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Prediction of Loss of Gait in Duchenne Muscular Dystrophy Using the Ten Meter Walking Test Rates

Tatiana Maciel Pizzato[1], Cyntia Rogean de Jesus Alves de Baptista[1], Edson Zangiacomi Martinez[2], Claudia Ferreira da Rosa Sobreira[3] and Ana Claudia Mattiello-Sverzut[1*]

[1]*Department of Biomechanics, Medicine and Rehabilitation of the Locomotor Apparatus, Ribeirão Preto Medical School, University of São Paulo, Brazil*
[2]*Department of Social Medicine, Ribeirão Preto Medical School, University of São Paulo,Brazil*
[3]*Department of Neurosciences, Ribeirão Preto Medical School, University of São Paulo, Brazil*

Abstract

Objective: To evaluate the performance of boys with DMD in the ten meter walking test (10 MWT) in order to predict gait loss.

Method: This longitudinal study consisted of consecutive evaluations, minimum of 3 and maximum of 12, conducted every 4 months, during 33 months, depending on time of inclusion in the study. Ambulant boys with DMD (n=18), ages 4 to 13 years, mean 7 (SD=2.22), were assigned to Ambulatory group (A; n=11) or Non-Ambulatory group (NA; n=7) according to their status at the end of the study. Diagnosis was based on the absence of dystrophin in a muscle biopsy and/or identification of a mutation of the dystrophin-gene. The main outcome measures were: 10 MWT total time and rates between two consecutive sessions. Secondary measures included: functional status and muscle strength of the hip, knee and ankle.

Results: The 10 MWT total time for the NA group oscillated over time, while remaining steady for the A group. The NA group showed mean of 16.18 s (CI 95% 14.38–17.98) and the A group showed mean of 10.2 s (CI 95% 9.08–11.24). The difference between groups was estimated as -5.98 s (CI 95%-8.11; -3.89). The linear model of mixed effects identified significant increase in 10 MWT time for the NA group and decrease for the A group. The rates were >1.25 for participants who became wheelchair users, indicating increased time to perform 10 MWT overtime.

Conclusion: Rates ≥ 1.25 indicate the borderline between independent gait and wheelchair confinement and are useful for predicting gait loss.

Keywords: Neuromuscular diseases; Functional evaluation; Gait; Muscle strength; Impairment

Abbreviations

DMD: Duchenne Muscular Dystrophy; ICC: Intra-class Correlation Coefficient; 10 MWT: 10 Meter Walking Test

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked progressive myopathy associated with dystrophin deficiency in the costameres. The most frequent clinical features of DMD are: Lower limb muscle weakness progressing from the proximal to the distal extremity, abnormal gait, frequent falls and difficulty climbing stairs [1]. Weakness of the hip extensor muscles, biomechanical changes and compensatory strategies to maintain balance and movement occur concomitantly with severe lumbar lordosis, shortening of the Achilles tendon and loss of gait. Loss of gait may vary from age 7 to 13 years [1]. Genotype and phenotype correlations have shown that dystrophin defects are related to greater severity of weakness and loss of ambulation at a younger age [1]. It is well known that depending on the severity of muscle and brain dysfunction, there are at least 4 subtypes of DMD: (A) early infantile DMD; (B) classical DMD; (C) moderate pure motor DMD; (D) severe pure motor DMD [2,3]. Various approaches have been used to study the relationship between gait and muscle strength in myopathies [4-6].

Decrease in muscular strength is used as prognostic factor and indicators of the progression of the disease, for example, values lower than grade 3 for hip extensors and grade 4 for ankle dorsiflexors indicate the need for wheelchair use within a 2 year period [6], however, these factors are not very reliable due to the fact that they might be maintained for a longer period of time and the patients might present sudden loss of ambulation [7].

A few studies in the literature describe a substantial quantity of instruments used in order to assess pediatric neuromuscular diseases, focusing on functional aspects [6,8-10], physical performance [4,11,12] and muscular strength [13-15]. In a review, Bushby et al. recommended strength testing of the lower extremity by manual muscle testing every 6 months, the timed 10 meter walk test (10 MWT) and the Vignos lower extremity scale for DMD management [16]. Since the main aim of most interventions is postponing gait loss, studies adopt the gait itself, and similar abilities such as standing and climbing stairs as clinical endpoints [16-18]. Clinical research is pointing in the direction of a consensus that isolated results, as changes in muscle strength are not appropriate to indicate intervention outcomes [19]. Studies using the 10 MWT have shown promising results for monitoring medication effects and assessing community gait [12], and verifying the capacity of patients with neuromuscular diseases in daily life activities (DLAs) [20]. According to Pereira et al., the 10 MWT is more clinically relevant while the 6 minute walking test (6 MWT) is suitable and significant for

***Corresponding author:** Ana Claudia Mattiello-Sverzut, Department of Biomechanics, Medicine, and Rehabilitation of the Locomotor Apparatus, Ribeirão Preto Medical School, University of São Paulo. Avenida dos Bandeirantes, 3900, CEP 14049-900 Ribeirão Preto, SP, Brazil, Tel: 005516-3602-4413 (or) 3315-0738; Fax: 005516-3633-0336; E-mail: acms@fmrp.usp.br

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research [21]. Nevertheless, there is significant correlation between the 6 MWT and the 10 MWT [5,11]. McDonald et al. found that a total of 5 seconds or less spent in the 10 MWT is correlated to an increase in the distance covered in the 6 MWT, whereas a total time of 10 s or more in the 10 MWT predicts loss of ambulation over a 12 month period, in DMD patients. In addition, the 10 MWT and 6 MWT tests show similarities from the motor development point of view [21]. Data from 345 healthy children (2 to 12 years old) indicate decrease in time spent in the 10 MWT until 6 years of age followed by a plateau, with total time staying at 10 sor less [22]. However, clinical heterogeneity of DMD (1,2) complicates the adoption of a "cut off" value in order to predict loss of gait.

According to Hyde et al., using a specific test or variable in order to establish a predictive profile can strengthen clinical decision making by allowing prognoses of changes in physical variables, guiding interventions and/or tailoring therapeutic drugs [23]. Thus, the 10 MWT should be further evaluated as a predictive tool in children with DMD, using consecutive evaluations of the test at different points in time, as a more realistic way to predict loss of gait.

The objective of this longitudinal study was to evaluate the performance of boys with DMD in the 10 MWT, as a way to predict the loss of gait over time.

Methods

Of the 30 DMD patients invited, only 18 participated in the study. 22 boys did not fulfil the inclusion criteria of independent ambulation and met the following exclusion criteria: younger than 4 years of age and with presence of cognitive disorder. The 18 boys with DMD had independent ambulation and were followed by the staff of the Rehabilitation Centre at Clinical Hospital of XX XX XX XX, over a period of 33 months. Their ages ranged from 4 to 13 years, mean 7 (SD=2.22). DMD diagnosis was based on the absence of the dystrophin in a muscle biopsy and/or identification of a mutation of the dystrophin-gene. All the participants and/or guardians gave written informed consent, and the Ethics Committee of XX XX XX, University XX XX XX approved the study.

The follow-up sessions were conducted every 4 months, and the physiotherapy evaluation was comprised of: functional scale (Vignos scale) testing, manual test of muscle strength using the scale of the Medical Research Council and the 10 MWT. The same researcher administered all the tests. The intraclass reliability was calculated by the intraclass correlation coefficient (ICC) of the 10 MWT. It was based on 2 identical evaluations (4 days between each evaluation) of 15 healthy boys of the same age. The inclusion of the DMD participants during the data collection was based on the hospital referral, which resulted in different amount of sessions, with a minimum of 3 and a maximum of 12 evaluations and re-evaluations. The 18 boys, who started with ambulation, were assigned to one of two groups according to their status at the end of this study: non-ambulatory (NA; n=7) and ambulatory (A; n=11) groups.

The muscle groups of the hip (flexors, extensors, hip abductors and adductors); knee (flexors and extensors) and ankle (dorsiflexor and plantar flexor) were evaluated by the manual muscle scale, graded from 0 to 5, without subdivisions. Each participant performed the 10 MWT without devices or shoes on a regular floor, starting from the standing position. They received an explanation about what to expect before the start of the test. The standardised verbal command was "walk as fast as possible without running and only stop when I give you the command to stop".

Statistical procedures

(1) The Intraclass Correlation Coefficient (ICC) of 2 identical evaluations of the 10 MWT was used to measure the minimum acceptable value of the reliability coefficient (ICC=0.75 or 0.80 according to Fleiss [24]); (2) Bayesian linear mixed-effects model based on the Gibbs sampling algorithm and non-informative prior distributions, where random effects correlated the different measures of the same participant during the follow up sessions. Total time in the 10 MWT for the NA and A groups was compared using this model; (3) The Bayesian linear mixed-effects model was used in order to evaluate the association between age and total time in the 10 MWT, as a way to verify the existence of linear tendency for changes in the 10 MWT according to age. The Bayesian method generates credibility intervals 95% (CI 95%) for parameters of interest (similar to the classical interval of confidence method). When CI 95% for an inclination measure does not include zero, the time to perform the 10 MWT and the participant age in a specific group is significant (similar to $p<0,05$). All Bayesian analyses were done with Open BUGS software (version 3.2.1); (4) o visually compare changes in the 10 MWT patterns between the A and the NA groups, we calculated the rate between successive tests (consecutive evaluation measurements) for each participant and the results were plotted in a line graphic.

Results

Table 1 shows demographic data for the participants. All the subjects used nocturnal orthosis (except 2 boys in the A group), and showed different functional scores according to the Vignos 5-point scale classification. The majority (88.9%) used corticosteroid therapy and all subjects were participating in physiotherapy sessions (conventional and aquatic therapy). The ICC value for the 10 MWT test was 0.71 (95% CI=0.43-0.95), when comparing two identical evaluation sessions of 15 healthy boys.

Timed test

As seen in Figure 1, the NA group showed a mean of 16.18 seconds (CI 95% 14.38–17.98) and the A group showed a mean of 10.2 s (CI 95% 9.08–11.24). The difference between the two groups is estimated at -5.98 (CI 95%-8.11; -3.89). Since this data does not include the value zero, the difference between groups is significant (similar to $p<0.05$).

Figures 2A and 2B show performance (set of evaluations over the period of this study) for the NA and the A groups, considering individual profiles throughout the evaluation sessions. Increased and decreased linear tendencies were identified on10 MWT for NA and A group participants, respectively.

Table 2 illustrates the values obtained in the linear model of mixed effects with the NA group showing positive values (mean=1.6) and the A group showing negative values (mean=-1.6). The CI 95% for these inclination coefficients does not include the zero value. This result indicates a significant increase in time to complete the 10 MWT for the NA group (positive coefficients) and decrease in time for the A group (negative coefficients).

Figure 3 shows rates from the 10 MWT, obtained from 2 consecutive sessions. When the rates are greater than 1, they indicate increased time to complete the 10 MWT when comparing one session to the other. All participants who became wheelchair users, i.e., the NA group, showed at least one rate greater than 1.25. There was an increase of 25% in total time spent in the 10 MWT, when compared to the previous session for this group. This pattern was less frequent

Group	Boys (*n*=18)	Age (years)	Height (meters)	Weight (Kilograms)	Functional core (Vignos)	Glucocorticoid use	AFO	Pt sessions per week	Follow-up (number of evaluations)
Non-ambulatory	1	4	102	14.8	4//5	no*	Nocturnal	3	3
(NA)	2	8	133	26.7	3//4	Yes	nocturnal/day use	4	6
	3	6	118	21	2//3	no**	Nocturnal	2	5
	4	13	132	31.5	5//5	Yes	Nocturnal	2	4
	5	6	127	23.2	3//5	Yes	nocturnal	2	5
	6	5	107	23.9	3//4	Yes	nocturnal	2	8
	7	7	126	23.4	4//5	Yes	nocturnal	3	5
Ambulatory	8	10	143	35.2	2//2	Yes	none	2	9
(A)	9	5	108	18	2//2	Yes***	nocturnal/day use	2	4
	10	7	127	23.4	2//2	Yes	nocturnal/day use	3	9
	11	5	110	21	2//2	Yes	nocturnal	2	11
	12	9	124	40.3	1//3	Yes	nocturnal	2	10
	13	4	102	19	1//2	Yes	none	3	3
	14	7	110	23.2	1//2	Yes	nocturnal/day use	3	3
	15	8	129	31.4	1//2	Yes	nocturnal	3	6
	16	7	132	31.3	1//2	Yes****	nocturnal/day use	3	11
	17	8	127	33.4	3//4	Yes	nocturnal/day use	2	12
	18	7	123	24.4	3//2	Yes	nocturnal/day use	2	12

*This boy started medication 1 year after admission; **Parents refused to adopt medication; ***Boy began medication 10 months after admission; **** Boy began medication 6 months after admission; AFO = ankle foot orthosis; functional scores are shown as x//y, representing the scores on the first and last evaluation, respectively.

Table 1: Demographics, functional score, therapies and number of follow-up sessions.

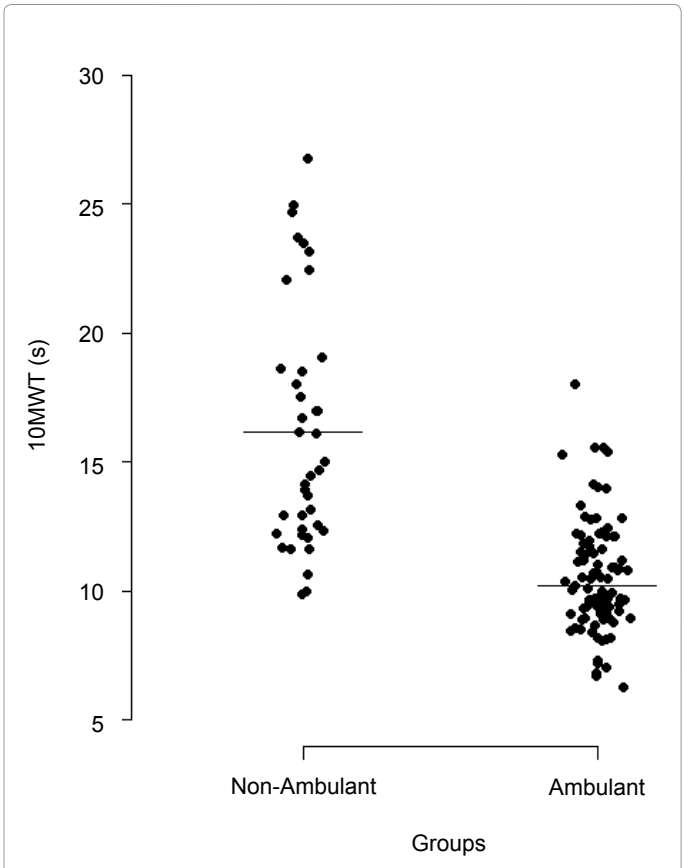

Figure 1: Mean values of T 10 MWT for ambulatory and non-ambulatory group.

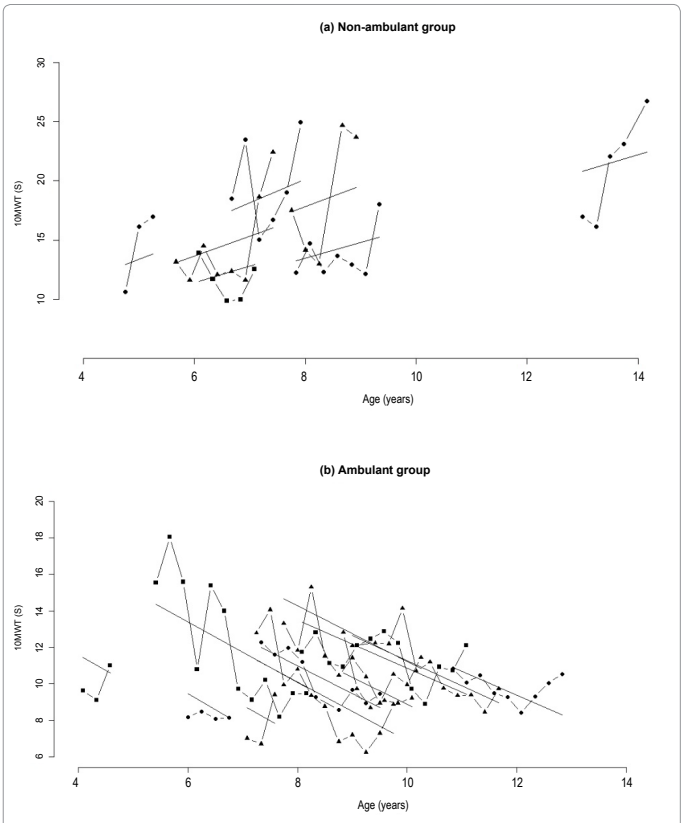

Figure 2: Performance of 10 MWT obtained by non-ambulatory (A) and ambulatory participants (B) throughout the evaluation sessions with linear tendency lines.

for participants that preserved gait until the end of the study, only 3 A group participants showed rate greater than1.25. The higher rates for the NA group were: 1.52, 1.48, 1.25, 1.36, 1.31, 1.6 and 1.9, while for the A group they were: 1.1, 1.03, 1.12, 1.42, 1.15, 1.2, 1.4, 1.04, 1.21, 1.22 and 1.29. The rates higher than 1.25 can indicate future loss of gait, considering the sample analysed in this study.

Muscle strength

Individual profile analyses for the NA and A groups showed symmetry between the right and left lower limbs and a decrease in the muscle strength of both groups in the assessments (data not shown). As seen in the Table 3, analysis of muscle strength obtained in the evaluation that preceded the loss of gait for NA group showed that all participants had decreased muscle strength grades for the hip extensor/flexor, hip abductor/adductor, knee extensors and ankle dorsiflexors and, notably the hip extensors showed grade 2 and knee extensors showed grade 3.

Discussion

This study aimed to identify the predictive value of the 10 MWT, a test routinely used in clinical physiotherapy, for assessing loss of gait in boys with DMD, over a period of 33 months. While the NA group showed a predominantly functional score (Vignos scale) between 3 and 5, the A group showed scores between 1 and 3. The higher scores are associated with pronounced lower limb impairment and are consistent with the longer 10 MWT execution time for the NA group.

Based on the rates obtained from two consecutive 10 MWT sessions, it is remarkable that the subjects in the NA group showed increase in time spent to complete the 10 MWT, when compared to the A group which showed a more consistent time to complete the test throughout the study. In addition, rates ≥ 1.25 can indicate the borderline between independent gait and wheelchair confinement, which can be useful for the rehabilitation staff.

Several studies have used the 10 MWT in the DMD population [7,16,23,25]. The application of the test is simple, and the task requires walking at a maximum self-established speed. In addition, other authors have indicated that the 10 MWT is sensitive enough to detect changes in gait performance of boys with DMD [6,22,24].

The individual profiles for the NA group muscle strength and performance in the 10 MWT (defined as oscillation of time over the course of several evaluations throughout the study) revealed similar results to those described by Bakker et al. [7]. Our analyses show increased time spent in the 10 MWT in the session that preceded gait loss. In addition, our results show decrease in strength for hip flexors, extensors, abductors and adductors and knee extensor and ankle dorsiflexors. Grades 2 and 3 muscle strength for the extensors of the hip and knee were coupled with lower functional gait capacity. Muscular strength lower than grade 3 for the hip extensors and lower than grade 4 for the ankle dorsiflexors is a prognostic factor for loss of gait and an indicator of disease progression in a period of 2 years [7]. In addition, as reported by other authors, muscle strength measurement is more informative when associated with another measurement [8,15,20]. In the present study, strength measurements and 10 MWT data were successfully used to indicate a progression of the disabilities in boys with DMD. Predicting the loss of independent gait in boys with DMD is very important because, such prediction makes it possible for caregivers and health professionals to implement specific treatment strategies, focusing on the functional impairment and quality of life. To the best of our knowledge, there are no studies in the literature with DMD subjects using the 10 MWT test as a predicting tool. We conclude that using the 10 MWT and calculating rates is very important for the clinical evaluation of patients with DMD. The test is easy to use, low

Non- ambulatory group							
S. No.	**Intercept (a_{ik})**	**CI 95%**			**Inclination (b_{ik})**	**CI 95%**	
1	4.283	(-10.09	13.27)		1.817	(0.2961	4.779)
2	2.789	(-13.91	12.83)		1.333	(0.1483	3.243)
3	2.967	(-12.32	12.52)		1.404	(0.0063	3.665)
4	2.973	(-17.18	13.53)		1.372	(0.4987	2.845)
5	4.502	(-11.07	14.25)		1.953	(0.5830	4.227)
6	3.609	(-11.95	12.92)		1.675	(0.2972	4.054)
7	3.814	(-12.89	13.65)		1.751	(0.4995	3.812)
Mean	3.516	(-12.34	13.08)		1.615	(0.3609	3.778)
Ambulatory group							
S. No.	**Intercept (a_{ik})**	**CI 95%**			**Inclination (b_{ik})**	**CI 95%**	
1	24.93	(15.92	34.95)		-1.296	(-2.130	-0.5199)
2	19.79	(13.57	27.99)		-1.723	(-3.058	-0.7007)
3	23.18	(15.61	30.96)		-1.525	(-2.458	-0.6354)
4	23.32	(16.14	31.03)		-1.657	(-2.769	-0.6348)
5	25.00	(16.20	34.21)		-1.373	(-2.238	-0.5339)
6	18.47	(13.38	26.35)		-1.718	(-3.492	-0.6549)
7	20.64	(13.95	29.00)		-1.686	(-2.892	-0.6999)
8	23.71	(15.44	32.65)		-1.484	(-2.421	-0.6057)
9	22.94	(15.37	31.11)		-1.605	(-2.555	-0.6928)
10	24.03	(16.05	31.90)		-1.318	(-2.124	-0.4899)
11	26.55	(17.01	36.63)		-1.534	(-2.651	-0.4973)
Mean	23.09	(15.79	30.12)		-1.562	(-2.453	-0.646)

Table 2: Intercept and inclination values for lines that describe individual 10 MWT performances for non-ambulatory and ambulatory participants.

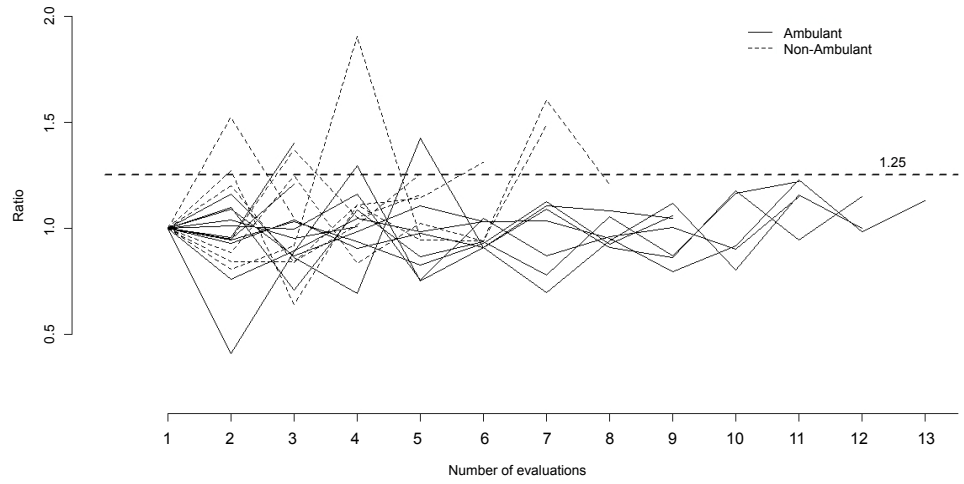

Figure 3: Rates between successive evaluation sessions of 10 MWT.

		Muscle groups							
NA participant	**10 MWT Session**	**HF**	**HE**	**HABD**	**HAD**	**KE**	**KF**	**ADF**	**APF**
1	2nd	4	3	4	4	3	5	4	5
2	6th	3	3	3	3	3	5	3	4
3	5th	3	3	3	3	3	4	3	4/5
4	2nd	3	2	3	3	3	5	4	5
5	3rd	3	2	4	3	3	4	3	5
6	7th	3	2	3	3	3	4	3	4
7	4th	3	2	3	3	2	3	4	4

NA: non-ambulantory; HF: hip flexor; HE: hip extensor; HABD: hip abductor; HAD: hip adductor; KE: knee extensor; KF: knee flexor; ADF: ankle dorsiflexor; APF: ankle plantar flexor.

Table 3: Muscle strength (hip, knee and ankle) for the NA group evaluated during the 10 MWT session that preceded loss of gait.

cost and has great potential to indicate the natural course of the disease and its ambulation limitations.

Study limitations

We did not evaluate possible interactions between the use of medication, ankle foot orthosis and/or physiotherapy on the gait of the participants. There are other factors besides reduction of muscle strength and the execution ability of motor tasks in lower limbs that influence the loss of gait in DMD patients. The limitations of our study are related to health service regulations, the subject's age at the time of the DMD diagnosis and their socio-economic and cultural level. We are unable to document the psychological and motivational factors influencing the caregiver and their level of acceptance and involvement.

Conclusion

Calculating the rates between consecutive sessions in the 10 MWT every 4 to 6 months is extremely important, in order to detect the probability of future ambulation limitations in boys with DMD. Combining lower limb muscle strength tests and the 10 MWT is useful to predict the loss of gait in this population.

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Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. Dubowitz V (1995) Muscle disorders in childhood. Bailliere Tindall.
2. Pegoraro E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, et al. (2011) SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology 76: 219–226.
3. Desguerre I, Christov C, Mayer M, Zeller R, Becane HM, et al. (2009) Clinical heterogeneity of Duchenne muscular dystrophy (DMD): Definition of sub-phenotypes and predictive criteria by long-term follow-up. PLoS One 4: e4347.
4. Siegel KL, Kepple TM, Stanhope SJ (2007) A case study of gait compensations for hip muscle weakness in idiopathic inflammatory myopathy. Clin Biomech 22: 319–326.
5. McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, et al. (2010) The 6 min walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve 41: 500–510.
6. Mazzone ES, Pane M, Sormani MP, Scalise R, Berardinelli A, et al. (2013) 24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy. PLoS One 8: 4–9.
7. Bakker JPJ, De Groot IJ, Beelen A, Lankhorst GJ (2002) Predictive factors of cessation of ambulation in patients with Duchenne muscular dystrophy. Am J Phys Med Rehabil 81: 906–912.

8. Beenakker EA, Maurits NM, Fock JM, Brouwer OF, van der Hoeven JH (2005) Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients. Eur J Paediatr Neurol 9: 387–393.

9. Uchikawa K, Liu M, Hanayama K, Tsuji T, Fujiwara T et al. (2004) Functional status and muscle strength in people with Duchenne muscular dystrophy living in the community. J Rehabil Med 36: 124–129.

10. Bérard C, Payan C, Hodgkinson I, Fermanian J (2005) A motor function measure scale for neuromuscular diseases. Construction and validation study. Neuromuscul Disord 15: 463–470.

11. Mazzone E, Martinelli D, Berardinelli A, Messina S, D'Amico A et al. (2010) North Star Ambulatory Assessment, 6 min walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord 20: 712–716.

12. Watson MJ (2002) Refining the ten metre walking test for use with neurologically impaired people. Physiotherapy 88: 386–397.

13. Pirpiris M, Wilkinson a J, Rodda J, Nguyen TC, Baker RJ, et al. (2003) Walking speeds in children and young adults with neuromuscular disease: Comparison between two assessment methods. J Pediatr Orthop 23: 302–307.

14. Bonifati MD, Ruzza G, Bonometto P, Berardinelli A, Gorni K, et al. (2000). A multicenter, double-blind, randomized trial of Deflazacort versus prednisone in Duchenne muscular dystrophy. Muscle Nerve 23: 1344–1347.

15. Nair KPS, Vasanth A, Gourie-Devi M, Taly AB, Rao S, et al. (2001) Disabilities in children with Duchenne muscular dystrophy: A profile. J Rehabil Med 33: 147–149.

16. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. Lancet Neurol 9: 177–189.

17. Mayhew JE, Florence JM, Mayhew TP, Henricson EK, Leshner RT et al. (2007) Reliable surrogate outcome measures in multicenter clinical trials of Duchenne muscular dystrophy. Muscle Nerve 35: 36–42.

18. Voit T, Topaloglu H, Straub V, Muntoni F, Deconinck N, et al. (2014) Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): An exploratory, randomised, placebo-controlled phase 2 study. Lancet Neurol 13: 987-996.

19. Alemdaroğlu I, Karaduman A, Yilmaz ÖT, Topaloğlu H (2015) Different types of upper extremity exercise training in Duchenne muscular dystrophy: effects on functional performance, strength, endurance and ambulation. Muscle Nerve 51: 697–705.

20. McDonald CM, Henricson EK, Abresch RT, Han JJ, Escolar DM, et al. (2013) The cooperative international neuromuscular research group Duchenne natural history study--a longitudinal investigation in the era of glucocorticoid therapy: Design of protocol and the methods used. Muscle Nerve 48: 32–54.

21. Vandervelde L, Van den Bergh PYK, Renders A, Goemans N, Thonnard JL (2009) Relationships between motor impairments and activity limitations in patients with Neuromuscular disorders. J Neurol Neurosurg Psychiatry 2009 80: 326–332.

22. Pereira AC, Ribeiro MG, Araujo AP de QC (2016) Timed motor function tests capacity in healthy children. Arch Dis Child 101: 147–151.

23. Hyde SA, Steffensen BF, Fløytrup I, Glent S, Kroksmark AK, et al. (2001) Longitudinal data analysis: An application to construction of a natural history profile of Duchenne muscular dystrophy. Neuromuscul Disord 11: 165–170.

24. Donner A, Wells G (1986) A comparison of confidence interval methods for the intraclass correlation coefficient. Biometrics 401-412.

25. Yilmaz Ö, Karaduman A, Topalo□lu H (2004) Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. Eur J Neurol 11: 541–544.