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Increased supernormality in patients with multiplet discharges: Evidence for a common pathophysiological mechanism behind multiplets and fasciculations

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HIGHLIGHTS

- In patients with motor neuron disease, distal stimulation can evoke multiplet discharges (MDs).
- In patients showing electrically evoked MDs, motor axonal excitability changes suggest K^+ conductance impairment.
- Distally evoked MDs may arise from the same pathophysiological mechanism as fasciculations of distal origin in motor neuron disease.

ABSTRACT

Objective: To determine whether there is a relation between electrically evoked multiplet discharges (MDs) and motor axonal excitability properties. We hypothesized that electrically evoked MDs share their underlying pathophysiological mechanism with fasciculations.
Methods: High-density surface EMG and motor nerve excitability recordings of the thenar muscles were performed in 22 patients with motor neuron disease (MND) in their differential diagnosis and who were referred for EMG examination.
Results: Supernormality (hyperexcitable phase following the refractory period) was significantly increased in patients with MDs ($n = 10$) compared to patients without MDs ($n = 12$) (25.5% vs 17.0%; $p = 0.02$). Depolarizing threshold electrotonus differed significantly between both groups as well (TEd-peak, 76.6% vs 66.6%, $p < 0.01$; TEd90-100 ms, 51.7% vs 44.3%, $p < 0.01$)
Conclusions: Our findings imply that the same pathophysiological excitability changes are involved in generating MDs and fasciculations. Yet, MDs may be quantified more easily, and may be more specific for abnormal distal excitability than fasciculations, because fasciculations may originate along the motor axon as well as in the neuron cell body.
Significance: MDs are potentially useful as objective measure of increased distal axonal excitability at individual motor unit level and might complement clinical studies in MND.

1. Introduction

Altered motor axonal excitability is commonly suggested to provide a mechanism for the generation of fasciculations (Kanai et al., 2006; Nakata et al., 2006; Bae et al., 2013). In patients with motor neuron disease (MND), where fasciculations are an important clinical feature, several studies have observed changes in axonal excitability as evidenced by an increased supernormality, elevated depolarizing threshold electrotonus, and an increase in the strength-duration time constant (SDTC) (Kanai et al., 2006; Vucic and Kiernan, 2006; Cheah et al., 2012). These changes are believed to originate from increased sodium and reduced

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potassium channel conductance in the distal segments of the motor axon (Bostock et al., 1995; Kanai et al., 2006; Nakata et al., 2006; Vucic and Kiernan, 2006).

Altered excitability properties may also explain the occurrence of electrically elicited multiplet discharges (MDs), which were observed in MND patients in a previous high-density surface EMG (HDsEMG) study (Maathuis et al., 2012). Detailed analysis of these distally evoked MDs showed that their spike intervals were restricted to the supernormality period. This suggests that MDs result from altered axonal excitability in much the same way as fasciculations of distal axonal origin (Kleine et al., 2008).

If electrically elicited MDs and fasciculations do indeed arise from the same membrane instability, this may imply a similar diagnostic significance in MND patients (de Carvalho et al., 2008; Schrooten et al., 2011). However, whereas fasciculations appear at random and may originate at various anatomical sites including the cell body (Roth, 1982, 1984; Mills, 1995; de Carvalho et al., 2000; Hirota et al., 2000; Kleine et al., 2008), MDs have the benefit of being highly localized (in the most distal part of the axon) and under control of the investigator. As yet no relation has been established between MDs and the above mentioned motor nerve excitability changes associated with the generation of fasciculations. Assessing this relation was the purpose of the present study.

2. Materials and methods

2.1. Patients

Twenty-two patients (17 men, 5 women; mean age 62 years, range 32–78 years; median disease duration from symptom onset to recording 15.0 months) participated in this study. All patients had MND in their differential diagnosis and after progression of symptoms, were classified according to the revised El Escorial criteria as probable or definite amyotrophic lateral sclerosis (ALS) ($n = 15$) or progressive muscular atrophy (PMA) ($n = 6$). One patient was initially diagnosed with PMA, but due to atypical progression of symptoms, some indication of conduction block, and the absence of a clinical response to repeated intravenous immunoglobulin (IVIg), a differential diagnosis of multifocal motor neuropathy (MMN) could not be excluded. Therefore, this patient will be further referred to as "undetermined".

All patients were recruited through our neuromuscular outpatient clinic at the time they were referred for an EMG examination. Both MD registration and motor nerve excitability testing were restricted to the thenar muscles (cervical region). Hence, the scoring (presence or absence) of fasciculation potentials (FPs) recorded by needle EMG during the EMG examination from muscles only in this region was considered as relevant for this study. Patients with clinical symptoms and/or electrodiagnostic evidence of carpal tunnel syndrome were excluded. The median time interval between HDsEMG and motor nerve excitability recordings in the 22 patients was 4.5 weeks. We used control data from 29 normal subjects (21 men, 8 women; mean age 39 years, range 23–58 years), which was available through the Qtrac software (Kiernan et al., 2000). The experimental protocol was approved by the medical ethical committee of the Erasmus MC. All patients gave written informed consent.

2.2. Motor nerve excitability testing

Nerve excitability was assessed using the QTRAC-S software package (TROND-F, version 20/01/2010, Institute of Neurology, London, UK). The cathode of the stimulator (Red dot electrode; 3 M Health care) was fixed at the level of the wrist over the median nerve; the anode was placed approximately 15 cm more proximally on the ulnar side of the forearm. The active recording electrode was attached to the skin over the abductor pollicis brevis muscle (APB) and the reference electrode was placed over the interphalangeal joint of the thumb. A ground electrode was placed at the base of digits 3 and 4. Skin temperature was kept > 30 °C and measured near the stimulation site during the study.

The protocol consisted of five tests. In short, in the initial test, a stimulus-response curve was derived and used to set a target response (40% of maximum CMAP amplitude) for the other four excitability tests (strength-duration, recovery cycle, threshold electrotonus, and current-threshold). In the strength-duration test, the change in stimulus intensity required to reach the target response was obtained for different stimulus durations. To assess the recovery cycle, after every supramaximal conditioning stimulus a test stimulus was applied at varying time intervals to determine the changes in axonal excitability. In the threshold electrotonus and current-threshold (I/V) relationship tests, a conditioning stimulus was applied to depolarize or hyperpolarize the axons. In general, a depolarizing current increases the excitability of an axon, decreasing the strength of the subsequently applied test stimulus that is necessary to elicit the target response. A hyperpolarizing current has the opposite effect. The strength of the test stimulus required to elicit the target response is automatically adjusted. By varying the intensity and duration of the conditioning stimulus and by applying test stimuli at varying intervals during or just after the conditioning stimulus, axonal membrane properties can be characterized (Bostock et al., 1998; Burke et al., 2001).

2.3. MD registration with HDsEMG recordings

To detect MDs we used a 126-electrode high-density array attached to the skin over the APB in combination with an HDsEMG amplifier system (ActiveTwo, Biosemi, Amsterdam, The Netherlands) (Maathuis et al., 2008). The reference electrode was attached to the dorsal side of the metacarpophalangeal joint of the second finger, the ground electrode to the dorsum of the hand. The stimulator (circular felt-pad electrodes, diameter of 5 mm) was positioned over several sites along the median nerve, all in vicinity of the site of the cathode in the motor nerve excitability tests. At each site, stimulus intensity was gradually increased until a few (usually 4–6) MUs were activated, according to the visual feedback of the response on HDsEMG. Since most MUs that generate MDs are known to do so in response to only a small percentage of applied triggers, many stimuli may need to be administered to elicit and detect an MD. Therefore, subsequently 500 stimuli (2 Hz, 0.1 ms) were applied at each site, and responses were recorded. In this way, up to approximately 20 different motor unit action potential (MUAP) profiles were collected per patient. Finally, the maximum CMAP amplitude was recorded and divided by the mean of the collected MUAPs to derive a motor unit number estimate (MUNE), as described in more detail elsewhere (van Dijk et al., 2008).

MD analysis was performed by post-processing the HDsEMG recordings in Matlab (R2013a: The MathWorks, Natick, MA) using previously described decomposition software (Blok et al., 2005; van Dijk et al., 2008) that was slightly adapted to facilitate MD analysis. In contrast to single-channel surface or needle EMG, HDsEMG presents a MUAP as a spatiotemporal profile. The extra spatial MU information provided by the array of electrodes aids the recognition of single MUAPs during decomposition. The result of this analysis is an overview, listing per stimulation site, per MUAP profile found, and for each of the 500 applied triggers whether or not the MU corresponding to a MUAP profile was activated by the trigger. Not all MUs were activated all 500 times, due