Explanatory factors of dynamic balance impairment in myotonic dystrophy type 1

Nicolas Bélair PhT[1], Isabelle Côté M Sc[2], Cynthia Gagnon PhD[2,3,4,5], Jean Mathieu MD[2,4], Elise Duchesne PhD[1,2,5,6]

1 – Unité d'enseignement en physiothérapie, Département des sciences de la santé, Université du Québec à Chicoutimi, 555, boul. de l'Université, Chicoutimi, Québec, G7H 2B1, Canada.

2 – Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires (GRIMN), Centre intégré universitaire de santé et de services sociaux du Saguenay–Lac-Saint-Jean, Hôpital de Jonquière, Québec, Canada.

3 – Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CR-CHUS), Sherbrooke, Québec, Canada.

4 – Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Québec, Canada.

5 – Centre Intersectoriel en Santé Durable (CISD), Université du Québec à Chicoutimi, Québec, Canada.

6 – Centre de recherche Charles-Le Moyne (CRCLM), Sherbrooke, Québec, Canada

Corresponding author

Elise Duchesne, pht, Ph.D.
Professeure agrégée
Unité d'enseignement en physiothérapie
Local H2-1030
Université du Québec à Chicoutimi
555, boul. de l'Université
Chicoutimi (Québec) G7H 2B1

418 545-5011, poste 6148
elise1_duchesne@uqac.ca

Abstract word count: 218 words

Manuscript word count: 2379 words

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

None of the authors has any conflicts of interest to disclose.

ACKNOWLEDGEMENT

This research was supported by the Marigold Foundation. The authors would like to thank the participants for their involvement in the study and Djamal Berbiche, who participated in the elaboration of the regression model. C.G. holds a career-grant funding from the Fonds de recherche du Québec-Santé (no. 31011).

Explanatory factors of dynamic balance impairment in myotonic dystrophy type 1

Abstract

Introduction/Aims

Myotonic dystrophy type 1 (DM1) is a neuromuscular disease affecting many systems and for which muscle weakness is one of the cardinal symptoms. People with DM1 also present with balance-related impairments and high fall risk. The aim of this study was to explore explanatory factors of dynamic balance impairment in the DM1 population.

Methods

A secondary analysis of data collected as part of a larger study was performed. The Mini Balance Evaluation System Test (Mini-BESTest) was used to assess dynamic balance. Age, sex, and CTG repeat length in blood were retrieved from medical records and research files. The maximal isometric muscle strength of five lower limb muscle groups (hip flexors and extensors, knee flexors and extensors, and ankle dorsiflexors) was quantitatively assessed as well as fatigue. Standard multiple regression analysis was used.

Results

Fifty-two individuals (31 men) aged between 24 and 81 years were included. The final model explains 65.9% of the balance score; ankle dorsiflexor muscle strength was the strongest explanatory factor, followed by CTG repeat length, age and fatigue to a lesser extent.

Discussion

Dynamic balance is impaired in people with DM1. Results of this study suggest that rehabilitation interventions aimed at improving strength of the ankle dorsiflexors and managing fatigue could help to improve dynamic balance in this specific population.

KEYWORDS: Rehabilitation; physiotherapy; balance; explanatory factors; quantitative muscle testing

INTRODUCTION

In myotonic dystrophy type 1 (DM1), muscle weakness is a cardinal symptom [1] that progresses at a different rate for the adult phenotype compared to the late-onset, and for men compared to women [2]. People with DM1 also demonstrate impaired dynamic balance, mobility and walking speed [3, 4]. The number of falls reported is eightfold higher than healthy control, and 50% of them result in an injury [5]. Moreover, DM1 patients with a history of falling had more severe self-reported muscle weakness and lower balance confidence. Static balance is highly impaired among the adult and late-onset phenotypes, with 22-59% of participants showing performance below reference values [4]. In addition, muscle strength explained 62% of the Berg Balance Scale score [4]. However, this scale demonstrated a ceiling effect in our population, and other tests are now recommended by the International Outcome Measures in Myotonic Dystrophy type 1 (OMMYD) group including the Mini Balance Evaluation System Test (Mini-BESTest) [6]. This test has shown evidence of validity in this population, especially in individuals with the adult phenotype, in which strong associations with walking capacity were found [7]. The influence on dynamic balance impairment of muscle strength and other factors that have a large impact on daily life such as fatigue, daytime sleepiness and other central nervous system manifestations [8-14] remains unknown. By identifying the main contributors of balance impairment, specific rehabilitation programs could be developed. The aim of this study was to explore explanatory factors of dynamic balance impairment in the DM1 population.

METHODS

Design

This was a secondary analysis of a larger longitudinal study that started in 2002 and included four data collection times. The present study used the data collected from phase 3 (2015-2016). Variables were selected based on previous literature on balance in populations with balance disorders and DM1.

Participants

Participants of this study were recruited at the Saguenay Neuromuscular Clinic of the *Centre Intégré Universitaire de Santé et de Services Sociaux du Saguenay–Lac-St-Jean* (Quebec, Canada) [2, 11, 15, 16]. Of 115 persons who participated to the second phase, 97 were still alive in 2015, and were invited to participate to the third phase. To increase the sample size, new individuals were also invited for this third phase. Inclusion criteria were: 1) genetic diagnosis of DM1 with the juvenile, adult or late-onset phenotype; 2) aged 18 years old or older; and 3) able to give informed consent. People with other physical limitations that may influence clinical assessments were excluded from the study. Participants were classified as late-onset phenotype if they had 2 of the 3 following criteria at diagnosis: 1) cytosine-thymine-guanine (CTG) trinucleotide repeat length of < 200; 2) Muscular Impairment Rating Scale (MIRS) score of 1 (no muscle impairment) or 2 (minimal signs); and 3) age at onset of symptoms > 40 years. All other participants with a juvenile or an adult phenotype were classified according to Dogan et al. [17]. The study was approved by the Ethics Review Board of the *Centre Intégré Universitaire de Santé et*

Services Sociaux du Saguenay–Lac-St-Jean. Written informed consent was obtained from all participants.

Variables

Dependent variable. Participants performed the Mini-BESTest to assess dynamic balance. Testing consists of 14 items, divided into four subcomponents: anticipatory postural adjustments (three items) (subscale 1), reactive postural control (three items) (subscale 2), sensory orientation (three items) (subscale 3), and dynamic gait (five items) (subscale 4) [17]. Shoes and orthoses are allowed when performing this test. Scoring is based on the ability of the participant to perform the task and each item is scored 0, 1 or 2, where 0 means severe balance limitation and 2 no balance limitation, for a total of 28 with a higher score indicating better balance. As indicated in the Mini-BESTest instructions, if a participant required physical assistance to perform an item, a score of 0 is given for that item and if an assistive device was used, the item was scored one category lower.

Independent variables and covariates. Age, sex and CTG repeat length were included based on previous studies [1, 17, 18]. The sociodemographic characteristics were obtained from a general questionnaire (age, sex) and the medical and research records (CTG repeat length in blood and phenotype). In addition, the MIRS, a DM1-specific scale, was documented for descriptive purposes only. Its score range from 1 (no muscular impairment) to 5 (severe proximal weaknesses) [19].

Fatigue was assessed with the Krupp Fatigue and Severity Scale (KFSS). The KFSS has 9 items, each scored on a 7-point Likert scale, where 1 means “Strongly disagree” and 7 means “strongly agree”. Summation of items gives the total score, with a higher score corresponding to more severe fatigue.

Maximal isometric muscle strength was assessed using quantified muscle testing (QMT). The following muscle groups were selected based on their significant impact on mobility in patients with DM1 [3, 4, 20, 21]: hip flexors, hip extensors, knee flexors, knee extensors and ankle dorsiflexors. The QMT protocol used in this study was developed by Hébert et al. to ensure the best reproducibility of handheld dynamometry evaluations and was used in previous studies [1, 22-24]. The handheld dynamometer used was the MEDup™ linear electronic handheld dynamometer (Atlas medic, Québec, Canada). QMT has shown evidence of reliability and validity for knee extension in the DM1 population [25]. For each muscle group, at least two trials were done: if results differed by more than 10%, a third or fourth trial was done. The mean of the two closest trials for each side was kept. The mean of the two sides was used for data analysis.

Statistical analysis

For descriptive statistics, continuous variables (age, CTG repeat length, muscle strength, fatigue) are presented as means and standard deviation. Categorical variables (sex, phenotype, MIRS) are presented as frequencies and percentages. The Mini-BESTest score was compared between groups of participants based on sex using a Mann-Whitney *U* test.

The first step of the analyses determined the correlations between the score of the Mini-BESTest (dependent variable) and disease-related characteristics (independent variables and covariates) using Pearson *r* coefficients. Variables that correlated at a significance level of $p < 0.2$ were used in multivariable analyses (standard multiple regression) as independent predictors of the Mini-BESTest score. The final model was checked for collinearity with the Variable Inflation Factor (VIF, must be ~ <10) and statistical significance was set at $p < 0.05$. Statistical analyses were conducted with SPSS version 20.0 (IBM, Armonk, NY).

RESULTS

Ninety-one subjects participated inphase 3 of the longitudinal study. From these, 39 were excluded due to incomplete or non-valid data for QMT (2 or more muscle group values were missing or execution was limited by an injury) and/or for Mini-BESTest (one item was not completed due to a delay in material acquisition or bias of performance). Characteristics of the sample (n=52) are presented in Table 1.

The mean Mini-BESTest score for the whole group was 20.2 ± 6.8 (scores obtained for each participant in each of the Mini-BESTest subscales are available in Supplementary Table 1) and was not significantly different between men and women (Men: mean = 21.1, confidence interval = 18.8 – 23.4; Women: mean = 19.0, confidence interval = 15.5 – 22.4; *p* value = 0.340). Also, associations between the Mini-BESTest score and all variables included in the model are presented in Table 2. The univariate correlation analysis revealed

associations with a significance level lower than 0.2 between all independent variables and the Mini-BESTest score. Thus, all variables were included in the model.

The regression model explained 65.9% of the balance variance measured by the Mini-BESTest (Table 3). Among variables included in the model, those inducing significant variation of the Mini-BESTest score were, in ascending order of influence: fatigue, age, CTG repeat length and ankle dorsiflexors muscle strength.

DISCUSSION

Our results showed that lower limb muscle strength and fatigue would contribute to explain dynamic balance as assessed by the Mini-BESTest in individuals with the juvenile, adult and late-onset phenotypes of DM1. Muscle strength of ankle dorsiflexors, the most affected muscle group [3], was the main explanatory factor influencing the balance score. This is in accordance with our previous work on static balance having demonstrated that it explained the higher percentage of variation observed in the Berg Balance Scale score as well [4]. This is also in accordance with previous studies in which ankle dorsiflexor muscle strength is related to frequency of falls in the adult DM1 population [3] and could limit the ability of elderly adults to maintain balance [26]. Rehabilitation of this muscle group should be studied as a factor to improve balance. Furthermore, other muscle groups could also be targeted given the documented relationship between lower limb muscle weakness in several groups and rate of falls and stumbles [21], in addition to our moderate associations between each muscle groups and balance.

Our results identified three others factors: age, CTG repeat length and fatigue. More precisely, older participants and those with a higher number of CTG repeats were found to have lower scores on the Mini-BESTest. Because DM1 is a progressive disease, it is not surprising to find that age was a key explanatory factor of balance score. This is reinforced by the fact that DM1 has been considered to be a model of premature ageing [27], and that balance disorders are common in older adults [28]. Although correlations between CTG repeat length and the severity of the symptoms are not highly robust [29], it is well-recognized that the number of CTG repeats decreases from the congenital to the late-onset form [30]. The contribution of CTG repeat size in balance impairment found in this study reflects the previously published significant difference observed between adult and late-onset phenotypes in Mini-BESTest score [7]. Finally, the presence of self-reported fatigue is contributing to lower balance score. Similar results were found in our previous study on self-reported restriction in mobility-related participation in daily life [31]. This is important, as a recent study of fatigue self-management among patients with neuromuscular diseases showed encouraging preliminary results. Indeed, 96% of the participants were entirely or largely satisfied with the results of the intervention and 88% reported improvement in symptom management [32].

LIMITATIONS

The main limitation of this study is the small sample size, limiting the conclusions regarding the effect of phenotype on the Mini-BESTest performance. This limitation is partially addressed by the fact that the number of CTG repeats, a key element for the phenotype classification, was included in our analyses. A second limitation is the lack of

tools assessing central nervous system impact on balance among our population, but these factors were not considered since the scope of the paper was to provide physiotherapists with contributing factors that can be assessed in a clinical context and targeted by clinical interventions.

CONCLUSION

Our results show that balance variation among the adult DM1 population is mainly explained by the strength of ankle dorsiflexion, and, to a lesser extent, by fatigue. The development of rehabilitation interventions targeting strength of the ankle dorsiflexors and/or fatigue should be studied to improve muscle strength and dynamic balance in this population.

List of abbreviations

CTG	cytosine-thymine-guanine
DM1	myotonic dystrophy type 1
KFSS	Krupp fatigue and severity scale
Mini-BESTest	Mini balance evaluation system test
MIRS	Muscular impairment rating scale
OMMYD	International outcome measures in myotonic dystrophy type 1 group
QMT	quantified muscle testing

REFERENCES

1. Petitclerc, E., et al., *Lower limb muscle strength impairment in late-onset and adult myotonic dystrophy type 1 phenotypes.* Muscle Nerve, 2017. **56**(1): p. 57-63.
2. Gagnon, C., et al., *A 9-year follow-up study of quantitative muscle strength changes in myotonic dystrophy type 1.* J Neurol, 2018. **265**(7): p. 1698-1705.
3. Hammaren, E., et al., *Factors of importance for dynamic balance impairment and frequency of falls in individuals with myotonic dystrophy type 1 - a cross-sectional study - including reference values of Timed Up & Go, 10m walk and step test.* Neuromuscul Disord, 2014. **24**(3): p. 207-15.
4. Petitclerc, E., et al., *Relationships between lower limb muscle strength impairments and physical limitations in DM1.* J Neuromuscul Dis, 2018. **5**(2): p. 215-224.
5. Berends, J., et al., *High incidence of falls in patients with myotonic dystrophy type 1 and 2: A prospective study.* Neuromuscul Disord, 2019. **29**(10): p. 758-765.
6. Gagnon, C., et al., *Report of the third outcome measures in myotonic dystrophy type 1 (OMMYD-3) international workshop Paris, France, June 8, 2015.* J Neuromuscul Dis, 2018. **5**(4): p. 523-537.
7. Duchesne, E., et al., *Validity of the Mini-BESTest in adults with myotonic dystrophy type 1.* Muscle Nerve, 2020. **62**(1): p. 95-102.
8. Tremblay, M., et al., *Accomplishment of instrumental activities of daily living and its relationship with cognitive functions in adults with myotonic dystrophy type 1 childhood phenotype: an exploratory study.* BMC Psychol, 2021. **9**(1): p. 56.

9. Van Heugten, C., et al., *Participation and the Role of Neuropsychological Functioning in Myotonic Dystrophy Type 1.* J Neuromuscul Dis, 2018. **5**(2): p. 205-214.
10. Fujino, H., et al., *Cognitive impairment and quality of life in patients with myotonic dystrophy type 1.* Muscle Nerve, 2018. **57**(5): p. 742-748.
11. Gallais, B., et al., *Cognitive decline over time in adults with myotonic dystrophy type 1: A 9-year longitudinal study.* Neuromuscul Disord, 2017. **27**(1): p. 61-72.
12. Winblad, S., et al., *Cognition in myotonic dystrophy type 1: a 5-year follow-up study.* Eur J Neurol, 2016.
13. Gallais, B., et al., *Prevalence and correlates of apathy in myotonic dystrophy type 1.* BMC Neurol, 2015. **15**: p. 148.
14. Laberge, L., C. Gagnon, and Y. Dauvilliers, *Daytime sleepiness and myotonic dystrophy.* Curr Neurol Neurosci Rep, 2013. **13**(4): p. 340.
15. Raymond, K., et al., *Progressive decline in daily and social activities: A 9-year longitudinal study of participation in myotonic dystrophy type 1.* Arch Phys Med Rehabil, 2019. **100**(9): p. 1629-1639.
16. Raymond, K., et al., *A 9-year follow-up study of the natural progression of upper limb performance in myotonic dystrophy type 1: A similar decline for phenotypes but not for gender.* Neuromuscular Disorders, 2017. **27**(7): p. 673-682.
17. Dogan, C., et al., *Gender as a Modifying Factor Influencing Myotonic Dystrophy Type 1 Phenotype Severity and Mortality: A Nationwide Multiple Databases Cross-Sectional Observational Study.* PLoS One, 2016. **11**(2): p. e0148264.

18. Fu, Y.H., et al., *An unstable triplet repeat in a gene related to myotonic muscular dystrophy.* Science, 1992. **255**(5049): p. 1256-58.

19. Mathieu, J., et al., *Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy.* Neurology, 2001. **56**(3): p. 336-340.

20. Lindeman, E., et al., *Quadriceps strength and timed motor performances in myotonic dystrophy, Charcot-Marie-Tooth disease, and healthy subjects.* Clin Rehabil, 1998. **12**(2): p. 127-35.

21. Wiles, C.M., et al., *Falls and stumbles in myotonic dystrophy.* J Neurol Neurosurg Psychiatry, 2006. **77**(3): p. 393-396.

22. Hebert, L.J., et al., *Isometric muscle strength in youth assessed by hand-held dynamometry: a feasibility, reliability, and validity study.* Pediatr Phys Ther, 2011. **23**(3): p. 289-99.

23. Roussel, M.P., et al., *Assessment of muscular strength and functional capacity in the juvenile and adult myotonic dystrophy type 1 population: a 3-year follow-up study.* J Neurol, 2021.

24. Roussel, M.P., L.J. Hébert, and E. Duchesne, *Strength-training effectively alleviates skeletal muscle impairments in myotonic dystrophy type 1.* Neuromuscul Disord, 2020. **30**(4): p. 283-293.

25. Roussel, M.P., L.J. Hébert, and E. Duchesne, *Intra-Rater Reliability and Concurrent Validity of Quantified Muscle Testing for Maximal Knee Extensors Strength in Men with Myotonic Dystrophy Type 1.* J Neuromuscul Dis, 2019. **6**(2): p. 233-240.

26. Fujimoto, M., et al., *Ankle dorsiflexor strength relates to the ability to restore balance during a backward support surface translation.* Gait Posture, 2013. **38**(4): p. 812-7.

27. Mateos-Aierdi, A.J., et al., *Muscle wasting in myotonic dystrophies: a model of premature aging.* Front Aging Neurosci, 2015. **7**: p. 125.

28. Salzman, B., *Gait and balance disorders in older adults.* Am Fam Physician, 2010. **82**(1): p. 61-8.

29. Thornton, C.A., *Myotonic dystrophy.* Neurol Clin, 2014. **32**(3): p. 705-19, viii.

30. De Antonio, M., et al., *Unravelling the myotonic dystrophy type 1 clinical spectrum: A systematic registry-based study with implications for disease classification.* Rev Neurol (Paris), 2016. **172**(10): p. 572-580.

31. Gagnon, C., et al., *Predictors of disrupted social participation in myotonic dystrophy type 1.* Arch Phys Med Rehabil, 2008. **89**(7): p. 1246-55.

32. Veenhuizen, Y., et al., *Mixed methods evaluation of a self-management group programme for patients with neuromuscular disease and chronic fatigue.* BMJ Open, 2021. **11**(8): p. e048890.

Table 1: Patient characteristics

	Total (n = 52)
Age, y	
mean (SD)	50.0 (12.7)
[min-max]	[24-81]
Sex, n (%)	
Men	31 (59.6)
Women	21 (40.4)
Phenotype, n (%)	
Juvenile	19 (36.5)
Adult	15 (28.8)
Late	18 (34.6)
CTG repeat length	
mean (SD)	449.2 (380.4)
[min-max]	[70-1800]
Krupp Fatigue Severity Scale	
mean (SD)	37.58 (14.7)
[min-max]	[10-63]
Muscle Impairment Rating Scale, n (%)	
Grade 1	9 (17.3)
Grade 2	3 (5.8)
Grade 3	12 (23.1)
Grade 4	26 (50.0)
Grade 5	2 (3.8)
Muscle Strength, Nm	
Hip flexors	
mean (SD)	74.6 (28.9)
[min-max]	[27.0-147.9]
Hip extensors	
mean (SD)	184.4 (67.8)
[min-max]	[61.5-319.0]
Knee extensors	
mean (SD)	79.2 (41.5)
[min-max]	[11.4-176.7]
Knee Flexors	
mean (SD)	54.2 (24.1)
[min-max]	[18.7-110.5]
Ankle dorsiflexors	
mean (SD)	17.3 (8.6)
[min-max]	[2.0-38.0]

Abbreviations: CTG: cytosine thymine guanine trinucleotide; max: maximum; min: minimum; SD: standard deviation.

Table 2: Associations between the Mini-BESTest score and the continuous variables included in the model

Variables	**Pearson r**	***p*-value**
Age	-0.169	0.118
CTG repeat length	-0.636	<0.001
Muscle strength		
Hip flexors	0.517	<0.001
Hip extensors	0.452	<0.001
Knee extensors	0.485	<0.001
Knee flexors	0.512	<0.001
Ankle dorsiflexors	0.650	<0.001
Fatigue	-0.464	<0.001

Abbreviation: CTG: cytosine thymine guanine trinucleotide.

Table 3: Regression model between clinical variables and the Mini-BESTest score

Adjusted R^2	F value	*p*-value	Independent variables	β	95% CI	β_{std}	*p*-value	VIF
0.659	9.096	<0.001	Constant	40.558	[25.792 ; 55.325]	---	<0.001	---
			Age	-0.215	[-0.330 ; -0.101]	-0.402	<0.001	1.7
			CTG repeat length	-0.008	[-0.012 ; -0.004]	-0.452	<0.001	1.7
			Sex	-0.152	[-3.502 ; 3.198]	-0.011	0.928	2.1
			Muscle strength					
			Hip flexors	-0.048	[-0.176 ; 0.081]	-0.198	0.456	10.1
			Hip extensors	-0.040	[-0.084 ; .003]	-0.395	0.068	6.5
			Knee extensors	0.051	[-0.015 ; 0.116]	0.307	0.127	5.7
			Knee flexors	0.016	[-0.115 ; 0.146]	0.055	0.807	7.4
			Ankle dorsiflexors	0.378	[0.101 ; 0.655]	0.470	0.009	4.3
			Fatigue	-0.163	[-0.250 ; -0.074]	-0.346	0.001	1.3

Abbreviations: $\beta_{std:}$ standardized β coefficient; CI: confidence interval; CTG: cytosine thymine guanine trinucleotide; VIF: variance inflation factor.