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ORIGINAL RESEARCH

Upper limb function in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy

Funcionalidade de membro superior em pacientes deambuladores e não deambuladores com distrofia muscular de Duchenne

Funcionalidad de los miembros superiores en pacientes caminantes y no caminantes con distrofia muscular de Duchenne

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ABSTRACT | New treatments proposed for patients with Duchenne muscular dystrophy (DMD) have their efficacy evaluated by lower limb tests. However, upper limb function tests evaluate both ambulatory (A) and non-ambulatory (NA) people. Thus, this work aimed to compare the upper limb function of patients A and NA with DMD and to correlate disease staging and upper limb function. This is a cross-sectional study in which patients were divided into A and NA according to the Vignos scale. Subsequently, the upper limb function was evaluated by the performance of upper limb (PUL) scale. The independent t-test, chi-square test, Mann-Whitney test, linear regression and Spearman's correlation test were performed by SPSS, version 22. The research dealt with 51 patients, 20 A and 31 NA. There were differences between the groups reference age (p=0.001), body mass index (BMI) (p=0.016), schooling (p=0.011), Vignos score (p<0.001) and upper limb function (p<0.001). The linear regression analysis showed that whether the patient was A or NA influenced the upper limb function in 18 points on the PUL scale. There was a strong correlation between disease staging and upper limb function (r^2=−0.769, p<0.001). The functional condition of the upper limb depends on whether the patient is A or NA, being worse function in NA patients. We concluded that the upper limb function has a strong correlation with the staging of the disease.

Keywords | Muscular Dystrophy, Duchenne ; Upper Extremity; Physical therapy.

RESUMO | Novos tratamentos propostos para os pacientes com distrofia muscular de Duchenne (DMD) têm sua eficácia avaliada por testes de membros inferiores. Contudo, os testes funcionais de membros superiores (MMSS) avaliam tanto deambuladores (D) como não deambuladores (ND). Assim, este estudo se propôs a comparar a funcionalidade de MMSS de pacientes D e ND com DMD e correlacionar o estadiamento da doença e a função de MMSS. Trata-se de um estudo transversal no qual os pacientes foram divididos em D e ND de acordo com a escala Vignos. Posteriormente, a funcionalidade dos MMSS foi avaliada pela escala *performace of upper limb* (PUL). Foi realizado o teste t independente, teste qui-quadrado, teste Mann-Whitney, regressão linear e teste de correlação de Spearman pelo programa SPSS, versão 22. A pesquisa foi composta de 51 pacientes, sendo 20 D e 31 ND. Houve diferença entre os grupos em relação à idade (p=0,001), ao índice de massa corporal (IMC) (p=0,016), à escolaridade (p=0,011), quanto ao escore na escala Vignos (p<0,001) e na função dos

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MMSS (p<0,001). Na análise de regressão linear observamos que o paciente ser D ou ND influencia na função dos MMSS em 18 pontos na escala PUL. Houve forte correlação entre o estadiamento da doença e a função de MMSS (r^2=−0,769, p<0,001). A condição funcional dos MMSS depende se o paciente é D ou ND, sendo pior nos ND. Concluiu-se que a função de MMSS tem forte correlação com o estadiamento da doença.
Descritores | Distrofia Muscular de Duchenne; Extremidade Superior; Fisioterapia.

RESUMEN | Se evalúa la eficacia de los nuevos tratamientos propuestos para pacientes con distrofia muscular de Duchenne (DMD) mediante pruebas de miembros inferiores. Sin embargo, las pruebas funcionales de las extremidades superiores (MMSS) evalúan tanto a los caminantes (C) como a los no caminantes (NC). Este estudio tuvo como objetivo comparar la funcionalidad de MMSS de pacientes C y NC con DMD y correlacionar la estadificación de la enfermedad y la función de MMSS. Este es un estudio transversal en el cual se dividieron a los pacientes en C y NC, según la escala de Vignos. Posteriormente, se evaluó la funcionalidad de las extremidades superiores utilizando la escala de rendimiento de la extremidad superior (PUL). La prueba t independiente, la prueba de chi-cuadrado, la prueba de Mann-Whitney, la regresión lineal y la prueba de correlación de Spearman se realizaron utilizando el programa SPSS, versión 22. Participaron 51 pacientes, de los cuales 20 C y 31 NC. Hubo una diferencia entre los grupos con respecto a la edad (p=0,001), índice de masa corporal (IMC) (p=0,016), nivel de estudios (p=0,011), con respecto al puntaje en la escala de Vignos (p < 0,001) y la función de los MMSS (p<0,001). En el análisis de regresión lineal, observamos que ser C o NC influye en la función de las extremidades superiores en 18 puntos en la escala PUL. Hubo una fuerte correlación entre la estadificación de la enfermedad y la función de los MMSS (r^2=−0.769, p<0,001). La condición funcional de los MMSS depende si el paciente es C o NC, empeorando cuando NC. Se concluyó que la función de los MMSS tiene una fuerte correlación con la estadificación de la enfermedad.
Palabras clave | Distrofia Muscular de Duchenne; Extremidad Superior; Fisioterapia.

INTRODUCTION

The quality and life expectancy of patients with Duchenne muscular dystrophy (DMD) has improved with the advancement of technology and multidisciplinary performance[1,2]. The proposed treatments have slowed the disease progression, that is, they have delayed functional dependence and cardiorespiratory[2,3] impairment.

However, studies that propose treatments for this population evaluate the therapeutic proposal through the performance of the lower limbs, commonly assessed by the 6-minute walk test[4,5]. However, such studies are limited to expressing therapeutic efficacy in ambulatory patients (A).

Although there is a specific tool that assesses the function of the upper limbs, national[6] and international studies[2,3] emphasize the attention to upper limbs only at the stage when the patient loses gait, guiding the diagnosis and treatment of patients with DMD.

Also, we understand that patients with DMD have functional dependence on their caregivers for clothing, personal hygiene and walking tasks[7] – that require performance of the upper limbs. Thus, there is a scarcity of studies that demonstrate the importance of the upper limb function for patients with DMD.

Therefore, the hypothesis of this study is that ambulatory (A) and non-ambulatory (NA) patients have different upper limb functionality, and that there is a correlation between the function of upper limbs and the staging of the disease.

Given the above, the objective was to compare the functionality of upper limbs of A and NA patients with DMD, and to correlate the staging of the disease and the upper limb function.

METHODOLOGY

Participants

This is a cross-sectional study in which patients diagnosed with DMD were selected by genetic tests (multiplex ligation-dependent probe amplification or sequencing) or muscle biopsy, seen at the outpatient clinic of the neuromuscular diseases sector at the Federal University of São Paulo (Unifesp), who agreed to participate in the research by signing the Informed Consent Term (ICF) and/or the Term of Assent (TA). However, patients who had undergone previous surgical procedures or had deformities in the upper limbs, lower limbs and/or spine were excluded; and also those who had another diagnosis besides DMD; difficulty understanding simple verbal commands; cognitive deficit (MMSE≤10 points), visual and/or auditory deficits

that make it impossible to apply the research protocol or who, for whatever reason, have refused to continue with the evaluation protocol.

Procedures

The assessment instruments were applied in the Investigation in Neuromuscular Diseases Sector of the Department of Neurology and Neurosurgery at Unifesp. We divided patients into A and NA according to the Vignos scale. Patients with Vignos ≥7 were considered NA, and with Vignos ≤6, A. The sample calculation performed through the OpenEpi website was 18 patients in each group, with a power of 0.8 and a significance level of 0.05. Subsequently, we evaluated the cognitive aspect by the mini mental state examination (MMSE) and the functionality of upper limbs by the performance of upper limb (PUL).

The Vignos scale, a clinical staging scale for muscular dystrophies, was used in order to characterize the level of lower limb functionality of patients. The scale score ranges from 1 to 10, the higher the score, the worse the patient's functional performance[8].

The MMSE evaluates specific cognitive functions, such as: temporal orientation (5 points), spatial orientation (5 points), memory (3 points), attention and calculation (5 points), the recall of the three words (3 points), language (8 points) and visual constructive capacity (1 point)[9]. The maximum test score is 30 points, and its classification is according to the patient's education, although in this case, patients with a score ≤10 points were[10] excluded because the patient did not understand simple verbal commands.

PUL, version 1.2, was developed with the aim of evaluating both A and NA patients, based on the natural progression of DMDI[1]. Divided into the proximal (shoulder), intermediate (elbow) and distal (wrist) level, it comprises 22 items, the first being a definition of the patient's functional level, that is, if the patient obtained a score of <4 points in this item, the evaluation would start at the intermediate level. The score on each item varies with the task, it can be from 0 to 1, as in item M, "open pot", or even from 0 to 5, in item H, "move the weight on the table". The maximum score of the scale comprises 74 points, indicating better upper limb performance[12]. NA patients were assessed sitting in their wheelchairs, and A patients were seated in a chair with a backrest. All patients were positioned with 90º of hip, knee and ankle flexion. For the best data evaluation, a camera was positioned 2 meters from the patient, and the footage was analyzed for scoring.

Statistical analysis

The analysis was performed using the SPSS program, version 22. The Kolmogorov-Smirnov test verified the normality of the variables. The numerical variables were compared by the independent t-Student test or by the Mann-Whitney test, and the nominal categorical ones, by the chi-square test. In order to adjust the variables that could influence the dependent variable, PUL, a linear regression analysis was performed. The Spearman test demonstrated the correlation between the Vignos scale and the PUL ($r \geq 0.9$: very strong correlation; $0.7 \geq r \leq 0.89$: strong correlation; $0.5 \geq r \leq 0.69$: moderate correlation; $0.3 \geq r \leq 0.49$: weak correlation; $0 \geq r \leq 0.29$: very weak correlation)[13]. The significance level was 5%.

RESULTS

Sixty two patients were evaluated. However, 17.7% were excluded, as 1 presented agenesis in the upper limb; 4 had MMSE <10 points; another 4 had diagnoses other than DMD, such as autism; and 2 did not agree to participate in the research. Then, 51 patients (82.3%) were included and divided between A (n=21) and NA (n=31).

Table 1. Values presented as mean±standard deviation for the numerical variables compared by the t test; in percentage (%) for categorical variables, compared using the chi-square test; in median and [interquartile range] for variables with non-normal distribution compared by the Mann-Whitney test

Sample Feature	Ambulatory (n=20)	Non-ambulatory (n=31)	p
Age (years)	10.3±3.6	13.5±2.8	0.001*
Age of loss of gait (years)	–	10.5±1.9	
BMI (Kg/m²)	18.1±4.1	22.2±6.7	0.016*
Patient education (years)	4.8±3.4	6.8±2.3	0.011*
Caregiver education (years)	9.9±3.7	8.7±3.9	0.260
Vignos score	4 [1-6]	7 [7-9]	<0.001*
MMSE	24 [10-30]	25 [10-30]	0.636

(continues)

Table 1. Continuation

Sample Feature	Ambulatory (n=20)	Non-ambulatory (n=31)	p
North(%)	1(5)	3 (9.7)	
Northeast(%)	0 (0)	1 (3.2)	0.467
South (%)	1(5)	0 (0)	
Southeast (%)	18 (90)	27 (87.1)	
Physical therapy (%)	12 (60)	26 (83.9)	0.056
Hydrotherapy (%)	5 (25)	6 (19.4)	0.632
Corticotherapy (%)	18 (90)	22 (71)	0.107

BMI: body mass index; MMSE: mini-mental state examination; *: p≤0.05.

The characteristics of the sample are shown in Table 1 and indicate that both ambulatory (18.1±4.1) and non-ambulatory (22.2±6.7) patients were classified as overweight, according to the body mass index (BMI), with difference in age (p=0.001) and BMI (p=0.016) between groups. The average age of gait loss was 10.5 years (±1.9). The education of patients demonstrated that both groups did not finish elementary school: A (4.8±3.4) and NA (6.8±2.3), which is different between the groups (p=0.011). However, there was no difference regarding the caregiver's education (p=0.26), and those responsible for A patients completed elementary school. The cognitive assessment showed no difference between A and NA (p=0.636). Regarding the staging of the disease (Vignos), it is noted that the A did not climb stairs (Vignos 4), and the NA patients sat upright in the wheelchair, could touch it, and were independent in carrying out their activities of daily life (ADL) (Vignos 7) (Table 1). Regarding the region of residence, 90% of the A and 87.1% of the NA residents reside in the southeastern region of Brazil. The groups do not differ in relation to physical therapy treatment (p=0.056). However, there is a tendency for NA patients (83.9%) to undergo more physical therapy than A patients (60%) (Table 1).

Regarding upper limb functionality, there was a difference between A and NA patients (t=8.29, DF=49, p<0.001), with A patients showing better upper limb function (mean=50.6) when compared to NA (mean=29.1).

Linear regression indicated that there was no influence of age (t=0.64, p=0.53), BMI (t=-1.59, p=0.13) and physical therapy (t=0.77, p=0.46) in relation to the difference found in the functionality of the upper limb between the groups (Table 2); but the group factor interferes with the functionality of these patients' upper limbs (t=6.00, p<0.001). There is a difference of 18 points between A and NA in the evaluation of the function of upper limbs by the PUL scale.

Table 2. Results of the linear regression analysis with the variables of the performance of upper limb scale

Variables	Coefficients	CI 95%		R^2	Adjusted R^2	p
		Upper limit	Lower limit			
Constant	61.861					
Group	-18.24	-12.193	-24.29			0.001*
Age (years)	-0.381	0.444	-1.206	0.622	0.589	0.358
BMI (Kg/m^2)	-0.305	0.142	-0.752			0.176
Physical therapy (%)	-3.047	2.937	-9.03			0.311

CI: confidence interval; *:p<0.05.

Regarding the correlation between the upper limb functionality scale and DMD staging (Vignos), there is a strong correlation (r^2=0.769, p<0.001) in the quadratic equation and in the linear equation (r^2=0.723, with p<0.001). Therefore, the worse the MMSS function, the more advanced is the disease.

DISCUSSION

The general and clinical characteristics of the sample studied are in accordance with the DMD population. The results showed that A and NA patients are different with regard to age, BMI, education, disease staging and functionality of upper limbs.

The progression of muscle involvement was continuously reported, starting with lower limbs, with reports of children and their parents having difficulty running, climbing stairs and rising from the floor, and, subsequently, with the functional impairment of the upper limbs[14]. However, this study found that even ambulatory patients have difficulty performing functional tasks with the upper limbs, which corroborates the studies by Mattar and Sobreira[15], Pane et al.[16] and Janssen et al.[17].

The authors of the study by Brogna et al.[18] showed, by means of magnetic resonance imaging, that the lower the score obtained on the PUL scale, version 2.0, the greater the impairment of the stabilizing muscles of the scapula, shoulder, shoulder flexors, elbow, wrist and fingers and pronators and forearm supinators, also indicating that the extensor muscles were less affected[18]. The authors noted that the lower the score on the PUL scale, the greater the muscle involvement – as well as the results of this study, in which the lowest PUL score was perceived in the NA group, indicating greater impairment in the function of the upper limbs.

The study by Janssen et al.[19] found the presence of fat and connective tissue, measured by means of the echogenicity z score of the ultrasound exam, in the trapezius, deltoid, biceps and triceps muscles, wrist flexors and extensors. The absence of dystrophin or its dysfunction increases the influx of calcium, which causes degeneration and apoptosis of muscle tissue cells, replacing it with adipose and connective tissue[20]. The PUL scale, version 1.2, had a moderate correlation with ultrasound[19]. Such results inform that the decline in muscle functions is accompanied by functional limitations, which patients experience throughout the disease progression.

This study demonstrated a strong correlation between upper limb function and disease staging, and that the group factor interferes with the upper limb functionality of these patients, indicating that there is an 18-point difference between A and NA on the PUL scale. Also, we observed that the NA group showed difficulty at the proximal and intermediate level, that is, the items that need stability of the shoulder girdle and shoulder, as well as shoulder and elbow movements, especially those involving weight and stacking cans, were difficult for this group that, for the most part, failed to fulfill the function. In this way, all items of the proximal level and the items of taking the glass to the mouth (weight), moving weight on the table, stacking light cans and stacking heavy cans, of the intermediate level, probably differentiate the NA group from the A group. Both groups showed ease in executing the items at the distal level. Therefore, clinical assessments such as PUL are able to detect muscle weakness and allow preventive interventions for contractures, minimizing functional decline.

PUL version 2.0 is different from PUL version 1.2 in its total score (42 points, ranging from 0 to 2 or 0 to 1, depending on the item); by its subdivision of the proximal level (weightless, 500 g and 1000 g); the item "moving weight on the table" (100 g, 500 g and 1000 g); the item "stacking heavy cans"; the insertion of the item "lifting a heavy can diagonally", "taking a hand to the mouth" and "removing the weight of 200 g"; the item "lifting light cans", "stacking light cans" and tridigital forceps and thumb adduction[21]. Despite the PUL version update, weight items remained, the weightless items having been removed.

In this study, the difficulty of patients when trying to execute items with weight, especially NDs, was notorious. Pane et al.[21] report that PUL 1.2 is considered reliable, reproducible and suitable for international multicenter studies, that is, it is a sensitive instrument to measure the efficiency of medications such as corticosteroids, related to the six-minute walk test.

PUL 1.2 does not allow compensation for performing tasks: if the volunteer compensates, they will score zero or have a lower score, depending on the task. However, Janssen et al.[19] showed increased levels of electromyography in patients with DMD, that is, they use more muscle capacity than healthy volunteers, which may be related to the strategies that patients perform to maintain the function. Future studies with PUL 2.0, which allows and punctuates the compensations, will enable a better understanding of the electromyographic signal amplitude of patients with DMD.

Although we noticed impairment of the upper limb function in ambulatory patients, we limited it to evaluating only patients with DMD. Thus, we suggest that future studies evaluate children without dystrophinopathies, and compare them with ambulatory patients. Similarly, we recommend studies of clinical trials with methods of evaluation of the upper limbs to analyze the effectiveness of the therapeutic proposal. Thus, these studies will be covering a greater number and stages of the disease in this population. Another important fact to be encouraged is the preservation of upper limbs and their attention by physical therapists, in order to maintain the functional independence and quality of life of these patients[22], given the strong correlation that PUL has with the Vignos score.

FINAL CONSIDERATIONS

The functional condition of the upper limbs depends on whether the patient is ambulatory or non-ambulatory, with the function of the upper limbs worse in non-ambulatory. Finally, it is worth mentioning the strong correlation between the function of upper limbs and the staging of the disease.

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