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Motor unit number estimation as a complementary test to routine electromyography in the diagnosis of amyotrophic lateral sclerosis

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ABSTRACT

Electromyographic (EMG) abnormalities that reveal denervation and reinnervation caused by lower motor neuron degeneration do not reflect the number of motor units that determines muscle strength. Consequently, motor unit activity potential (MUAP) parameters do not reflect muscle dysfunction.

The aim of the study was to compare the value of motor unit number estimation (MUNE) and MUAP parameters as indicators of clinical muscle dysfunction in patients with amyotrophic lateral sclerosis (ALS), and to analyze the role of MUNE as a supplement to the EMG criteria for the diagnosis of ALS.

In 25 patients with ALS, MUNE by the multipoint incremental method in the abductor digiti minimi (ADM) and quantitative EMG in the first dorsal interosseous (FDI) were obtained. The Medical Research Council (MRC) scale was used to evaluate clinical muscle dysfunction. A strong correlation between the number of motor units evaluated by MUNE and ADM clinical function by the MRC scale was found ($P < 0.001$). An increased value of surface-detected single motor action potential was associated with a decreased MRC score for ADM ($P < 0.1$). No relation was found between MUAP parameters in FDI and MRC scores. Our data support the value of the MUNE method for the detection of motor unit loss in ALS, and it could be postulated that MUNE studies may be considered complementary tests for ALS in a future revision of ALS criteria.

1. Introduction

Neurophysiological testing is of importance in the evaluation of patients with motor neuron disease since denervation and subsequent reinnervation could be evaluated using electromyography (EMG) (Simon et al., 2014). Routine EMG and nerve conduction studies are still incorporated into the diagnostic criteria for amyotrophic lateral sclerosis (ALS) (El Escorial). However, these techniques have not been proven to be effective in monitoring disease progression or assessing treatment effects. By the El Escorial criteria, the electrophysiological signs of active denervation such as fibrillation potentials and positive sharp waves, and signs of chronic denervation such as large motor unit action potentials (MUAPs), reduced interference pattern, and MUAP instability should be found to confirm neurogenic muscle abnormalities (Brooks, 1994; Brooks et al., 2000).

Patients with a suspicion of amyotrophic lateral sclerosis (ALS) should undergo electrophysiological study such as conventional needle EMG and nerve conduction study (motor and sensory) to confirm lower motor dysfunction in clinically involved and uninvolved regions and to exclude other causes of muscle weakness and atrophy. Abnormal MUAP parameters reflect primary pathologic (denervation) and compensatory reinnervation changes that take place after lower motor neuron loss. Typically, EMG studies in patients with ALS show signs of active denervation such as fibrillation potentials and positive sharp waves. Signs of chronic denervation include large MUAPs of an increased duration, amplitude and size index with an increased percentage of polyphasic potentials, unstable MUAPs, and reduced interference patterns. In addition, fasciculation potentials are characteristic findings in ALS and the group of Awaji suggested that in the presence of chronic neurogenic changes in needle EMG, fasciculation potentials, preferably of complex morphology, are of an equivalent clinical significance to fibrillations and positive sharp waves (Carvalho et al., 2008).

This reorganization of the motor unit as a result of coexisting processes of denervation and reinnervation initially allows full

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compensation but finally leads to decompensation of muscle fiber innervation. In the initial disease stage, the values of MUAP parameters are increased because of efficient reinnervation of muscle fibers by collateral axonal sprouting (for amplitude up to 500% of the normal value, for duration up to 40% of the normal value) (Emeryk-Szajewska et al., 2003). During progression of ALS, motor unit potential area and amplitude may approach normal ranges because of decompensation of innervation and disintegration of the motor unit.

These processes in motor neuron disorders result in certain trends of MUAP parameter changes: a marked rise in MUAP amplitude and area in the early disease stages followed by a later fall toward normal values (Emeryk-Szajewska et al., 1997). The basic sequence is denervation–reinnervation-further denervation leading to decompensation, and there is a measurable clinical change at each stage (Emeryk-Szajewska et al., 2003).

Conventional EMG abnormalities that reveal denervation and reinnervation changes caused by lower motor neuron degeneration do not correlate well with muscle strength and thus MUAP parameters do not directly reflect clinical muscle dysfunction. However, another electrophysiological measure, motor unit number estimation (MUNE), may be a better indicator of clinical muscle dysfunction.

The aim of the study was to compare the value of MUNE and MUAP parameters of conventional EMG as indicators of clinical dysfunction of the involved muscle in ALS patients, and to analyze the role of MUNE as a supplement to the EMG criteria for the diagnosis of ALS.

As the compound motor action potential (CMAP) is the sum of all single motor unit potentials, the crucial and the most difficult step in MUNE tests is to assess the amplitude or area of a single motor unit potential. A number of techniques for estimating the average amplitude of single motor units have been suggested, most of them limited by a sampling bias and lack of reproducibility (Turner et al., 2013). Different techniques for MUNE have been used, including the spike-triggering averaging method using a voluntary muscle contraction to activate the motor unit, multiple point motor nerve stimulation, with stimulation at multiple sites along the nerve, motor unit number index (MUNIX) using a mathematical model based on CMAP and the surface EMG interference pattern, and many others (McComas et al., 1971; Doherty and Brown, 1993; Nandedkar et al., 2010; Neuwirth et al., 2011).

For the present study, the multipoint incremental method with the Shefner's modification (a combination of both multiple point stimulation and manual incremental stimulation) was selected (Shefner and Gooch, 2003; Shefner et al., 2004). This method is noninvasive, threshold stimuli are well tolerated, and a low variability of test–retest (9%) was shown in a previous study (Shefner et al., 2011; Gawel and Kostera-Pruszczyk, 2014).

The aim of the study was to evaluate if MUNE using the Shefner's modification reflects clinical muscle dysfunction in ALS compared to conventional EMG, and to assess whether the MUNE method should be complementary to needle EMG as a useful tool for motor unit number assessment.

2. Patients and methods

The study group consisted of 25 patients with ALS at the mean age of 59.04 ± 12.75 years (range 39–82 years), including 11 males (44%). By the El Escorial criteria, one patient fulfilled the criteria for definite ALS, 3 patients fulfilled the criteria for possible ALS, and 21 fulfilled the criteria for probable ALS. The mean duration of the disease was 17.9 months (3–84 months). The strength of the examined muscles was evaluated using the Medical Research Council (MRC) scale (score 0–5; 0-no action, 5-normal muscle strength). The mean MRC score was 3.9 for the abductor digiti minimi (ADM) and 3.8 for the first dorsal interosseous (FDI), with no significant difference between ADM and FDI MRC scores. The control group consisted of 36 healthy volunteers at the mean age of 58.6 ± 12.22 years (range 34–84 years). There was no significant age difference between patients and controls.

ALS patients with neurological abnormalities such as the history of upper extremity injury, diabetes mellitus, and other serious systemic diseases were excluded. Any control subjects were rejected if clinical symptoms of neuropathy or ulnar nerve injury were suspected.

The protocol of the study was approved by the Ethics Committee at the Medical University of Warsaw (No. KB 163/2011).

MUNE tests were performed using the Keypoint Classic Medtronic Functional Diagnostics EMG system (Natus Inc.m USA). Motor fibers of the ulnar nerve were studied. Disposable, self-adhesive recording electrodes (strips 12 × 22 mm) were placed on ADM innervated by the ulnar nerve of the more affected hand (recording area 4 × 7 mm, specific part number 9013L0202, Medtronic). Low-frequency filters (20 Hz) and high-frequency filters (10 kHz) were used. First, the maximal CMAP was obtained in the most distal location using supramaximal stimuli (Fig. 1).

Assuming that CMAP is the sum of all single motor unit potentials, the universal rule for MUNE with incremental stimulation is that MUNE may be calculated as the ratio of the average size of a surface-detected single motor action potential (SMUP) and the maximum CMAP. SMUP is acquired by averaging several potentials with an increased amplitude, using the "all or none" method with stimulation of an increasing intensity.

The ulnar nerve was stimulated in three locations: at the wrist crease, 4 cm proximally to the wrist crease, and 1 cm proximally to the ulnar grove at the elbow. Three "all or none" responses were obtained at the each location with gradually increasing stimulus intensity. The amplitude measurements for CMAP and SMUP were baseline to peak. The acceptable amplitude of the initial response was not less than 25 μV, and the difference between the amplitudes of the first and the second and the second and the third response was more than 25 μV (Fig. 2).

The amplitude of the three maximal responses at the three locations was summed and divided by 9 to obtain the mean amplitude of an average surface-detected SMUP. The SMUP amplitude was then divided by the maximum CMAP amplitude, thus allowing calculation of MUNE.

MUAPs were recorded using concentric needle electrodes with the uptake area of 0.07 mm^2 and a Keypoint Classic (Medtronic) EMG unit with the band pass of 20 Hz–10 kHz. The FDI muscle was examined in the same hand as the ABD tested using the MUNE method. The electrode was inserted perpendicularly to the course of muscle fibers in the area of the greatest muscle mass, with its position changed at least 5 times at the penetration of 5–10 mm into the muscle. Parameters of a single MUAP including amplitude, duration, and size index (SI) were analyzed (Buchthal and Kamieniecka, 1982; Nandedkar et al., 1988; Sonoo and Stalberg, 1993; Dumitru et al., 1997). The patient activated the FDI muscle so slightly that only a few MUAPs were picked up at one insertion.

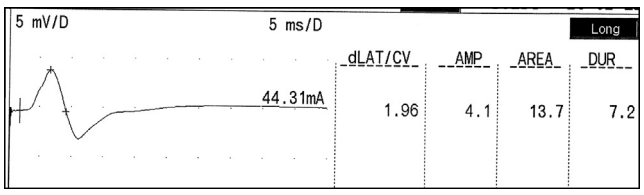

Fig. 1. First step in MUNE test – maximal compound motor action potential (CMAP) in ulnar nerve.