Brain & Development 40 (2018) 172–180

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

New quantitative method for evaluation of motor functions applicable to spinal muscular atrophy

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Received 11 July 2017; received in revised form 15 November 2017; accepted 4 December 2017

Abstract

Objective: The aim of this study was to develop and introduce new method to quantify motor functions of the upper extremity.

Methods: The movement was recorded using a three-dimensional motion capture system, and the movement trajectory was analyzed using newly developed two indices, which measure precise repeatability and directional smoothness. Our target task was shoulder flexion repeated ten times. We applied our method to a healthy adult without and with a weight, simulating muscle impairment. We also applied our method to assess the efficacy of a drug therapy for amelioration of motor functions in a non-ambulatory patient with spinal muscular atrophy. Movement trajectories before and after thyrotropin-releasing hormone therapy were analyzed.

Results: In the healthy adult, we found the values of both indices increased significantly when holding a weight so that the weight-induced deterioration in motor function was successfully detected. From the efficacy assessment of drug therapy in the patient, the directional smoothness index successfully detected improvements in motor function, which were also clinically observed by the patient's doctors.

Conclusion: We have developed a new quantitative evaluation method of motor functions of the upper extremity. Clinical usability of this method is also greatly enhanced by reducing the required number of body-attached markers to only one. This simple but universal approach to quantify motor functions will provide additional insights into the clinical phenotypes of various neuromuscular diseases and developmental disorders.

Keywords: Motor function; Motion capture; Spinal muscular atrophy; Clinical outcome; Quantitative outcome measure

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by weakness due to degeneration of anterior horn cells of the spinal cord [1]. Because the severity of SMA is highly variable, the international SMA Consortium categorizes SMA patients into four clinical groups based on their highest achieved motor milestones [2,3]. Patients with SMA type I never achieve the ability to sit, while those with SMA type II can sit but never reach the motor milestone of standing. SMA type III gain the ability to walk. SMA

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https://doi.org/10.1016/j.braindev.2017.12.003
0387-7604/

type IV describes patients who start showing the symptoms of muscle deterioration in adulthood [1].

Although validation of putative biomarkers of SMA is ongoing [4], functional motor scales are currently the best method of clinically monitoring meaningful changes in both non-ambulatory and ambulatory patients with SMA [5]. The Gross Motor Function Measure [6] was originally developed to detect changes in the motor function of disabled children with cerebral palsy and head injury, and its validity and sensitivity as an outcome measure in clinical trials of pediatric SMA patients has been demonstrated [7]. The Hammersmith Functional Motor Scale (HFMS) was devised specifically for assessment of SMA type II and non-ambulatory type III patients [8]. This scale was then restructured as the Modified HFMS [9], which minimizes position changes and includes concrete operational definitions and instructions for scoring. To eliminate ceiling effects in ambulatory type III patients, the Expanded HFMS [10] and Extended HFMS [9] were further developed. Because these scales provide ordinal scores for individual attributes related to motor function, new analytical methods such as Rasch analysis are being applied to these neuromuscular functional scales to establish how they work and to identify possible gaps in the scale or redundant items, with the goal of converting ordinal data to a linear measurement [5,11].

Quantitative outcome measures have been used to assess the clinical condition of SMA patients via two main approaches. One approach quantifies muscle strength using hand-held dynamometry, as was done in the clinical trial of albuterol [12]; the inter- and intra-rater reliability of this technique has been confirmed, except for measurement of ankle dorsiflexion [13,14]. Problems with hand-held dynamometry include the need for patient cooperation, which renders this technique impractical in younger children, and that evaluator training is necessary to reduce variability [15,16]. In addition to the intensive tester training for consistent evaluations, strict definition of the test protocol is also necessary, especially with respect to patient posture [17], because weakening muscles even result in deterioration of sitting stability.

The other quantitative measure of the clinical status of SMA patients is the timed Six-Minute Walk Test (6MWT), which is used to evaluate mobility in patients with neuromuscular disease. The correlation between 6MWT and established outcome measures such as the Expanded HFMS score has been confirmed [18], and the reproducibility and validity of the 6MWT has been substantiated [19]. The problems of 6MWT are the inapplicability to type I, type II, or non-ambulatory type III patients. For ambulatory patients, we have employed a more detailed approach using three-dimensional motion capture analysis of gait parameters, to quantitatively evaluate the efficacy of a thyrotropin-releasing hormone (TRH) analog for the treatment of SMA; TRH increases the levels of normal survival motor neuron (SMN) proteins [20]. In this paper, we describe two newly developed indices for the quantitative assessment of motor function in non-ambulatory patients through evaluation of the motor functions of the upper extremity. We demonstrate the usefulness of these methods in both healthy adults and SMA type II patients.

2. Methods

We employed a commercially available three-dimensional motion capture system (Vicon Motion Systems Ltd., Oxford, UK) to record the movements. The system consists of infrared cameras that capture the three-dimensional locations of *retro*-reflective markers attached to the subject. We set the sampling rate at 100 Hz. The target move was the shoulder flexion movement, repeating ten times. We asked the subject to move their arm as smoothly and high as possible without bending their elbow. The orientation of the subject is illustrated in Fig. 1a, and Fig. 1b shows the target move and the color scheme. The motion of the right elbow only was considered for the analysis.

In order to demonstrate the usefulness, we applied our method to a healthy adult, comparing trajectories under two conditions: without and with holding an 8-kg dumbbell. Since our target trajectory is anti-gravitational movement, the load will let the subject emulate the muscle impairment. We also applied our method to a SMA type II patient, comparing trajectories before and after TRH therapy. In this manner, we demonstrate the usefulness of our method for assessing the efficacy of drug therapy.

2.1. Spatial deviation and direction variance

In this section, we briefly explain about our newly developed two indices. The detailed mathematical description is provided in Supplement. The first index, spatial deviation (SpDe), measures how precise the repeatability of the movement is. From the repeated movement, we calculated the average trajectory. Then, the distance of each trajectory from the average was calculated to be the spatial deviation. SpDe was eventually scaled and adjusted with the length of the trajectory route to be comparable among individuals with a different body size or arm length.

The other index, direction variance (DiVa), considers the variance in direction of the movement. In a simple model of the up-down flexion movement, the moving direction changes linearly according to our observation. The linearity can be estimated by computing a generalized linear model using iteratively reweighted least squares. The mean of the squared residuals between the fitted points and the fitting linear model was defined