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Original article

Cumulative jerk as an outcome measure in nonambulatory Duchenne muscular dystrophy

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Abstract

Objectives: Quantitative or semiquantitative outcome measures for patients with Duchenne muscular dystrophy (DMD) are important, as they can be objective indicators of the natural history of DMD; these measures also aid in the evaluation of the efficacy of various treatments. However, the most widely used standard outcome measures in patients with DMD, such as the North Star Ambulatory Assessment and the 6-min walk test, cannot be applied after patients have become nonambulatory. We evaluated the utility and reliability of accelerometric analysis of motor activity in nonambulatory patients with DMD.

Methods: We measured the motor activity of the upper extremity in 7 nonambulatory patients with DMD, by using an accelerometer attached at the wrist of the dominant arm. To eliminate gravitational acceleration, we measured the changes in acceleration between measurements. The root of the sum of squared values of the changes per unit time in the 3 axes of the accelerometer was defined as a jerk. The total sum of the jerk values obtained at a measurement frequency of 15.625 Hz for 8 h was defined as the cumulative sum of jerks (*Cj*).

Results: The *Cj* values had significant and very strong or strong correlations with the Brooke Upper Extremity Scale ($r_s = -0.973$; $p = 0.00023$) and the arm function scores for the DMD Functional Ability Self-Assessment Tool ($r_s = 0.810$, $p = 0.027$). The values also had a very strong or strong correlation with the elbow flexion strength (nondominant arm: $r = 0.931$, $p = 0.002$; dominant arm: $r = 0.750$, $p = 0.052$).

Conclusion: *Cj* assessment is a useful method to evaluate motor activities in nonambulatory patients with DMD.

Keywords: Cumulative jerk; Accelerometer; Outcome measure; Duchenne muscular dystrophy; Nonambulatory

1. Introduction

Duchenne muscular dystrophy (DMD; OMIM #310200) is an X-linked degenerative muscular disease caused by mutations in the dystrophin gene. Patients with DMD lose ambulation ability before 13 years of age if not treated.

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Quantitative or semiquantitative outcome measures for patients with DMD are important, as they can be objective indicators of the natural history of DMD; these measures are also crucial in the evaluation of the efficacy of various treatments. Among the different outcome measures, the 6-min walk test (6MWT) or the North Star Ambulatory Assessment is one of the most widely used standard measures for evaluating the motor function of ambulatory patients with DMD and has been used in clinical tests for various newly developed medicines [1–3]. Naturally, however, these tests cannot be applied to patients who have lost the ambulation ability. For the nonambulatory patients, there are several other quantitative scales, including the Brooke Upper Extremity Scale, the DMD Functional Ability Self-Assessment Tool (DMDSAT), the Jebsen Hand Function Test, the 9-Hole Peg Test and the Performance of Upper Limb (PUL) [4–9]. Among these, the Jebsen Hand Function Test and 9-Hole Peg Test, similar to the 6MWT, can be used to obtain values measured on a ratio scale. However, these are timed tests and, therefore, require the patient to concentrate and to have an incentive to obtain reliable results. As the patients with DMD are often complicated with intellectual and/or autistic spectrum disorder, making the patient to keep concentration during these tests can be difficult. The Brooke Upper Extremity Scale and DMDSAT, on the other hand, do not require concentration. However, an ordinal scale is used for these tests and, therefore, functional changes cannot be quantified unless they are sufficiently large to reach a different level of function, as defined according to the scale. Compared with these outcome measures, the use of an accelerometer has some advantages. The equipment can measure the patients' motor activity during normal daily activities such as studying at school, working or resting at home. Therefore, the data are not influenced by patients' concentration or incentive for the measurement. Additionally, the data are measured on a ratio scale. Hence, any degree of change in the activity can be analyzed quantitatively. To evaluate the reliability and utility of the accelerometric analysis, we measured 3-axis acceleration from equipment attached to the wrist of 7 nonambulatory patients with DMD and compared the data with the Brooke Upper Extremity Scale, the arm function scores of DMDSAT and arm muscle strengths. We also compared the accelerometric data with the patients' subjective view on their physical and mental status assessed by a visual analog scale (VAS).

2. Methods

2.1. Patients

Seven nonambulatory male patients with DMD, diagnosed definitively by molecular analysis of the dystrophin gene, were enrolled in this study. The study was approved by the ethical committee of Shiga Medical Center for Children. A written informed consent was obtained from the parents as well as from the patients over 15 years of age.

2.2. Measurements

2.2.1. Measurement of 3-axis acceleration

We used a 3-axis accelerometer; Silmee™ Bar-type Light, manufactured by Toshiba Corporation, Tokyo, Japan (currently manufactured by TDK Corporation, Tokyo). The unit of acceleration for this equipment is G (9.8 m/s^2) and the measurable range is from −2 G to +2 G. The lowest detectable acceleration is 3.91 mG. The measurements were taken every 64 ms. Therefore, the measurement frequency (f) was 15.625 Hz. The accelerometer was attached at the dorsal face of the dominant forearm near the wrist by an adhesive tape designed and supplied for this equipment by the manufacturer. The parents and the patients were instructed on how to use this accelerometer, and the equipment was attached and switched on at home on a weekday morning before leaving for school or work. Measurements were taken for at least for 8 h. After completing the measurements, the equipment was switched off and sent back to us by mail for analysis.

2.2.2. Definition and calculation of jerk

As the accelerometer also measures the gravitational acceleration, even if the patient stays still, the measured value does not become zero. To eliminate the factor of gravitational acceleration, we tried to measure the acceleration change per unit time, which is called a jerk (J). The jerk, the rate of change of acceleration, was calculated by measuring a difference in the accelerations obtained at two consecutive measurements (ΔG) divided by the time between the measurements (expressed in second unit). As the reciprocal of the time between the two consecutive measurements is equal to the measurement frequency f (15.625 Hz in our setting), the jerk is calculated as $\Delta G \times f$. The accelerometer measures the acceleration in 3 axes (x and y axes that are horizontal and z axis that is vertical to the equipment), so the composite vector jerk is calculated as follows: $J = \sqrt{(\Delta Gx \times f)^2 + (\Delta Gy \times f)^2 + (\Delta Gz \times f)^2}$ [10]. Then, we summed all J values obtained at every measurement during the 8-hour measurement and this summed value was defined as cumulative sum of Js (Cj) for 8 h. These calculations were completed using Microsoft Excel, on which the measured data were downloaded from the equipment. We regarded the Cj values as the indicator of the motor activity (mostly of the dominant arm) in nonambulatory patients.

2.2.3. Muscle strength measurement

The muscle strength of the arm was measured in Newton units by a hand-held dynamometer, Micro-FET2™ (Hoggan Scientific, Salt Lake City, UT, USA) with the low-threshold mode. We measured the strength of flexion and extension of the elbow while the elbow was placed on a table or an armrest with the forearm in vertical position to eliminate the gravitation factor. The measurements were done in duplicate, and the mean values were recorded. We did not use the shoulder strength for the analysis because the shoulders of the most patients studied were too weak to obtain reliable data.

2.2.4. Assessment of the upper extremity function

To evaluate the function of the upper extremities semiquantitatively, we used the Brooke Upper Extremity Scale [8] as well as the DMDSAT [4]. The DMDSAT comprises 4 domains (arm function, mobility, transfers and ventilator support). We only used the scores of the arm function domain for the analysis. The higher the Brooke score or the lower the DMDSAT score, the more disabled the patients are.

2.2.5. Assessment of the patients' subjective view on their physical and mental status

We applied a visual analog scale using 100-mm horizontal lines drawn on an A4-size paper. At the left end of the line, the verbal descriptor and number 0 were written. At the right end, the descriptor and number 10 were written. No scale bars were drawn between the both ends. Patients were asked to mark with a pen whatever position on the line they felt was appropriate to answer the questions. The distance from the left end to the mark was measured in mm scale. All patients could hold a pen and draw a mark. The followings were the questionnaire: Q1. Do you feel difficulties because you cannot use your hands well? (0 = not at all, 10 = very much so); Q2. Do you feel fatigue easily? (0 = not at all, 10 = very much so); Q3. Are you active or very weak? (0 = very active, 10 = very weak); Q4. Do you think you are healthy or ill? (0 = very healthy, 10 = very ill); Q5. How do you feel every day? Are you happy or depressed? (0 = very happy, 10 = very depressed).

2.2.6. Statistical analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corporation). Normality of the data was tested by the Shapiro-Wilk test. Pearson's correlation analysis or Spearman's rank correlation analysis was chosen depending on the normality of the data as well as the type of the data scale (ratio or ordinal). The correlation coefficient was interpreted as follows: $r < 0.10$, negligible; $r = 0.10$–0.39, weak; $r = 0.40$–0.69, moderate; $r = 0.7$–0.89, strong; $r \geq 0.9$, very strong [11]. The statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patients' profile

All but one patient (Patient 3) were either currently on prednisolone treatment or did so until 10 years of age. The ages of the seven patients at assessment ranged from 12 to 24 years (median, 20 years). The ages at the loss of ambulation ranged from 8 years to 14 years, with the period from the loss of independent ambulation to the assessment age (nonambulatory period) ranging from 1 to 14 years (median, 10 years) (Table 1). All but one patient (Patient 4) used a motorized wheelchair. Patient 4 used a manual wheelchair. All patients were right-handed and cooperative in wearing the accelerometer.

3.2. Outcome measure scores and Cj values

As shown in Table 1, the Brooke Upper Extremity Scale scores ranged from 1 to 5 (median, 4), and the DMDSAT arm function scores ranged from 4 to 6 (median, 5). The *Cj* values ranged from 151,906 to 698,372 (mean, 352,072). Spearman's rank correlation coefficient (r_s) showed a very strong correlation between the *Cj* values and the Brooke Upper Extremity Scale scores: $r_s = -0.973$, $p = 0.00023$ (Fig. 1A). Similarly, the *Cj* values had a strong and significant correlation with the arm function scores of the DMDSAT: $r_s = 0.810$, $p = 0.027$ (Fig. 1B).

3.3. Muscle strength and Cj values

The elbow flexion strengths of the nondominant (left) side were too weak to measure in 4 patients (Table 1). Despite this limitation, Pearson's correlation analysis showed a significant and very strong correlation coefficient with the *Cj* values ($r = 0.931$, $p = 0.002$; Fig. 2A). The flexion strengths of the dominant elbow flexion were measurable in all patients. However, the data did not show a normal distribution. Spearman's rank correlation coefficient showed a strong but nonsignificant correlation with the *Cj* values ($r_s = 0.750$, $p = 0.052$; Fig. 2B). Pearson's correlation analysis showed a weak but nonsignificant ($r = 0.367$, $p = 0.418$) or negligible ($r = -0.04$, $p = 0.993$) correlation between the *Cj* values and dominant and nondominant elbow extension strengths, respectively (not shown).

3.4. Patients' subjective view and Cj values

The Shapiro-Wilk test revealed that the VAS values from the all questionnaires showed a normal distribution. Pearson's correlation analysis (Table 2) revealed a significant and strong correlation between the *Cj* values and the sense of weakness ($r = -0.825$, $p = 0.022$).

Table 1
Patients' profile and the measurement results.

Patients (Age)		P1 (16 y)	P2 (20 y)	P3 (20 y)	P4 (12 y)	P5 (24 y)	P6 (22 y)	P7 (12 y)
Age at the loss of ambulation ability (Nonambulatory period)		10 y (6 y)	8 y (12 y)	10 y (10 y)	11 y (1 y)	14 y (10 y)	8 y (14 y)	10 y (2 y)
Variants in the *dystrophin*		Deletion of exons 8–13	Deletion of exons 48–50	c.5252G > T (nonsense)	Deletion of exons 8–18	Duplication of exon 2	Deletion of exons 46–51	c.264 + 2_264 + 3insGT (r.264_265insgu)
Use of prednisolone		Currently	Currently	Never	Until 10 y of age	Currently	Until 10 y of age	Currently
Brooke Upper Extremity Scale		3	4	5	3	4	5	1
DMDSAT (Arm function score)		5	4	4	5	5	4	6
Elbow flexion strength (N)	Left	8.2	0	0	5.3	0	0	19.5
	Right	8.2	4.2	4	7.1	7.7	6.4	17.5
Elbow extension strength (N)	Left	8.7	11.7	12	13.3	13.8	5.1	9.3
	Right	12.7	7.8	10.6	16.2	15.6	7.3	11.6
Cumulative sum of jerk		479,656	275,579	148,654	500,906	209,433	151,906	698,372

The Brooke Upper Extremity Scale also showed a strong but nonsignificant correlation with the sense of weakness ($r = 0.713$, $p = 0.072$), and DMDSAT did not have a strong correlation with any of the questionnaire. Thus, the C*j* values seemed to be more sensitive to reflect the sense of weakness. The C*j* values had a strong correlation with the sense of depression as well ($r = -0.700$), however, the p value was 0.080.

4. Discussion

Once patients with DMD lose the ability to walk, quantitative assessment of their physical activity/ability becomes difficult; the 6MWT and North Star Ambulatory Assessment are no longer applicable and the evaluation needs to be limited to the activity of daily living and upper extremity functions. Among the validated outcome measures for the upper extremities, the 9-Hole Peg Test and Jebsen Hand Function Test may be comparative to the 6MWT in that these are timed tests [5,7,12]. However, similar to the 6MWT, these tests require a concentration and incentive for patients to obtain reliable data. Other outcome measures, including the Brooke Upper Extremity Scale [8] and DMDSAT [4], evaluate the motor functions, mostly by analyzing daily living abilities and simple performance tests, so the data would not be affected by patients' concentration. However, these measures cannot show any ability changes that are not sufficiently large to reach a higher or lower grade defined in the scale. Continuous monitoring of physical activities with an accelerometer can compensate for these disadvantages because the data use the ratio scale and the measurements are done in a normal daily living setting.

There are many commercially available accelerometers. Among them, Actigraph GT3X (Actigraph LLC, Pensacola, FL, USA) has been reported to be useful for evaluating motor activities in patients with DMD [13,14]. With its accompanying software, this accelerometer can estimate energy expenditure, number of steps taken and physical activity intensity. However, the calculation algorithm is not derived from the data obtained from wheelchair-bond patients with DMD. Therefore, rather than depending on the manufacture's software to assess the motor activity, we decided to use the raw acceleration data for the analysis. Among the different equipment, Silmee™ Bar-type Light allowed the raw data to be downloaded from the equipment.

Our method utilizing the jerk measurement can cancel the gravitational acceleration factor from the data, and as such, it can estimate only the movement. On the other hand, if the movement is in the same direction at a constant speed or acceleration, the measured values become zero. However, it is unlikely that the wrist wearing the equipment moves at a constant speed or constant acceleration for a significant amount of time during the measurement. In other words, false-negative activity data would be negligible. The *Cj* indicates the vigorousness of the arm movements during the 8-hour measurement.

We compared the *Cj* values with the Brooke Upper Extremity Scale scores and the arm function scores of DMDSAT. However, the accelerometer collects the acceleration of the trunk and wheelchair movements as

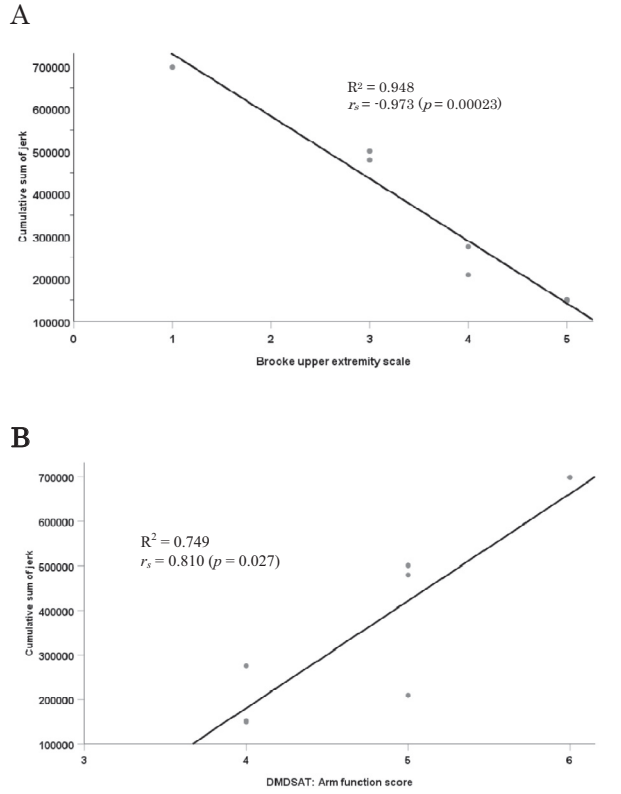

Fig. 1. Spearman's rank correlation coefficient (r_s) between the cumulative sum of jerk, the Brook Upper Extremity Scale (A) and the arm function scores of DMDSAT (B). The correlations were very strong or strong, and significant. R^2, Coefficient of determination.

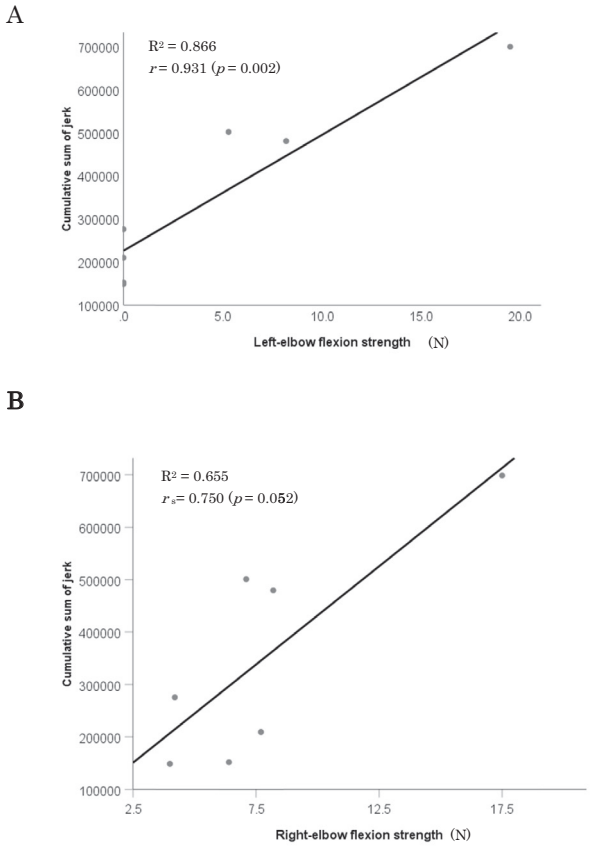

Fig. 2. Correlation between the cumulative sum of jerk and the elbow flexion strengths. The muscle strengths of the nondominant (left) elbow flexion were too weak to measure in 4 patients. Nevertheless, Pearson's correlation coefficient (the data had a normal distribution) showed a very strong and significant correlation (A). The muscle strength data in the dominant elbow did not show a normal distribution, and Spearman's rank correlation coefficient showed a strong but nonsignificant correlation (B).

well. If a patient uses a manual wheelchair to move, the acceleration detected during the wheelchair use must be mostly derived from the hand movements handling the wheel rather than the wheelchair movement itself, considering that the jerk reflects the vigorousness of the arm movements. Therefore, the data should reflect mostly the arm motor activity. However, if a patient uses a motorized wheelchair, the hand movement for the wheelchair use is small, so the accelerations measured must be mostly from the wheelchair movement. The jerk of a motorized wheelchair, which is usually moving at a fairly constant speed on a smooth surface, should be small. Considering these factors, we believe that it was reasonable to compare the *Cj* data from the arm with the outcome measure scores for the arm function.

The statistically significant and very strong or strong correlation coefficient between the *Cj* values and Brooke Upper Extremity Scale as well as the arm function scores of DMDSAT indicated that this method can be a useful, quantitative measure to estimate the arm activities of nonambulatory DMD patients. The significance of this method compared with that of conventional scales is that the data can show small changes of motor function that cannot be detected by the conventional ordinal scale outcome measures. Therefore, the *Cj* values can be a good indicator for evaluating treatment efficacy.

A significant improvement in an outcome measure scale with a treatment usually means a successful treatment efficacy. However, there may be an occasion where a statistically significant improvement in the measured value cannot be felt by the patient. In such a case, it may not be appropriate to call the treatment result clinically successful. In other words, the objective outcome measure results should correlate with the patients' subjective assessment in order for the measured results to become clinically meaningful. Therefore, we tried to compare the *Cj* values with patients' subjective views on their physical and mental status utilizing the VAS. Contrary to our assumption, patients did not feel difficulties in daily life due to hand disability irrespective of the *Cj* values. The correlation analysis between the sense of difficulties and Brooke or DMDSAT scales did not show a significant correlation either (Table 2).

Table 2
Pearson's correlation coefficient between VAS values from the questionnaire and Cj, Brooke's scale or DMDSAT.

Questionnaire		Q1. Difficulty	Q2. Easily fatigue	Q3. Weak	Q4. Ill	Q5. depressed
VAS values (mean, (SD))		29.9 (20.2)	57.3 (19.1)	24.0 (24.7)	41.1(12.9)	24.6 (21.0)
Cj	Correlation coefficient	−0.516	−0.298	−0.825	−0.387	−0.700
	p value (two-sided)	0.235	0.517	0.022*	0.391	0.080
Brooke's scale	Correlation coefficient	0.613	0.118	0.713	0.411	0.528
	p value (two-sided)	0.143	0.802	0.072	0.36	0.224
DMDSAT	Correlation coefficient	−0.648	0.064	−0.445	−0.354	−0.346
	p value (two-sided)	0.115	0.891	0.316	0.436	0.448

VAS, visual analog scale; C*j*, cumulative sum of jerk; DMDSAT, DMD self-assessment tool.
* Statistically significant.

On the other hand, the *Cj* values had a strong and significant correlation with the sense of weakness ($r = -0.825$, $p = 0.022$). The Brooke scale and DMDSAT scale did not show a significant correlation with weakness ($r = 0.713$, $p = 0.072$; $r = -0.445$, $p = 0.316$; respectively). This result indicated a possibility that the *Cj* method is more sensitive than the other two scales are to detect the self-assessed weakness. As the questionnaire did not specify the weakness as physical weakness, we do not know if the patients may have interpreted the weakness as a mental weakness. A non-significant but strong correlation between depression and the *Cj* values ($r = -0.700$, $p = 0.080$) indicates that the self-assessed weakness might include mental weakness.

There are several limitations in this study. First, the number of patients studied is very small. This small size created difficulty in evaluating the correlation between the *Cj* values and muscle strengths, and due to weakness, some patients' strengths were not measurable. Nevertheless, the correlation coefficients between the *Cj* values and the elbow flexion strengths were strong, indicating that a more significant correlation would be revealed as the number of patient increases. Another weakness is that the acceleration measurement time was only for 8 h. We chose the 8-hour-measurement from morning of a weekday because this seemed to be the most active period of the day. The Actigraph can continuously collect data for up to 3 weeks depending on the measurement frequency. Naturally, the longer the monitoring period, the more accurate the assessment of the daily motor activity becomes. As we assumed that frequent measurements are necessary to assess the activity accurately, we measured at the frequency of 15.625 Hz, the highest frequency for the equipment. With this frequency, the amount of data was too large to store in the equipment for multiple days. Therefore, to make sure that the patients were active during the measurement, we asked the parents to report if the patient took a nap (and if so, how long). No patients slept during the measurement. Finally, to use the *Cj* as a standard outcome measure, one has to measure the jerk with the same parameter setting, which was an 8-hour measurement with 15.625 Hz frequency and 3.91 mG sensitivity in this study. Thus, this method is less flexible than other accelerometric methods, including Actigraph.

In conclusion, the *Cj* values in the wrist have a strong and significant correlation with the Brooke Upper Extremity Scale as well as the arm function scores of the DMDSAT. The *Cj* values also correlated significantly with the patients' sense of weakness. As the *Cj* value is a ratio scale similar to the values from 6MWT, the value may be able to show the ability changes that cannot be detected by the Brooke scale or DMDSAT. Thus, the *Cj* measurement with an accelerometer attached at the wrist is a simple and accurate method for evaluating the motor activity in the non-ambulatory patients with DMD.

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Appendix A. Supplementary data

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