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Motor unit number estimation in the quantitative assessment of severity and progression of motor unit loss in Hirayama disease

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HIGHLIGHTS

- Compared to controls, patients with HD showed significant loss of functioning motor units in motor unit number estimation (MUNE).
- Abnormally low MUNE values were observed in asymptomatic hands in patients with HD.
- Motor unit loss in HD worsens as disease advances, even with illness duration over 4 years.

ABSTRACT

Objective: To investigate motor unit number estimation (MUNE) as a method to quantitatively evaluate severity and progression of motor unit loss in Hirayama disease (HD).
Methods: Multipoint incremental MUNE was performed bilaterally on both abductor digiti minimi and abductor pollicis brevis muscles in 46 patients with HD and 32 controls, along with handgrip strength examination. MUNE was re-evaluated approximately 1 year after initial examination in 17 patients with HD.
Results: The MUNE values were significantly lower in all the tested muscles in the HD group ($P < 0.05$). Despite abnormally low MUNE values, 54.3% (25/46) of patients with HD had normal ipsilateral grip power. There was a significant inverse correlation between MUNE values and disease duration ($P < 0.05$). A longitudinal follow-up MUNE analysis demonstrated slow progression of motor unit loss in patients with HD within approximately 1 year ($P < 0.05$), even in patients with an illness duration >4 years.
Conclusions: A reduction in the functioning motor units was found in patients with HD compared with that in controls, even in the early asymptomatic stages. Moreover, the motor unit loss in HD progresses gradually as the disease advances.
Significance: These results have provided evidence for the application of MUNE in estimating the reduction of motor unit in HD and confirming the validity of MUNE for tracking the progression of HD in a clinical setting.

1. Introduction

Hirayama disease (HD) is a benign neurological disease, which predominantly causes unilateral or asymmetric oblique muscular atrophy affecting the C7-T1 myotomes in young male patients but does not cause sensory deficits (Hirayama, 2008). The etiology of HD is unknown. One current hypothesis implicates chronic cervical spinal cord injury (ischemia and/or compression) caused by cervical flexion (Hirayama, 2000; Zheng et al., 2016a; Zheng et al., 2016b). Therefore, some studies suggest that neck collar therapy and surgical intervention may be effective treatments for HD because both long-time collar support and anterior cervical fusion may prevent cervical flexion in patients with HD (Verma

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et al., 2012; Lu et al., 2013; Yang et al., 2014). However, both treatments are considered controversial because it is difficult to determine whether changes in HD progression are due to treatment or the natural course of the disease. Conventional electrophysiological examinations, including nerve conduction study, repetitive nerve stimulation and needle electromyography (EMG), have been an important part of the diagnosis of HD (Yang et al., 2014; Zhou et al., 2010; Wang et al., 2012; Zheng et al., 2016b). Unfortunately, these electrophysiological techniques cannot identify both severity and clinical progression of HD. Thus, a quantitative evaluation method is needed to monitor HD severity, progress, and treatment effects in patients.

Motor unit number estimation (MUNE) is a quantitative method used to estimate the number of motor units that innervate a muscle or a muscle group (McComas et al., 1971; Bromberg, 2007). MUNE values are calculated by the formula as follows: the maximal compound muscle action potential (CMAP)/average single motor unit potential (SMUP) (Bromberg, 2007). Thus, MUNE is obviously not affected by either collateral reinnervation or disuse atrophy. Recently published studies also demonstrated the value of MUNE in evaluating the severity and clinical progression of ALS (Ahn et al., 2010; Shefner et al., 2011; Fathi et al., 2016). Unfortunately, there are few reports about the quantitative assessment of MUNE in HD, even though it may inform treatment for patients with HD.

This study aimed to estimate the number of functioning motor units in distal upper limbs in patients with HD. We also evaluated the ability of MUNE to provide a quantitative assessment of the severity and the clinical progression of HD.

2. Materials and methods

2.1. Subjects

Forty-six patients with HD (recruited from Huashan hospital) and 32 healthy subjects were included in this study from May 2013 to August 2016. The study protocol was approved by the Ethics Committee of Huashan Hospital (Fudan University, China), and informed consents were obtained from all participants.

The subjects in the control and patient groups were selected according to the inclusion and exclusion criteria that have been described previously (Zheng et al., 2016a; Zheng et al., 2016b).

2.2. Testing methods

2.2.1. Motor unit number estimation

The multipoint incremental stimulation method described by Shefner et al. was used in this study (Shefner et al., 2011) (Fig. 1). With subjects in the supine position, the maximal CMAPs were recorded bilaterally using a belly-tendon method from both abductor digiti minimi (ADM) and abductor pollicis brevis (APB) to supramaximal stimulation (Stimuli Duration: 0.2 ms; Resistance <5 kΩ; Gain: 1–5 mV; Filters: 10 Hz–10 kHz; Frequency: 1 Hz). Three stimulus locations were used for each muscle to record SMUPs (Stimuli Duration: 0.05 ms; Gain: 50–200 μV). At each stimulation point, the stimulus intensities were increased by increments (approximately 0.1–0.5 mA) to the levels at which the first, the second, and then the third subsequent SMUPs were elicited in an all-or-nothing manner, and only combinations of three SMUPs were accepted as motor unit samples. At all three stimulation points, nine distinct SMUPs were obtained from each tested muscle.

MUNE calculations were based on the negative peak amplitude. The minimum amplitude considered acceptable for recording was 25 μV. The number of motor units was estimated by dividing the amplitude of the maximal CMAP by the SMUP amplitude averaged from the nine distinct SMUPs. The following measurements were recorded: (1) the negative peak amplitude of the maximal CMAP; (2) the number of motor units; and (3) the average negative peak amplitude of the SMUP.

To evaluate the intra-rater reproducibility, MUNE in all the tested muscles were measured twice in one day by the same neurophysiologists with 30–60 min interval. Electrodes were completely removed and replaced for the second measurement.

In 17 patients with HD who did not accept either long-time collar support or surgical intervention and was willing to accept follow-up test, the same tests were repeated approximately 1 year after the initial examination.

Nihon Kohden MEB-9400 EMG unit (Tokyo, Japan) was used for all electrophysiological procedures at skin temperature above 32 °C. To exclude the influence of inter-rater variability, all tests were performed by the same experienced neurophysiologists blinded to whether the subjects had HD or were healthy at the initial examination.

2.2.2. Handgrip strength examination

Further examination of handgrip strength (HGS) was accomplished using the Jamar hydraulic hand dynamometer (Sammons Preston Rolyan, Illinois, USA) in all subjects. The standard instructions for the test were given along with a brief demonstration. All subjects performed the HGS test bilaterally according to the testing protocol described previously (Kozicka and Kostka, 2016; Teraoka, 1979). The grip strength measurement averaged from the three distinct maximum attempts with an interval of 1 min, and the results were recorded in kilogram force.

Measurements of each patient with HD were defined as abnormal if the responses were two standard deviations (SDs) above the average values for the healthy subjects in terms of the average SMUP amplitude or two SDs below the average values for the healthy subjects for the CMAP amplitude, the number of motor units, and the HGS.

2.3. Statistical methods

SPSS 12.0 (IBM, Armonk, NY) was used to analyze the data. The Kolmogorov–Smirnov test was used to test the normality of the distributions. All measurements of the patients with HD at the initial examination (first investigation) were compared with the parameters observed in the controls by an independent *t*-test or Mann–Whitney test based on the type of distribution of the data. The same methods were also used to compare the age, height, and disease duration between the patients with HD included in the follow-up study and the other HD cases. Furthermore, the measurements between the ADM and APB in the ipsilateral hand were compared with paired *t*-tests or Wilcoxon signed-rank tests according to whether the data were normally distributed. These statistical methods were also used to compare the measurements of HGS and MUNE between the initial and second examination in the follow-up patients with HD. The frequencies of MUNE decrement, reduced CMAP amplitude, and increased SMUP between the ADM and APB on the same hand were compared by chi-square tests (Pearson's chi-square or continuity correction) in patients with HD.

The test–retest reliability of MUNE in both the HD and control groups was measured by using both interclass correlation coefficient (ICC) methods and Pearson's or Spearman's correlation coefficient analysis (CCA) according to the type of data distribution. The correlations between the individual MUNE measurements and both disease duration and HGS were also analyzed by the Pearson's or Spearman's CCA. *P*-values <0.05 were considered statistically significant.