventions.

A number of studies have investigated the impact on DM1 on activities of daily living

quantified using measures other than the DM1-Activ^C. For example, Kierkegaard et al.[17]

studied functioning and disability in a sample of 70 patients with DM1 (mean age: 45 years;

59% female) using the extended Katz Index of Independence in Activities of Daily Living

and the Frenchay activities index (among other measures). In line with our results, although

not directly comparable due to different scales and definitions employed, the authors found

participation restrictions in social and lifestyle activities in 52% of patients and dependence

in personal and instrumental activities of daily living in 16% and 39%, respectively.

Impairment in performance of activities of daily living in DM1 was also reported by Van

Heugten et al.[18] based on data recorded via the Utrecht Scale for Evaluation of

Rehabilitation-Participation in a sample of 66 Dutch patients (mean age: 47 years; 46%

female). In particular, similarly to our data, the authors found most restrictions concerning

sports/leisure activities and activities outside the home environment, but also housekeeping.

Comparable findings were described by Gagnon et al.,[19] who found most impact in the

Recreation, Mobility, and Housing domains (in addition to Employment) based on the

Assessment of Life Habits (LIFE-H) tool in a sample of 158 Canadian adults with DM1

(mean age: 44 years; 61% female).

In our sample, the crude mean DM1-Activ^C total score was similar for women and men with the disease. In contrast, previous research has indicated that men are subject to greater morbidity, including more severe muscular disability and cognitive impairment, and higher mortality. In our previous research, we found that that a larger proportion of women with DM1 experienced considerable fatigue and depressive feelings; however, there was no difference between sexes with respect to the overall disease burden. Based on our data, it not possible to further analyze potential sources for these inconsistent findings, but future studies of these topics are warranted.

A limitation of our study concerns the precision and external validity of our results due to the relatively small sample size (although it should be noted that our sample was fairly large in the context of outcomes research in DM1[20]). It is also worth noting that we interpreted limitations in activities of daily living in relation to full ability, despite the fact that a non-trivial proportion of members of the general population also experience some impairment. Additionally, the DM1-Activ^C data may be subject to bias due to, for example, incorrect reporting. However, the inclusion criteria of this study filtered patients with congenital phenotype and/or those with significant cognition impairments, whom would be expected to increase the risk of these type of errors. Finally, it should be noted that it is always theoretically possible that an association between two variables detected in observational research is spurious in the sense that the association does not represent a causal effect of one of the variables on the other.[21] Consequently, we were unable to infer causality when interpreting results from our statistical analyses.

In conclusion, we show that DM1 impairs performance of activities of daily living, in particular those requiring a high degree of muscle strength, stability, and coordination. Yet,

across the lifetime of the disease, the majority of patients will still be able to perform most basic and instrumental activities of daily living.

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Tables

Table 1: Demographic and clinical characteristics of the patient sample

Age, mean (SD) years	46 (13)
Sex, female	97 (51%)
Age at first symptoms, mean (SD) years*	26 (16)
Disease duration, mean (SD) years**	20 (12)
Part-time wheelchair dependency	25 (13%)
Six-minute walk test result, mean (SD) meters***	418 (154)
Muscular Impairment Rating Scale (MIRS) score	
I	21 (11%)
II	55 (29%)
III	41 (21%)
IV	57 (30%)
V	18 (9%)
Education, mean (SD) years completed****	15 (3)
Current occupation	
Employed	79 (41%)
Retired	26 (14%)
Long-term sick leave	45 (23%)
Unemployed/other	42 (22%)

Note: Data presented as n (%), if not specified otherwise. Total sample: n = 192, excluding missing values for n = 9 patients (*), n = 10 patients (**), n = 8 patients (***), and n = 5 patients (****).

Figure Captions

Figure 1: Distribution of replies to the DM1-Activ^C items

Figure 2: Proportion of patients able to perform selected activities of daily living, by disease duration

Figure 3: Association between 6MWT result, MIRS score, CTG repeat size, and DM1-Activ^C total score