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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.

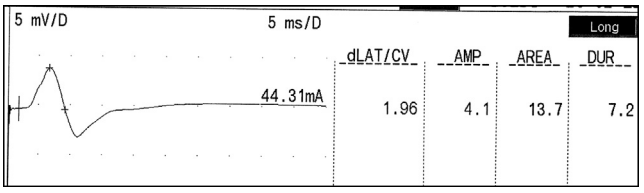

Fig. 1. First step in MUNE test – maximal compound motor action potential (CMAP) in ulnar nerve.

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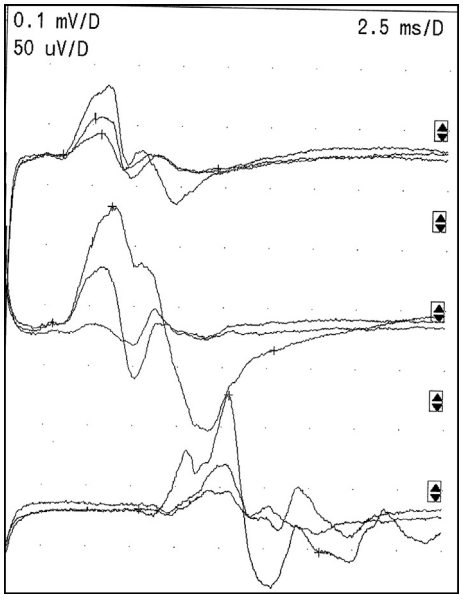

Fig. 2. The second step in MUNE calculation: three incremental responses at three sites of ulnar nerve stimulation (motor potentials).

In order to obtain meaningful values, at least 20 MUAPs at minimal voluntary activation were recorded. The MUAP amplitude from the highest positive to the lowest negative deflection of the curve was measured. The MUAP duration from its first deflection from the baseline to its final return was analyzed, and the deflections were selected manually. SI, which is a very sensitive MUAP parameter for detecting abnormalities, was calculated automatically as 2× log (amplitude) + area/amplitude of a single MUAP (Sonoo, 2002). The EMG results were compared with the normal values adopted by the Neurophysiological Unit of the Neurological Department, Medical University of Warsaw.

3. Results

The MUNE values in ADM ranged from 6.2 to 220.2 motor units in ALS and from 69.2 to 209.2 in the control group. The mean MUNE values in ADM were 88.1 ± 56.1 in ALS and 150.6 ± 40.7 in the control group. A significant difference was found between MUNE results in the ALS and control groups ($P < 0.0001$).

Surface-detected SMUP amplitude was evaluated as a parameter which could reflect the size of a single motor unit. SMUP amplitude in ADM ranged from 86.3 to 320.7 μV in ALS and from 35 to 73.1 μV in the control group. The mean values of SMUP amplitude in ADM were 86.3 ± 61.4 μV in ALS and 54.05 ± 9.5 μV in the control group. A significant difference was found between SMUP amplitude in the ALS and control groups ($P < 0.005$).

The CMAP amplitude in ADM ranged from 0.9 to 13.3 mV in ALS and from 5.1 to 10.56 mV in the control group. The mean values of CMAP amplitude in ADM were 5.89 ± 3 mV in SMA and 7.87 ± 1.35 mV in the control group. A significant difference was found between CMAP amplitude in the ALS group and the control group ($P < 0.001$).

Significant correlations were found in the ALS group between reduced ADM clinical function evaluated by the MRC scale and a decreased number of motor units calculated by MUNE ($P < 0.001$, $r = 0.71$) and between a reduced MRC score and reduced CMAP amplitude values ($P < 0.001$; $r = 0.74$) (Figs. 3 and 4). Interestingly, there was no significant correlation between the MRC score and SMUP, but a trend for a decrease in the MRC score with increasing SMUP values in the ADM muscle was noted ($P = 0.09$) (Fig. 5).

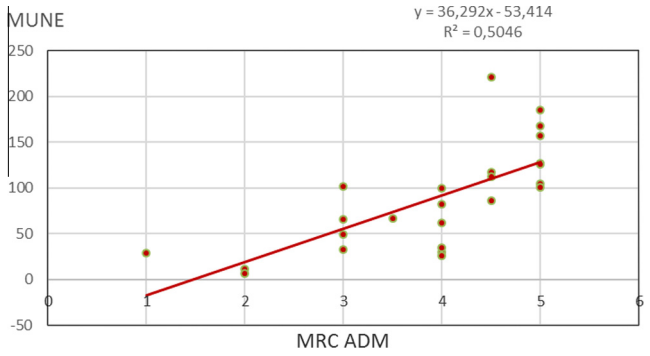

Fig. 3. Correlation between the clinical function of the abductor digiti minimi (ADM) by the Medical Research Council (MRC) scale and the motor unit number by MUNE.

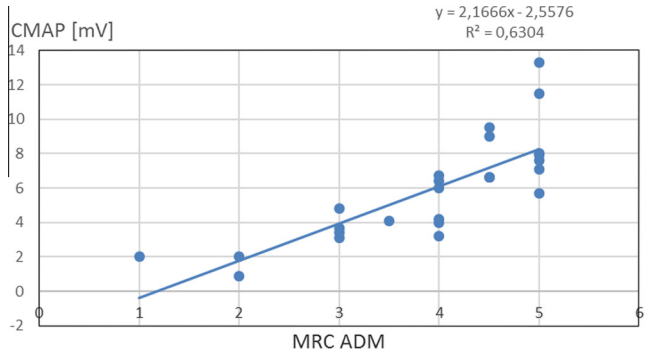

Fig. 4. Correlation between the clinical function of the abductor digiti minimi (ADM) by the Medical Research Council (MRC) scale and the compound motor action potential amplitude (CMAP) in ALS patients.

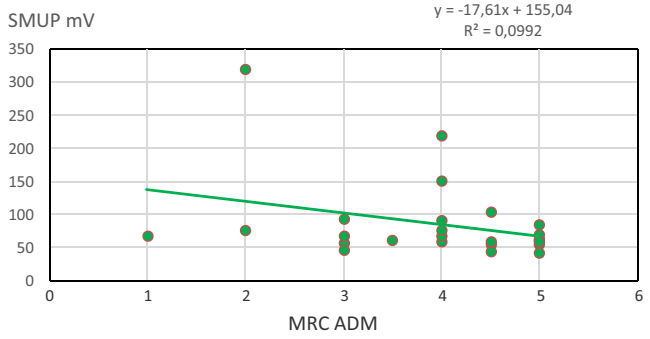

Fig. 5. The relation between the clinical function of the abductor digiti minimi (ADM) muscle by the Medical Research Council (MRC) scale and surface-detected single motor action potential (SMUP) in ALS patients.

We analyzed the relation between MUAP parameters and clinical dysfunction of the FDI muscle. No correlation was found between MUAP parameters including amplitude, duration and SI, and muscle function assessment by the MRC scale (Fig. 6).

We also analyzed the relation between the disease duration and MUNE in ADM and MUAP parameters in FDI, showing no such associations.

4. The complementary role of MUNE in the electrophysiological assessment in practice

The usefulness of MUNE in clinical assessment could be illustrated by the case of a 67-year-old man with a history of hand

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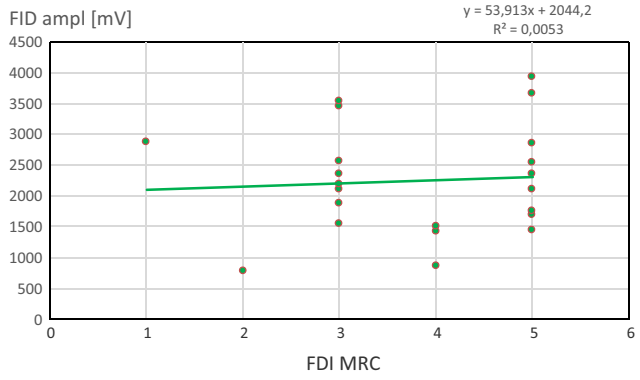

Fig. 6. The relation between the clinical function of the first dorsal interosseous (FDI) muscle (MRC) and MUAP amplitude in FDI.

weakness and gait impairment for 7 months. Neurological examination revealed lower and upper motor neuron signs as mild weakness and atrophy in the distal parts of the upper extremities and the proximal parts of the lower extremities, increased tendon reflexes in the upper and lower extremities, and the Babinski sign bilaterally. The MRC score for FDI was 2, there was no bioelectrical activity at rest, 16 MUAPs were recorded during slight effort, MUAP amplitude was 788 μV (normal range 505–926 μV), MUAP duration was 10.2 ms (normal range 8.1–10.7 ms), and SI was 0.98 (normal range 0.6–1.36). Although clinical dysfunction was found, MUAP parameters were normal due to decompensation of secondary reinnervation and pseudonormalization of MUAP parameters. For ADM, which also scored 2 by the MRC scale, MUNE was 62 (normal range 150.6 ± 40.7) and SMUP was 67 (54.05 ± 9.5 μV). EMG examination of the biceps brachii (BB) revealed fasciculations, fibrillations, positive sharp waves, and chronic denervation signs including increased amplitude, SI and prolonged MUAP duration. By the El Escorial criteria (Brooks et al., 2000), at least two muscles innervated by different roots should be shown to be involved in EMG to consider a given region of the spinal cord to be involved. In our patient, the cervical region could not be considered involved, because neurogenic abnormalities were found only in one examined muscle (BB) in routine needle EMG. In contrast, the result of MUNE for ADM reflected the loss of motor units and confirmed the involvement of the C8-Th1 region of the spinal cord. The number of electrophysiologically involved muscles/spinal regions is crucial for increasing the sensitivity of the diagnosis of ALS in accordance with the Awaji criteria modification for ALS, assigning equal diagnostic significance to neurogenic abnormalities in neurophysiological tests and clinical signs of lower motor neuron dysfunction in individual muscles.

5. Discussion

Results of our study indicate that MUNE correlates strongly with clinical muscle dysfunction, unlike parameters of MUAP recorded during routine needle EMG which are not related to muscle strength. Our results suggest that advanced loss of muscle strength which is significantly associated with loss of motor units is reflected by a diminished number of motor units by MUNE. In contrast, changes in MUAP parameters that occur in the course of compensation and decompensation processes related to muscle denervation and reinnervation do not directly reflect the degree of motor unit damage and therefore do not correlate with muscle strength.

The reinnervation process resulting in an increased area of the motor unit, reflected by SMUP, coexists with preservation of muscle strength in the early stage of disease but also occurs in more advanced stages when the muscles become weaker. Decompensation and a decrease in motor unit area and SMUP are observed in a very marked clinical dysfunction manifesting as weakness and massive atrophy. Because of the overlapping processes, only a trend for decreased MRC scores with increasing SMUP value in the ADM muscle was observed ($P = 0.09$).

In ALS, the condition for which most MUNE data are available, this approach appears to have greater sensitivity for disease progression compared to other clinical biomarkers (including CMAP amplitude, grip strength, MRC grade of weakness, and forced vital capacity) (Felice, 1997), and changes in MUNE are seen before the clinical onset of the disease (Ahn et al., 2010). Prospective studies of disease progression in ALS showed that over the period of 6–20 months, MUNE changes more than other measures of lower motor neuron function (Carvalho and Swash, 2010). Several studies were carried out in attempt to stratify the disease stage based on different progression rates determined by electrophysiological tests in patients with ALS. However, it is difficult to compare these results because of various MUNE methods used in the protocols. A method similar to our study but with 10-step incremental stimulation was used in the study by Liu et al. (2009). Highly significant correlations were found between the motor unit number at baseline and quantitative clinical parameters, including total MRC score but the relation between EMG parameters and MRC score was not assessed.

Both the MUNE method and quantitative needle EMG were used to evaluate the effects of upper motor neuron damage in stroke patients. MUNE results suggested a reduced motor unit number at the paretic side, while at the same time MUAP parameters were normal, which could be explained by a functional inactivity of anterior horn cells in stroke rather than true neuronal loss in stroke subjects. The mechanisms of stroke and neurodegeneration in ALS are, however, different, as in our study, the MUNE results reflected the clinical stage of muscle dysfunction better than routine EMG (Kouzi et al., 2014).

MUNE methods are usually used as an attractive endpoint measure mainly in drug clinical trials in ALS because this approach directly assesses loss of lower motor neurons and is sensitive to disease progression (Felice, 1997; Jagtap et al., 2014) while the importance of all other markers and electrophysiological measures declines with time after the diagnosis. MUNE is considered to be of value in the assessment of progressive axon loss in ALS and may be used as an endpoint measure in clinical trials (Wijesekera and Leigh, 2009).

A dispersion of MUNE results between different centers has been observed, and thus it is recommended to establish individual reference ranges for MUNE values in every EMG laboratory (Gawel et al., 2015).

The MUNE approach includes a number of different methods (incremental, multiple point stimulation, spike triggering averaging, and F-wave and statistical methods), each having specific advantages and limitations. The MUNE method with the Shefner's modification is easy to perform, even in patients with a very low CMAP amplitude and marked loss of motor units. It does not require patient cooperation, in contrast to other methods in which patients are asked to perform a gradually increased effort. It is not painful for the patient and it is well tolerated because stimuli of a very low intensity are used in this method. Moreover, no specialized equipment and software is necessary to perform the tests. One of the crucial aspects is to obtain CMAP with a maximal amplitude, and thus the most quantifiable location for the stimuli over the bulk of the muscle should be found. In addition, the MUNE method with the Shefner's modification is characterized by a very low variability of 7%, as revealed in our previous study (Gawel and Kostera-Pruszczyk, 2014).

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Our results suggest that MUNE could be used as a method useful not only for estimation of disease progression but also as a complementary method for the initial assessment of muscle.

This example shows that the MUNE method may be especially useful in muscles at the stage of decompensation when MUAP parameters could be pseudo-normal but the actual number of motor units has already decreased dramatically. The MUNE test does not depend on the compensatory processes in the course of disease progression and therefore may be considered more objective.

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.

Conflict of interest

The authors declare that there are no conflicts of interest.

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