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Major involvement of trunk muscles in myotonic dystrophy type 1

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Objectives – The motor impairments in Myotonic Dystrophy 1 (DM1) are assumed to progress from distal toward proximal parts of the extremities in the Juvenile and Adult forms of DM1. On occasion and late in progress spine deformity is observed. In this study we have examined whether and to what extent trunk muscles are impaired in DM1, and if this impairment is correlated with the duration of the disorder, walking capacity, mobility, balance, and CTG-repeats. *Materials & methods* – Manual muscle testing (MMT) of skeletal muscle strength in trunk and extremities, reassessment of the mutation size, time since first symptom, the 6 min walk test (6MWT), Rivermead mobility index (RIM) and Timed up & go (TUG) were sampled in 38 adult DM1 outpatients. *Results* – We found significant impairment in trunk muscles. Trunk muscle strength decreased significantly with increasing mutation size ($r = -0.64$, $P < 0.001$). Reduced walking capacity, mobility and balance were significantly related to decreased trunk muscle strength. *Conclusion* – DM1 affects trunk muscle groups. The trunk impairments seem to occur relatively early in disease progression. Awareness of trunk impairments may be of importance for everyday functioning and for understanding the risk of injuries due to falls reported among DM1 patients. It may also help in identification of DM1 patients and considered outcome measure in future clinical trials.

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Introduction

Myotonic Dystrophy 1 (DM1) is a progressive autosomal dominantly inherited multisystem disorder caused by a CTG nucleotide repeat expansion in the Myotonic dystrophy protein kinase (DMPK) gene in chromosome 19 (1–3). It is one of the most prevalent neuromuscular disorders affecting about 1 in 8000 (2). The motor impairment in DM1 is documented to progress from the distal to the proximal part of the extremities. Early involvement of the face and anterior neck muscles are also common (2, 4–7).

Spine deformity and general weakness in Juvenile and Adult forms of DM1 are anecdotally reported to occur late in DM1 progression (4), but no systematic investigation of strength in trunk muscles are documented. The disease specific motor impairment scale (MIRS) (5) which is recommended in the Scandinavian reference program for DM1 does not include assessment of trunk muscles (8). The research team has observed that DM1 patients frequently display abnormal alignments and decreased movements in the trunk during walking, indicating muscular impairment in this part of the body. These clinical findings led us to systematically assess strength in trunk flexor muscles and back extensors. The need for systematic evaluation of trunk muscle strength is underscored by pathological (replacement of muscle by connective tissue and fat) MRI findings in m. Rectus abdominis and m. Erector spinae muscles in a small DM1 sample (9). Strength in trunk muscles is of importance for everyday life through its stabilizing role in mobility and balance (10). A Swedish study of balance and falls leading to injury in DM1 patients highlights the importance of several tests for information about different aspects of postural control in DM1 (11).

The aim of this study was to detect whether and to what extent trunk muscle groups are impaired in DM1 patients and to investigate the progression of muscular impairment in these patients by relating muscle strength to disease duration. Furthermore, we wanted to examine whether strength in the various muscle groups is correlated with the number of CTG repeats and walking capacity, mobility and balance measured by the 6MWT, Rivermead mobility index (RMI) and Timed up and go (TUG).

Material and methods

Standard protocol approvals, registrations, and patient consent

All included patients gave their written informed consent to participate and the study was approved by the Ethic committee of Norwegian Health authorities, region South East.

Participants

All patients above the age of 15 with a genetically confirmed diagnosis of DM1 and referred to the Department of Habilitation at Drammen hospital between 2012 and 2014 were asked to participate in the study. Among these, 23 of the patients were referred from local neurologists for regular follow-ups, seven patients were recruited for this study through Oslo University Hospital and eight through the patient organization. The congenital form of DM1 was excluded because of the different clinical characteristics compared to the other (4). Two patients declined to participate, 38 patients were thus included.

Study design

The present study has a clinical observational design combining data from interdisciplinary clinical examinations, standardized assessment tools and new measures of the CTG expansion. Information about time of first DM1 symptom is based on retrospection. Evaluation of progression of disease is done by cross-sectional analysis.

Procedure

An experienced neurologist performed the examinations according to a standardized clinical protocol, allowing collection of neurological history and neurological examination and information about current medication. The measures of strength and function were performed by an experienced physical therapist with 13% (all muscle groups in 5 of 38 participants) scored independently by another experienced tester and full inter-rater agreement was achieved.

Measures

Age at onset – Determined by questioning the patients about age at onset of at least one of the following well-known DM1 symptoms and signs: difficulty in walking or running, fine motor problems, difficulties loosing grip, swallowing difficulties, decreased strength, stiffness, cataract, arrhythmia or episodes of apnea (12).

DM1 subgroup – DM1 subgroup was determined by age at onset; Childhood form: onset between 1 and 10 years, Juvenile form 11 to 18 years, Classic adult form: 19 to 39 years and Mild adult form: first symptoms after the age of 40.

Disease duration – Defined by difference between age at onset and age at the time of examination. Four disease duration groups were defined based on the distribution of disease duration in our sample with the principal aim of as equal group sizes as possible: Group 1: <11 years ($n = 10$), group 2: 11–17 ($n = 10$), group 3: 18–27 ($n = 10$) years and group 4: more than 27 years ($n = 8$).

CTG expansion – All participants were previously genetically confirmed DM1 patients. Expansion size reassessment was done using Southern Blot analysis of lymphocytes in order to have information about mutation size at the time of clinical examination.

Skeletal muscle strength – Muscle strength was assessed with the standardized MRC 0–5 scale for MMT (13). This procedure has been used in previous studies of muscle strength in trunk muscles groups in neuromuscular diseases (14). MMT is chosen over Quantitative Muscle Test (QMT) in this study since the MMT is an easy and inexpensive way of measuring trunk-muscle strength in the clinic. MMT is an accepted method and has been found reliable for evaluating muscle strength (13, 15, 16). It has been criticized for its unequal width of its response options, providing only ordinal data, and for physicians inability to discriminate between the categories, especially grade 4 and 2 (17–19). To counteract these limitations, the MRC 0–5 scale was rescored to a modified 0–3 scale according to Vanhoutte et al. (19). By Rasch modeling of strength measure data from 1065 patients with different neuromuscular disorders (including DM1), Vanhoutte et al. (19)

documented reliability, and restored thresholds enabling the modified 0–3 scale to be analysed as an interval scale. All muscle groups tested in our study, including the trunk flexors and the back extensors, were included in the Vanhoutte study (Table 1).

Test positions were used according to standard MMT (20). Joint mobility, muscle length, and pain that could influence strength assessment were controlled for. Strength was measured twice with a 3 min interval, reporting the mean of the two. The 11 muscle groups in the DM1-specific MIRS were tested, except for the plantar flexion of the ankle and finger flexors (5). The plantar flexion of the ankle is known to be less affected than the dorsal flexion, therefore this test was excluded due to risk of exhaustion (6). Grip strength is not suitable to measure with MMT (20). Our dynamometer-data on grip strength is thus not included in this report for simplicity purposes. The following muscles were measured: In the upper limb, three proximal muscle groups (shoulder abductors, elbow flexors, elbow extensors) and one distal group (wrist extensors). In the lower limb, three proximal groups (hip flexors, knee flexors, knee extensors) and one distal group (foot dorsal flexors) were tested. Due to reported symmetry in DM1 (6) and to prevent exhaustion, only the dominant side was tested. In addition, the anterior trunk flexors and the back extensors were tested. For grading of muscle strength of the trunk the patient's arms were placed in different positions offering various levels of resistance, as described in Table 2; See also Kendall (20) for further details. To measure strength in trunk flexion in a safe manner, the examiner stabilized the head and neck during curl up for participants with neck flexion score below MRC grade 3. Details about grading are presented in Table 2.

Table 1 Recoding the Medical research council MMT score; from six-point to modified 0–3 scale

Six-point ordinal scale	0–3 interval scale
0 = No muscle contraction	0 = Paralysis
1 = Flicker or trace of muscle contraction	1 = Severe weakness defined as >50% loss of strength
2 = Active movement with gravity eliminated	
3 = Reduced power but active movement against gravity	2 = Slight weakness <50% loss of strength
4 = Reduced power but active movement against gravity and resistance	
5 = Normal power against full resistance	3 = Normal strength

Walking capacity – Walking capacity was measured by using the 6MWT according to the American Thoracic Society (ATS) guidelines on a track in a corridor (21), one exception being the track distance, which in this trial was 20 instead of 30 m. The 6MWT is found feasible and reliable as a measure for walking capacity in DM 1 (22).

Timed up & go – Timed Up & Go (23) is used for evaluation of mobility and balance. The time used to rise up from a chair with armrest (0.45 m high), walk three meters, turn, walk back and sit down, was recorded. The patients were instructed to walk in a safe manner. The procedure was done twice, and the second test was recorded. Acceptable test–retest stability are documented in DM1 patients (24).

Rivermead mobility index – Rivermead mobility index (25) was used to evaluate overall mobility. This 15 item scale comprises items ranging from the ability to turn in bed to the ability to run. The scale is considered valid and reliable in various populations (26–28), and is recommended for use in DM1 (27).

Table 2 Grading of muscle strength in trunk

Muscles	Test position	Fixation	Movement	Resistance	Grades
Trunk flexors	Supine, legs straight	At feet after trunk curl	Full trunk curl, then sit up	Arms behind neck	5
				Arms folded over chest	4
				Arms along the body	3
		None	Posterior tilt pelvic	Arms along the body	2
Back extensors	Prone	On tights or hips*	Full extension of the spine	Behind neck	5
				Arms along the body, and by examiner†	4
				Arms along the body	3
			Extension of the spine	Arms along the body	2

*When hip extensors are impaired, fixation on hips.
†Resistance by examiner: Hand placed mid back, exerts pressure.

Body mass index – Height and weight was measured and BMI was calculated for each patient.

Wechsler abbreviated scale of intelligence – Wechsler Abbreviated Scale of Intelligence was used for assessment of general cognitive level (IQ).

Data analyses

Since the modified 0–3 scale is documented to have properties of an interval scale (11), parametric statistics are used for all analyses of muscle strength. Data are presented with mean, range, percent and standard deviation. Pearson's r is used for correlation. Two-tailed P values < 0.05 were deemed statistically significant and are reported for the correlations; exact P values are reported unless $P < 0.001$. Group differences are analysed by Independent sample t-tests; mean difference, confidence interval [CI], degrees of freedom (df) and exact P values are reported for the t-test. Inter-item reliability of constructed sums are calculated with Cronbach's alpha. All analyses were conducted in IBM SPSS v. 21.

Results

Participants

Thirty eight genetically confirmed DM1 patients were recruited, 21 men and 17 women. 21 fulfilled the criteria of early adult/juvenile, 15 of classic form and two mild adult form. 35 participants were walking independently, two in need of walking aid (walking frame), and one was in need of a wheel chair. No participants fulfilled a diagnosis of intellectual disability. Characteristics of the participants and the results of the measures of mobility and balance are summarized in Table 3. We lack CTG reassessment of one patient due to anxiety of needles. One patient did not fulfill criteria for inclusion in the 6MWT due to the need of a wheelchair. Three patients did not fulfill criteria for inclusion in the TUG, one due to the need of wheelchair, and two due to risk of falls. Two participants did not finish their IQ test due to fatigue.

None of the patients were on symptomatic treatment for myotonia or other medication that could influence their motor skills.

Skeletal muscle strength

Figure 1 presents mean muscle strength for each muscle group tested. Neck and trunk flexion scores are the lowest and the only muscles measured within severe weakness, (1.58 and 1.52). Back extension is within slightly weakness (2.22). The highest modified 0–3 score in this sample is the knee extension, knee flexion, and elbow flexion (2.86, 2.83, and 2.69) all within the area of slight weakness.

Figure 2 show the distribution of impairment within the MRC 0–3 scale, in each muscle group. No individuals in our sample scored 0 (paralysis) in any muscle groups. Severe weakness (modified 0–3 grade 1) in trunk flexion muscles was found in 52.6% of the participants. Participants scored within area of severe weakness in neck flexion, ankle dorsal flexion, back extension, and wrist extension (42.1%, 10.5%, 5.3% and 2.6%). More than half of the sample had normal strength in knee extension, knee flexion, elbow flexion, and hip flexion (86.6%, 81.6%, 71.1% and 63.2%).

To investigate progression of muscle impairments in different parts of the body, skeletal muscle groups were put in three categories: Distal extremity group (DE-mg): dorsal extension wrist, dorsal extension ankle, Proximal extremity group (PE-mg): Hip flexion, knee flexion, knee extension, shoulder abduction, elbow flexion, elbow extension, and trunk muscle group (T-mg): abdominal flexion, back extension, neck flexion. The internal

Table 3 Characteristics of the 38 patients

	N	Mean	SD	Min – Max
Age (years)	38	39	12.4	20–63
CTG expansion (kb)*	38	1.75	1.39	0.23–5.4
Duration of disease (years)	38	18.1	9.9	5–42
IQ	36	92.4	14.8	64 –137
BMI	38	27.7	6.9	17–53
6MWT (m)	37	362.2	145.5	40–615
TUG	35	6.7	1.95	3.4–11.0
RMI	38	13.2	2.71	6–15

*Number of CTG triplets equals kb/3.

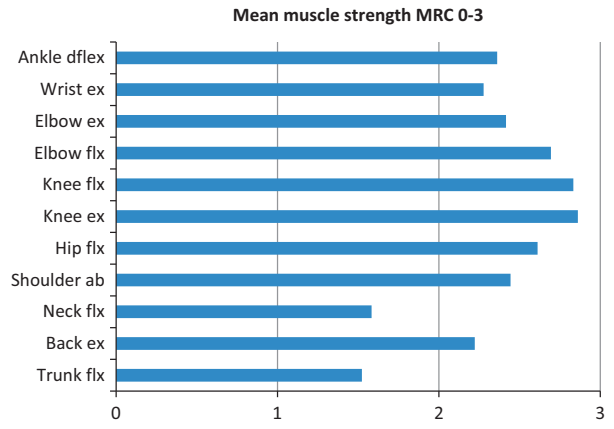

Figure 1. Display the mean MRC 0–3 muscle strength in all muscles tested.

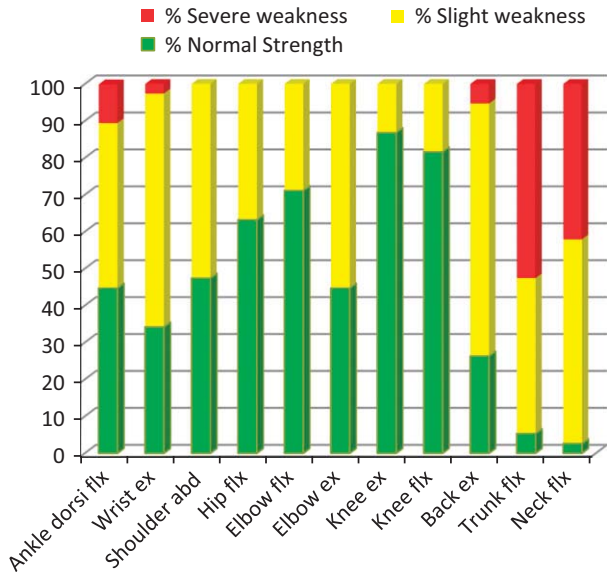

Figure 2. The distribution of MRC 0–3 severity grading in all muscles tested.

consistencies in the three sums as measured by Cronbach's Alpha are satisfactory. Alpha for T-mg 0.74, DE-mg 0.79, and PE-mg 0.73; all items in the three sums contribute positively to the Alpha. The mean strength scores in the three muscle groups of all disease duration groups are shown in Fig. 3.

Neither age at examination nor age of first symptom was related to strength in any muscle groups. All skeletal muscle groups are significantly correlated with disease duration (T-mg: $r = -0.56$, $P < 0.001$, P-mg: $r = -0.50$ $P = 0.001$, D-mg: $r = -0.33$, $P = 0.04$).

Muscle strength varies significantly across some disease duration groups for trunk muscle groups (1 > 2–4; P's < 0.05) and for proximal muscle groups (1 > 4, 2 > 4; P's < 0.05). No group difference in DE-mg reached statistical significance. Details are shown in Table S1.

Muscle strength; relation to expansion size, walking capacity, balance, and general mobility

T-mg strength and PE-mg strength was highly correlated with CTG expansion ($r = -0.64$, $P < 0.001$ & $r = -0.57$, $P < 0.001$), the relation between DE-mg and CTG expansion was ($r = -0.40$, $P = 0.015$).

Distance in the 6MWT was highly correlated with all skeletal muscle groups. Highest correlation was found between 6MWT and T-mg ($r = 0.67$, $P < 0.001$), and PE-mg ($r = 0.62$, $P < 0.001$). DE-mg was related to 6MWT at ($r = 0.45$, $P = 0.005$).

TUG was highly correlated with T-mg. ($r = -0.58$, $P < 0.001$), less so to DE-mg ($r = -0.43$, $P < 0.001$) and not significantly correlated to PE-mg ($r = -0.3$, $P = 0.08$).

RMI was correlated with all muscle groups: PE-mg. ($r = 0.72$, $P < 0.001$), T-mg. ($r = 0.66$, $P < 0.001$), DE-mg. ($r = 0.43$, $P = 0.005$).

9/38 were in need of respiration aid (BPAP), these participants had markedly reduced strength in abdominal flexors and back extensors compared to the participants without BPAP. Due to the small BPAP sample, no further analysis was done.

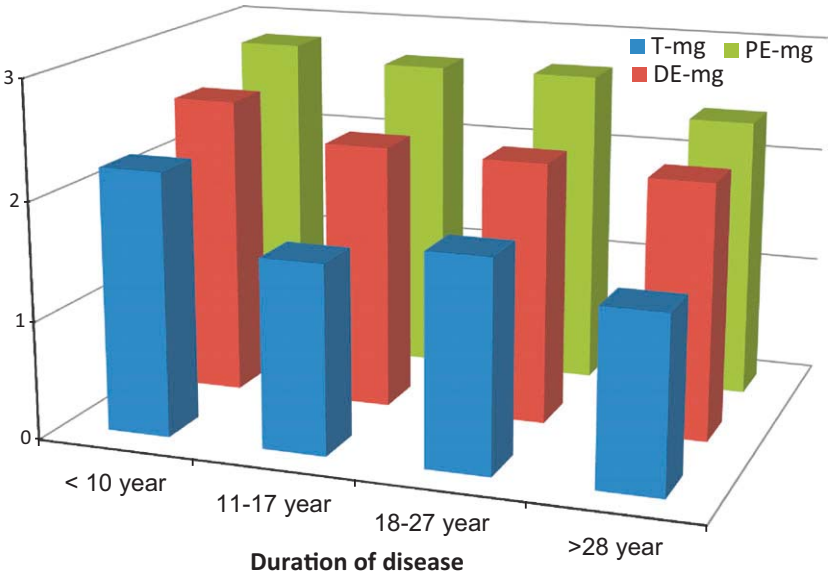

Figure 3. The mean MRC 0–3 score in the three body parts across disease duration groups. Disease duration groups are based on time since first DM1 symptom.

Possible confounders

BMI is not related to any of the skeletal muscle groups (T-mg $r = -0.11$, $P = 0.53$, DE-mg $r = -0.09$, $P = 0.58$; PE-mg $r = 0.03$, $P = 0.87$). No gender differences were found in muscle strength (T-mg: mean diff = 0.16 CI [−0.14 to 0.46], df = 36, $t = 1.08$, $P = 0.29$; DE-mg: mean diff = 0.71 CI [−0.43 to 0.29], df = 36, $t = -0.40$, $P = 0.69$; PE-mg: mean diff = 0.11 CI [−0.08 to 0.31], $t = 1.15$, $P = 0.26$).

Discussion

This is, to our knowledge, the first extensive clinical study on strength in trunk skeletal muscles of patients with DM1. We show that impairment of strength in these muscles are frequent, severe and occur relatively early in the progression of DM1. After 11 years of disease we find severe weakness of trunk muscles. These findings question the established assumption that motor impairment in DM1 progress from distal to proximal in the extremities. Trunk involvement has rarely been discussed in the DM1 literature. An exception from this is observations of spine deformity and general weakness, which implies trunk impairment. But these phenomenon are considered to occur late in the progression of the disease (4).

DM1 myopathy as the mechanism behind trunk impairment is strengthened by the previously reported pathological MRI findings of trunk muscles in 9 of 15 DM1 patients (9). Trunk flexors are known to be influenced by BMI and by pregnancies (20). However, in our study there is no significant correlation between trunk flexor strength and BMI and no gender differences. In general, decreased strength in the back extensors is not expected unless some kind of pathology is present (20). The relation observed between strength in trunk muscle groups and CTG repeat size are also in line with DM1 myopathy being a probable mechanism for the observed trunk muscle impairment.

Walking capacity (6MWT), balance (TUG) and measures of general mobility (RMI) were all highly related to muscle strength in trunk muscles. The relation between trunk strength and functions measured by TUG and RMI are understandable as they include transfer from prone to sitting and standing which involve big movements of the trunk; in walking, the relation to trunk strength is less clear since the lower extremities are the main producers of mobility. However a certain amount of stability is needed for locomotion. The trunk impairments documented may thus be relevant for everyday functioning and for understanding the risk of injuries due to falls reported among DM1 patients (11).

Knowledge about the trunk impairments documented in this study may also be relevant for detection of DM1 patients.

A tendency for a relation between impairments in trunk muscles and respiration problems is found in this study. This relation may be of clinical significance and should be investigated further.

Patients with Myotonic Dystrophy type 2 is generally regarded as having more proximal muscle impairments than patients with DM1 (2). A study, comparing strength and functioning of trunk muscles in DM1 and DM2, should be initiated.

In DM1 patients, low back pain has been reported to be a common problem (29). Whether our current findings may be relevant in understanding the mechanisms behind back pain in these patients requires further studies.

The pathophysiology of the impaired trunk function documented should be investigated by MRI. Supplemental EMG studies of axial muscles in DM1 patients could confirm possible myopathic changes.

A limitation of our study is the lack of longitudinal data on progression of impairment. The cross-sectional findings reported may be due to cohort biases. Duration of disease is based on self-reported first symptoms. Such self-reported data are prone to inaccurate recollection. Nevertheless, it is necessary for defining disease duration in this group, since the diagnosis often is delayed.

The lack of equivalent data from grip strength obviously influenced the sum score on distal extremity muscles. This contributes to a higher impairment in trunk muscles than distal extremity muscles in our study. The scores of trunk flexion for individuals with neck flexion below MRC grade 3 may be influenced by the examiners stabilization of the patients head and neck. This may have led to a higher score in our participants.

Additional information about the effect of trunk muscle impairment on everyday function are available in RIM if one quantify the quality of the exercises in question (e.g. the use of auxiliary manoeuvre's when turning in bed and sitting up). This information should be gathered for future studies.

Our findings in the group of patients described could be due to a particular "Norwegian subtype" of DM1. On the other hand, regarding all other parameters, such as strength in the extremities, mutation size, BMI and walking capacity, our results are in line with findings from other populations (6, 11, 22).

It is important to investigate the effect of targeted physical therapy on trunk muscles in DM1 patients. Strength in trunk muscle groups should be considered an outcome measure in future clinical trials where specific objective outcome measures are demanded (30).

Acknowledgments

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Conflict of interest

The authors report no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Mean muscle strength in all muscles across disease duration groups.

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