How do physical capacity, fatigue and performance differ in children with duchenne muscular dystrophy compared with their healthy peers?

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ABSTRACT

الأهداف: مقارنة مستويات التعب والنشاط البدني للأطفال الذين يعانون من الضمور العضلي الدوشيني (DMD) على مستويات وظيفية مختلفة مع الأطفال الأصحاء.

الطريقة: أجريت دراسة مستعرضة في وحدة الأمراض العصبية والعضلية للأطفال في قسم العلاج الطبيعي والتأهيل، كلية العلوم الصحية، جامعة هاستيب خلال الفترة من مارس 2015م ويناير 2016م. وقد تم تشخيص 55 طفلا DMD في المستوى I-III وفقا لمقياس التصنيف الوظيفي بروك و 17 أطفال أصحاء أدرجوا في الدراسة. تم استخدام اختبار ستة دقائق للمشي (6MWT)، مقياس تقييم نورثستار الإسعافية (NSAA)، مؤشر التكلفة الفسيولوجية (PCI)، واختبار وقت الأداء لتقييم الأطفال.

النتائج: أظهرت المقارنة من حيث PCI الفرق بين المستويين 2 و 3، والمستويين 1 و 3 (p<0.0083). تم العثور على فرق في الصعود والنزول 4 درجات بعد 6MWT عندما تم تقييم التعب بعد النشاط.

الخاتمة: كانت مسافات المشي، ومستويات التعب والنشاط البدني من مرضى DMD أعلى من أقرانهم الأصحاء. وكان هذا الاختلاف أكثر وضوحاً مع انخفاض المستوى الوظيفي.

Objectives: To compare the fatigue levels and energy expenditure of children with Duchenne Muscular Dystrophy (DMD) at different functional levels with healthy children.

Methods: The cross-sectional study was carried out in the Unit of Pediatric Neuromuscular Diseases in the Department of Physiotherapy and Rehabilitation, Faculty of Health Science, Hacettepe University between March 2015 and January 2016. Fifty two children diagnosed with DMD in Level I-III according to the Brooke Functional Classification Scale and 17 healthy children were included in the study. The Six Minute Walk Test (6MWT), Northstar Ambulatory Assessment Scale (NSAA), Physiological Cost Index (PCI), and Timed performance tests were used to assess the children.

Results: Comparison in terms of PCI indicated a difference between Levels 2 and 3, and Levels 1 and 3 (p<0.0083). A difference was found in ascending and descending 4 stairs after 6MWT when fatigue after activity was evaluated.

Conclusion: The walking distances, fatigue levels and energy expenditure of DMD patients were higher than the healthy peers. This difference was more prominent with decreasing functional level.

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Duchenne Muscular Dystrophy (DMD), the most common muscular dystrophy in childhood, is an inherited disease characterized by progressive muscle weakness and affects cardiopulmonary functions and ambulation level.[1,2] It makes up 85% of dystrophies and has an unfavorable prognosis. The structure of the dystrophin protein which provides the connection between the extracellular matrix and the cytoskeleton in muscle tissue is disrupted due to deletion, duplication or point mutations in the Xp21.2 region of the dystrophin gene with X-linked recessive inheritance and the protein cannot function.[2-4] Although the initial clinical symptoms emerge at the age of one, they usually become visible in the period where they start to walk

and the preschool period.[5] Duck-like walking, walking on toes, pseudohypertrophy in the gastrocnemius and soleus muscles, Gower's sign (climbing on oneself by supporting the hands from the thighs while straightening up, legs in the abduction position while getting off the ground) and difficulty in ascending the stairs are seen in these children. While the functional level is preserved between the ages of 3-6 years, a decrease is seen between the ages of 6-8.[3,4] Functional movements become limited between the ages of 9-12 and the children become dependent on the wheelchair.[6]

One of the most important symptoms in children with DMD is excessive fatigue,[7] identified as the failure of a muscle to maintain the strength expected to perform an activity.[8] Although the etiopathogenesis is yet unknown, genetic factors, metabolic products accumulating in the body, muscle metabolism changes, the disease process, sleep status, activity/rest, disease treatment, psychological states, oxygenation, energy change, homeostatic changes, environmental factors, and social factors are among the relevant factors.[9] Fatigue is also one of the most important factors causing a limitation of exercise and activities. The fatigue and physical activity level are closely related to the functional dysfunction in daily life.[10] Thus, fatigue decreases the physical capability of the individuals, increases dependency levels, and lowers the quality of life.[11]

A close relationship between the fatigue and physical activity level and the functional dysfunction level in daily life is recognized in neuromuscular disorders and patients are recommended to increase their physical activity levels.[12]

Only a few studies are available on the fatigue levels in children with DMD in the literature. We did not come across any study comparing the fatigue and energy levels in children with DMD at various stages with that of healthy children. This study was planned to compare the fatigue levels and energy expenditure of children with DMD at different function levels and healthy children.

Methods. ***Participants.*** The cross-sectional study was carried out in the Unit of Pediatric Neuromuscular Diseases in the Department of Physiotherapy and Rehabilitation, Faculty of Health Science, Hacettepe University between March 2015 and January 2016. Children with Duchenne Muscular Dystrophy at the first 3 levels according to the Brooke Lower Extremity Functional Rating Scale and healthy children in a similar age group were included. A total of 52 DMD patients; 18 from Level 1, 17 from Level 2 and 17 from Level 3 together with 17 healthy individuals were included in the study as a result of statistical power analysis. Name, surname, demographic data and physical characteristics such as height, body weight and body mass index (BMI) were recorded for all children. All the DMD patients consisted of children who were regularly followed-up at our unit with a home program and family training and were using an ankle foot orthosis during the night. The children were included in the study after obtaining informed assent from the healthy children and informed consent from their families. Permission was also obtained for the study from Hacettepe University Non-Interventional Clinical Studies Ethics Committee in March 2015. The study was performed in accordance to the Helsinki Declaration.

The inclusion criteria of the cases were determined as: Diagnosed with Duchenne Muscular Dystrophy, aged 6 to 11 years, able to cooperate with the instructions of the physiotherapist, no acute disease, no history of any injury or neurologic or orthopedic surgery within the past 6 months.

Exclusion criteria were the withdrawal of consent and not using steroids.

Outcome measures. Functional status. The functional levels of the cases were identified according to the Brooke Lower Extremity Functional Classification. This classification method was prepared based on the method determined by Vignos et al to identify the functional status of the lower and upper extremity during the clinical evaluation of Duchenne Muscular Dystrophy in 1981.[13] The Brooke Lower Extremity Functional Classification scale[14] evaluates the functional level of children with DMD in 10 levels.

Children in the first 3 levels were selected for this study. Level 1: The child can walk and ascend 4 stairs without help. Level 2: The child can walk and ascend 4 stairs by holding the handrail (walks and ascends the stairs in less than 12 seconds by holding the handrail). Level 3: The child can slowly ascend 4 stairs (walks and ascends the stairs in longer than 12 seconds by holding the handrail).

Six-minutes Walking Test (6MWT). The 6MWT is an accepted evaluation method for physical functional capacity and endurance. Its validity and reliability in

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DMD has been proven and it is used commonly.[15] It is a submaximal walking test that can easily be used in children to measure the distance they can walk in 6 minutes on level ground. It is a simple and easy-to-use evaluation that does not require a high-technology tool and can be performed at the child's own walking tempo.[3]

Fatigue evaluation. We used the duration of ascending and descending 4 stairs in the evaluation of the acute effect of fatigue in our study.[16] The durations of ascending and descending 4 stairs (as fast as possible and as much as possible without holding the handrail against time) without resting before and after the 6MWT test were recorded by stopwatch. We therefore estimated the fatigue of the children in Level 1, Level 2, and Level 3 and the control groups after the activity with an objective method that expresses physiologic fatigue after activity.

Energy expenditure. The easy-to-use Physiological Cost Index (PCI) [(walking heart rate) - (resting heart rate)) / (walking speed)] was used for 6 minutes to calculate the energy expenditure of the children.[17] The children were seated in a chair for 10 minutes before starting the test and the resting heart rate was measured with a fingertip pulse oximeter. When they were ready, the children were asked to stand up and start to walk. As soon as they started to walk, the chronometer was started and the heart rates were measured again every 3 minutes. They were then asked to sit on the chair again at the end of the 6 minutes, and the heart rate was again measured. The walking distance was recorded to calculate the walking speed. After all parameters were obtained, the PCI, i.e. the energy consumed was calculated.

Timed performance tests. Duration from lying supine to standing up, duration of walking/running a distance of 10 meters, and duration of ascending and descending 4 stairs were recorded in order to evaluate the functional performances of the patient group and the healthy group against time.[18]

Northstar ambulatory assessment scale. The ambulation level of the DMD patients was evaluated with the North Star Ambulation Assessment (NSAA). North Star Ambulation Assessment is graded as the patient ambulating normally and without help, ambulating with compensation, and unable to perform the activity independently. North Star Ambulation Assessment contains 17 items that evaluate the abilities required to continue functional ambulation such as standing on foot, walking 10 meters, jumping, and running. It is scored between 0 and 34 and conducted without the brace or orthoses used by the child in daily life.[19]

Statistical analysis. The IBM Statistical Package for the Social Science Version 20 (IBM Corp., Armonk, NY, USA) program was used for the statistical analyses. The compliance of the variables with the normal distribution was evaluated with Skewness, Kurtosis and Histogram Analysis, the Kolmogorov-Smirnov Test and the variation coefficient. The data were not consistent with a normal distribution. Descriptive analyses were presented as mean±standard deviation and minimum and maximum for numerical data and by using frequency tables for non-numerical data. Data with numerical variables were compared with the Kruskal-Wallis test. Post-hoc analyses for pairwise comparisons were conducted by using the Mann-Whitney U test with Bonferroni correction. The total type-1 error level was accepted as 5% and the *p*-value as smaller than 0.05 for statistical significance.

Results. Demographic information of the groups Level 1, 2, 3 and the healthy group are shown in **Table 1.** There was no difference between the children at Level 1, 2, 3 and the healthy group in terms of height, weight and body mass index, but a difference was found between Level 1 and 3 in terms of age ($p<0.0083$).

Descriptive statistics of PCI, 6MWT, ascending 4 stairs before 6MWT, descending 4 stairs before 6MWT, 10 meters walk/run, and standing from supine used in the study are presented in **Table 2.** The comparison of the evaluation parameters of the Level 1, 2, 3 groups and the healthy group are shown in **Table 3.**

A difference was found for ascending and descending 4 stairs after 6MWT when fatigue after activity was evaluated, except the duration of descending the stairs in Level 2. When compared in terms of the 6 minutes walking distance, differences were found between all groups, for example, Level 1 and 2, Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 ($p<0.0083$).

Comparison in terms of PCI revealed a difference between Level 2 and 3, and Level 1 and 3 ($p<0.0083$), but not between the other groups.

When compared in terms of ascending 4 stairs before and after 6MWT, a difference was found between all groups, for example, between Level 1 and 2, Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 ($p<0.0083$).

Comparison of the descending 4 stairs before and after 6MWT values revealed a difference between Level 2 and 3, Level 1 and 3, Healthy group and Level 1, Healthy group and Level 2, and Healthy group and Level 3 ($p<0.0083$), but no difference between Level

Table 1 - Physical features of the groups.

Demographic information	DMD			Healthy Group n=17	*p*-value
	Level 1 n=18	Level 2 n=17	Level 3 n=17		
	Mean±SD				
Age (months)	93.66±16.94	102.47±17.41	113.23±16.96	102.88±18.78	0.020*
Height (cm)	119.00±9.80	123.41±9.46	127.76±9.51	126.35±11.72	0.079
Weight (kg)	25.72±5.44	27.26±6.88	31.58±8.32	30.35±9.75	0.110
BMI (kg/m^2)	18.06±15.36	17.70±2.68	19.10±3.47	18.71±3.15	0.403

*Level 1- Level 3 (p<0.0083 after the Bonferroni correction), BMI - body mass index, DMD - Duchenne Muscular Dystrophy, SD - Standard Deviation, cm - centimeter, m - meter, kg - kilogram

worsened. Although children at Level 1 and Level 2 had similar energy expenditure to the healthy group, their walking distances were very different. This shows that the patients and healthy group show different performances with the same energy expenditure. Level 3 consumed the highest energy among the children with DMD with an energy expenditure 3 times higher than the healthy group. We found the functional level in children with DMD and especially at Level 3 according to the Brooke classification to be important in terms of performance as well as energy expenditure. These results should be taken into account when planning the treatment programs, determining the intensity of exercise, and preventing excess energy expenditure and fatigue in children with DMD.

Exercise limitation can develop in these patients due to the potential destructive effects of the exercises related to neuromuscular disorders as mentioned in the literature. Studies have proven that submaximal exercises are useful in DMD patients since maximal exercise causes fatigue and muscle destruction.[23] Belanger et al[24] examined the contraction of foot dorsal and plantar flexors by having muscular dystrophy patients hit a ball and found more muscle fatigue in the dominant extremity, indicating damage due to excessive use of muscles.[24] The patient group was seen to show more fatigue than the control group with 2 minutes of maximal voluntary contraction of the biceps muscle in a study conducted by Schillings et al[25] on various neuromuscular disorder groups and a healthy group. The 6MWT was used and the estimated fatigue calculated according to the differences in distance walked in the first and sixth minutes of the 6MWT. The largest difference was found in patients with Spinal Muscular Atrophy and a small difference was found with DMD. They reported that the relationship between weakness and fatigue varied according to the disease mechanism as an outcome of the study.[26] When the fatigue of 1 and 2. When compared in terms of the 10 meters walking/running duration, differences were found between all groups (p<0.0083). Comparison of the values for standing from the supine position again showed differences between all groups (p<0.0083). The total NSAA score of the children with DMD showed a difference between Level 1 and 2, Level 2 and 3, and Level 1 and 3 (p<0.016).

Discussion. This study was planned to compare the physical capacity, fatigue and performances of children with DMD at different functional levels with healthy children. We found that the walking distance, fatigue level and energy expenditure of the children with DMD were lower than in their healthy peers and that this difference became more prominent as the functional level decreased. Children with DMD performed all the timed performance tests in significantly longer durations than the healthy children and Level 3 consumed the highest energy with an energy expenditure 3 times higher than the healthy group. We believe that the data obtained from our evaluations can be easily put to practical use by physiotherapists and can guide the physiotherapy and rehabilitation procedures of these patients.

The energy expenditure can be measured with sophisticated instruments but the PCI method is easy and practical.[20] This method is based on the proportional relationship of the oxygen used by the individual and the heart rate. Its validity in the measurement of oxygen expenditure has been shown in disabled children walking at their own speed.[20,21] A study has reported a PCI value of 0.40 for a 9-year-old and 0.20 for a 6-year-old healthy child when walking 10 meters.[22] This indicates that the energy consumed increases with development. The difference in energy expenditure between Level 1 and 3 and between Level 2 and 3 in our study indicated that energy expenditure increased as the functional level

Table 2 - Descriptive statistics of all outcome measures used in the study

Parameters	Mean±SD	Upper Limit (%95 CI)	Lower Limit (%95 CI)	Min./Max.	IQR
Level 1					
PCI (beat/m)	0.25±0.15	0.17	0.33	0.025/0.619	0.25
6MWT (m)	434.02±57.95	405.20	462.84	335/523	104.75
Ascending four stairs before 6MWT (sn)	2.59±0.91	2.14	3.05	1.17/4.61	1.38
Descending four stairs before 6MWT (sn)	2.07±0.55	1.79	2.35	1.13/2.91	0.91
Ten meters walk/run (sn)	4.75±0.75	4.38	5.13	3.60/6.12	1.22
Standing from supine (sn)	4.93±1.74	4.07	5.80	2.33/9.23	2.36
Level 2					
PCI (beat/m)	0.34±0.20	0.24	0.45	0.089/0.752	0.37
6MWT (m)	367.44±63.34	334.35	400.52	255/490	81.50
Ascending four stairs before 6MWT (sn)	4.82±1.66	3.96	5.67	2.34/8.19	5.85
Descending four stairs before 6MWT (sn)	2.93±1.31	2.25	3.61	1.38/6.81	1.52
Ten meters walk/run (sn)	6.27±1.51	5.49	7.05	4.60/10.30	1.34
Standing from supine (sn)	8.09±2.52	6.80	9.39	3.51/12.06	4.41
Level 3					
PCI (beat/m)	0.95±1.34	0.26	1.65	0.11/5.63	0.73
6MWT (m)	227.47±93.84	179.21	275.72	25/350	142.50
Ascending 4 stairs before 6MWT (sn)	20.53±11.25	14.75	26.32	4.31/40.80	6.69
Descending 4 stairs before 6MWT (sn)	10.83±8.70	6.36	15.31	4.31/40.80	6.69
Ten meters walk/run (sn)	12.98±8.24	8.74	17.22	7.62/43.12	5.55
Standing from supine (sn)	31.89±18.21	22.53	41.26	12.90/73	28.53
Healthy Group					
PCI (beat/m)	0.33±0.21	0.21	0.44	0.08/0.91	0.31
6MWT (m)	541.44±62.41	509.34	573.53	415/632	100
Ascending four stairs before 6MWT (sn)	1.41±0.30	1.25	1.57	1.00/2.16	0.35
Descending 4 stairs before 6MWT (sn)	1.22±0.30	1.06	1.37	0.86/1.90	0.35
Ten meters walk/run (sn)	3.23±0.46	2.99	3.47	2.38/4.19	0.43
Standing from supine (sn)	1.79±0.47	1.54	2.03	1.07/2.89	0.65

SD - Standard Deviation, PCI - Physiological Cost İndex, 6MWT - 6 Minute Walk Test, m - meter, sn - second

the groups after activity was examined, the duration of ascending and descending the stairs after 6MWT was seen to have increased even in the control group. The largest mean duration increase after 6MWT was experienced by Level 3 children and the smallest by the control group. The physiological fatigue of the children with DMD was seen to increase in relation to worsening functional level. The duration of descending the stairs did not change after 6MWT in Level 2 children. This may have 2 reasons: The children use gravity to their advantage for this activity and also make good use of the postural compensations that develop secondary to the muscle weakness in DMD.

It has been reported that using a combination of the standard evaluation methods such as the NSAA ambulation test, 6MWT, and timed performance tests to determine functionality in DMD patients will provide more effective results compared to using only one of these methods.[27] The 6MWT, NSAA and timed performance tests were used in a study conducted on 112 ambulatory children with DMD. The mean 6MWT distance was less than 300 meters in children with a total NSAA score under 17 and 400 meters in those with a total NSAA score over 29.[28] A difference was found between the groups in terms of total scores in our study. This result is similar to those reported in other articles. While Level 1 patients had values close to the maximum possible score, their score was also 3 times higher than in Level 3. Martini et al[29] evaluated timed performance tests in 14 cases with DMD and investigated the relationship between activity durations and the compensating movements used. These

Table 3 - The results of all outcome measures of the Groups.

Parameters	DMD						Healthy Group	
	Level 1 (Mean±SD) n=18	Z-value/ *p*-value	Level 2 (Mean±SD) n=17	Z-value/ *p*-value	Level 3 (Mean±SD) n=17	Z-value/ *p*-value	(Mean±SD) n=17	Z-value/ *p*-value
*Ascending 4 stairs before 6MWT (sn)	2.59±0.91	-2.699 0.007	4.82±1.66	-2.959 0.003	20.53±11.25	-3.053 0.002	1.41±0.30	-3.531 0.0001
*Ascending 4 stairs after 6MWT (sn)	2.96±1.08		5.32±1.73		24.63±14.09		1.72±0.36	
*Descending 4 stairs before 6MWT (sn)	2.07±0.55	-2.179 0.029	2.93±1.31	-1.775 0.076	10.83±8.70	-2.320 0.020	1.22±0.30	-2.538 0.011
*Descending 4 stairs after 6MWT (sn)	2.33±0.81		3.15±1.35		12.31±10.55		1.40±0.44	
*Standing from supine (sn)	4.93±1.74		8.09±1.52		31.89±18.21		1.78±0.47	
*10 meters walk/run (sn)	4.75±0.75		6.27±1.51		12.98±8.24		3.23±0.46	
*6MWT (m)	434.02±57.95		367.44±64.34		227.47±93.84		541.44±62.41	
†PCI (beat/m)	0.25±0.157		0.34±0.205		0.95±1.349		0.30±0.21	
*NSAA (0-34)	29.88±2.56		21.29±3.73		11.05±3.26		N/A	

*p-value=0.0001, †p-value=0.012, ($p<0.0083$ and $p<0.016$ after the Bonferroni correction), DMD - Duchenne Muscular Dystrophy, SD - Standard deviation, 6MWT - 6 Minute Walk Test, NSAA - Northstar Ambulatory Assessment Scale, PCI - Physiological Cost Index, sn - second, N/A - Not Applicable

compensating movements used in standing from the supine position and ascending and descending from the stairs were found to be related to the activity duration and to be variable.

We found that the children with DMD took significantly longer than healthy children for all the timed performance tests we used in the study. The standing from the supine position duration was 4 times longer in Level 1, 4 times longer in Level 2 and 16 times longer in children with DMD compared to their healthy peers. The ascending and descending the stairs durations were again longer in the children with DMD compared to the healthy children.

As a conclusion, the walking distances, fatigue levels and energy expenditure of DMD patients were higher than the healthy peers. This difference was more prominent with decreasing functional level. The fatigue increases 13 times at Level 3 according to the Brooke classification.

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References

1. Kohler M, Clarenbach CF, Bahler C, Brack T, Russi EW, Bloch KE. Disability and survival in Duchenne muscular dystrophy. ***J Neurol Neurosurg Psychiatry*** 2009; 80: 320-325.
2. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. ***Lancet Neurol*** 2010; 9: 77-93.
3. Goemans N, Van den Hauwe M, Wilson R, Van Impe A, Klingels K, Buyse G. Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. ***Neuromuscul Disord*** 2013; 23: 618-623.
4. Karaduman A, Yılmaz Ö, Alemdaroğlu İ. Pediatric Physical Therapy and Rehabilitation in Neuromuscular Disorders Ankara (Turkey): Pelikan press; 2014.
5. McDonald CM, Abresch RT, Carter GT, Fowler Jr WM, Johnson ER, Kilmer D, et al. Profiles of neuromuscular diseases: Duchenne muscular dystrophy. ***Am J Phys Med Rehabil*** 1995; 74: 93.
6. Tunçbay T, Tunçbay E. Muscular Dystrophies: Neuromuscular Disorders. İzmir (Turkey): Nobel Medical Publications; 2004. p. 418-497.
7. Mathieu J, Boivin H, Meunier D, Mathieu J, Boivin H, Meunier D, et al. Assessment of a disease-spesific muscular impairment rating scale in myotonic dystrophy. ***Neurology*** 2001; 56: 336-340.
8. Edwards RH. Human muscle function and fatigue. In Human muscle fatigue: physiological mechanisms. ***Pitman Medical London*** 1981; 82: 1-18
9. Maclaren DP, Gibson H, Parry-Billings MARK, Edwards RH. A review of metabolic and physiological factors in fatigue. ***Exerc Sport Sci Rev*** 1989; 17: 29-66.
10. Kalkman JS, Schillings ML, Van der Werf S, Padberg GW, Zwarts MJ, van Engelen BGM, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. ***J Neurol Neurosurg Psychiatry*** 2005; 76: 1406-1409.
11. Miller RG. Role of fatigue in limiting physical activities in humans with neuromuscular diseases. ***Am J Phys Med Rehabil*** 2002; 81: 99-107.
12. Kalkman JS, Schillings ML, Zwart MJ, van Engelen BG, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. ***J Psychosom Res*** 2007; 62: 571-579.

13. Vignos PJ, Spencer GE, Archibald KC. Management of progressive muscular dystrophy of childhood. ***Jama*** 1963; 184: 89-96.
14. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy. I. The design of the protocol. ***Muscle nerve*** 1981; 4: 186-197.
15. McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, Elfring GL, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. ***Muscle Nerve*** 2010; 41: 500-510.
16. Feasson L, Camdessanché JP, El Mhandi L, Calmels P, Millet GY. Fatigue and neuromuscular diseases. ***Ann Readapt Med Phys*** 2006; 49: 375-384.
17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. ***Am J Respir Crit Care Med*** 2002; 166: 111.
18. Mcdonald CM, Henricson EK, Abresch RT, Florence JM, Eagle M, Gappmaier E, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. ***Muscle nerve*** 2013; 48: 343-356.
19. Mazzone ES, Messina S, Vasco G, Main M, Eagle M, D'Amico A, et al. Reliability of the North Star Ambulatory Assessment in a multicentric setting. ***Neuromuscul Disord*** 2009; 19: 458-461.
20. Ijzerman MJ, Nene AV. Feasibility of the physiological cost index as an outcome measure for the assessment of energy expenditure during walking. ***Arch Phys Med Rehabil*** 2002; 83: 1777-1782.
21. Keefer DJ, Tseh W, Caputo JL, Apperson K, McGreal S, Morgan D. Comparison of direct and indirect measures of walking energy expenditure in children with hemiplegic cerebral palsy. ***Dev Med Child Neurol*** 2004; 46: 320-324.
22. Boyd R, Fatone S, Rodda J, Olesch C, Starr R, Cullis E, et al. High- or low- technology measurements of energy expenditure in clinical gait analysis. ***Dev Med Child Neurol*** 1999; 41: 676-682.
23. Aboussouan LS. Mechanisms of exercise limitation and pulmonary rehabilitation for patients with neuromuscular disease. ***Chron Respir Dis*** 2009; 6: 231-249.
24. Bèlanger AY, Noël G, CÔte C. A comparison of contractile properties in the preferred and nonpreferred leg in a mixed sample of dystrophic patients. ***Am J Phys Med Rehabil*** 1991; 70: 201-205.
25. Schillings ML, Kalkman JS, Janssen HM, Van Engelen BGM, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. ***Clin Neurophysiol*** 2007; 118: 292-300.
26. Montes J, Blumenschine M, Dunaway S, Alter AS, Engelstad K, Rao AK, et al. Weakness and fatigue in diverse neuromuscular diseases. ***J Child Neurol*** 2013; 28: 1277-1283.
27. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better. ***Orphanet J Rare Dis*** 2013; 8: 160.
28. Mazzone E, Martinelli D, Berardinelli A, Messina S, D'Amico A, Vasco G, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. ***Neuromuscul Disord*** 2010; 20: 712-716.
29. Martini J, Hukuda ME, Caromano FA, Favero FM, Fu C, Voos MC. The clinical relevance of timed motor performance in children with Duchenne muscular dystrophy. ***Physiother Theory Pract*** 2015; 31: 173-181.