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Interplay of upper and lower motor neuron degeneration in amyotrophic lateral sclerosis

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HIGHLIGHTS

- Variability of recruited motor units can be estimated by using mean consecutive differences (MCD)
- MCD is reduced in patients with marked upper motor neuron involvement.
- This tool can be developed for clinical application.

ABSTRACT

Objective: We studied motor unit recruitment to test a new method to identify motor unit firing rate (FR) variability.
Methods: We studied 68 ALS patients, with and without upper neuron signs (UMN) in lower limbs, 24 patients with primary lateral sclerosis (PLS), 13 patients with spinal cord lesion and 39 normal subjects. All recordings were made from tibialis anterior muscles of normal strength. Subjects performed a very slight contraction in order to activate 2 motor units in each recording. 5–7 motor unit pairs were recorded in each subject. Mean consecutive differences (MCD) were calculated for each pair of potentials. The mean MCD for each muscle was estimated as the mean from the total number of pairs recorded. A p value < 0.01 was accepted as significant.
Results: MCD of FR frequency was less in the subjects with spinal cord lesion and PLS. In addition, the FR frequency of the 1st motor unit in a pair of units was markedly reduced in PLS, and in subjects with spinal cord lesions.
Conclusion: These results support a lower threshold and reduced FR fluctuation in spinal motor neurons of spastic patients.
Significance: This method can be developed for detection of UMN lesions.

1. Introduction

The firing rates, and variability of firing rates, of motor units are modulated in health by upper and lower motor neuron activity. Motor unit firing rates and their variability can be studied by concentric needle electromyography (CNEMG) using the motor unit potential (MUP) analysis software available on modern EMG equipment. Detection of upper motor neuron (UMN) signs by clinical examination in amyotrophic lateral sclerosis (ALS) is notoriously difficult and contentious (Swash, 2012). However, since UMN signs are important in the clinical diagnosis of ALS there is a need for practical and more sensitive methods to demonstrate UMN abnormalities. In a previous study we have shown that UMN lesions due to primary lateral sclerosis (PLS), ALS with lower limb spasticity, and UMN signs from other causes, are associated at low voluntary recruitment levels with reduced variation in motor unit firing rates (de Carvalho et al., 2012). Although more sophisticated techniques for detection of UMN dysfunction have been

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-UMNLL, ALS patients with signs of upper motor neuron lesion in lower limbs; ALS-noUMNLL, ALS patients with no signs of upper motor neuron lesion in lower limbs; CNEMG, concentric needle electromyography; EMG, electromyography; LMN, lower motor neuron; MCD, mean consecutive differences; MR, magnetic ressonance; MUP, motor unit potential; PLS, primary lateral sclerosis; UMN, upper motor neuron.

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Table 1
Results.

Subject groups (Males/Females)	Median age (1st-3rd IQR)	Median disease duration (1st-3rd IQR)	Number of MUs analysed	Median MCD of MU firing frequency (1st-3rd IQR)	*p* values for MCD comparisons between groups. **p < 0.01** was considered as significant	Median firing frequency (Hz) of 1st MU (1st-3rd IQR)	*p* values for the firing frequency of 1st MU in the pair. **p < 0.01** was considered as significant
Normal subjects (16/14)	57.5(45.8–65.0)	–	350	2.47 Hz (2.00–2.82)	Controls v ALS-noUMMLL = 0.64 Controls v ALS-UMMLL = 0.45 Controls v PLS < **0.001** Controls v Spinal cord < **0.001**	8.20 Hz (6.90–9.70)	Controls vs ALS-noUMMLL = 0.051 Controls vs ALS-UMMLL = 0.06 Controls vs PLS < **0.001** Controls vs Spinal cord < **0.001**
ALS-noUMNLL (20/14)	60.5(53.0–70.0)	15.5 months(9.3–22.3)	388	2.39 Hz (1.48–2.88)	ALS-noUMMLL v ALSUMMLL = 0.32 ALS-noUMMLL v PLS < **0.001** ALS-noUMMLL v Spinal cord = **0.003**	7.70 Hz (6.70–8.90)	ALS-noUMMLL vs ALSUMML = 0.03 ALS-noUMMLL vs PLS < **0.001** ALS-noUMMLL vs Spinal cord = **0.006**
ALS-UMNLL (20/12)	60.0(51.0–67.5)	12.0 months(6.8–17.3)	368	2.39 Hz (1.39–2.58)	ALS-UMMLL v PLS < **0.001** ALS-UMMLL v Spinal cord = **0.001**	7.95 Hz (7.18–9.50)	ALS-UMMLL vs PLS < **0.001** ALS-UMMLL vs Spinal cord < **0.001**
PLS (14/9)	60.0(53.0–68.0)	6.0 years(5.0–8.0)	280	1.20 Hz (1.10–1.44)	PLS vs Spinal cord = 0.58	7.10 Hz (6.30–8.10)	PLS vs Spinal cord = 0.97
Spinal Cord Lesion (11/2)	55.0(47.0–61.0)	6.0 years(2.5–17.0)	156	1.12 Hz (0.83–1.82)	–	7.00 Hz (6.28–8.30)	

N – number; UMNLL- upper motor neuron signs in lower limbs; noUMNLL- absent upper motor neuron signs in lower limbs; PLS – primary lateral sclerosis; M – males; F – females; MCD – mean consecutive difference; IQR – interquartile range; FR – firing rate; MU - motor unit.
$p < 0.01$ was considered as significant (bold).

advocated these involve relatively complex and expensive methodologies, such as transcranial magnetic stimulation of motor pathways (Vucic et al., 2013) or MR imaging.

In this report we consider whether a new method to analyse the spontaneous motor unit firing rates in a muscle, expressed as firing frequencies, can be useful to identify changes in motor unit firing rate variability at low firing rates in patients with UMN lesion. Moreover, we explore this method to detect signs of UMN injury in ALS, a disorder in which there is also pronounced dysfunction in the lower motor neuron (LMN).

2. Methods

2.1. Subjects

The diagnosis of ALS was made according to the El Escorial criteria supported by the Awaji recommendations for electrophysiological testing (de Carvalho et al., 2008). Patients with respiratory symptoms unable to lie comfortably recumbent, or with dementia were excluded. Any subjects with peripheral neuropathy were excluded from the investigation. Progression on follow-up was required for confirmation of the diagnosis of ALS. Five groups of patients were studied (Table 1).

2.2. ALS patients with and without spasticity in the lower limbs

There were two groups of subjects with ALS.

One group of 32 patients with Charcot ALS had upper motor neuron signs in the lower limbs (ALS-UMNLL), consisting of abnormal tendon reflexes (>1 of the following 4 features: very brisk, decreased threshold, clonus, and reflex irradiation) and extensor plantar responses, and/or spasticity (present in 12 patients).

The second ALS group consisted of 34 patients without clinically detectable UMN signs in the lower limbs (ALS-noUMNLL); 12 of these had prominent bulbar involvement (brisk jaw reflex and atrophic tongue with fasciculations); 8 had UMN signs in the upper limbs (persistent tendon reflex in spite of atrophic and very weak upper limbs and/or positive Hoffman reflex), and 14 presented with the features of the progressive muscular atrophy variant of ALS, without clinically detectable UMN signs.

Patients with severely spastic lower limbs (modified Ashworth scale >3) were not investigated since the experimental protocol required an ability to perform a maintained slight contraction of the tibialis anterior muscle.

2.3. Primary lateral sclerosis (PLS)

A third group of 23 subjects had PLS; none of these PLS patients had clinical or EMG evidence of LMN involvement, and all had undergone full clinical investigation including MR imaging, and biochemical, haematological and immunological investigations. Further, all these subjects with PLS had been followed for more than 4 years as required by accepted diagnostic criteria (Gordon et al., 2006). Spasticity in lower limbs was scored as mild to moderately severe (modified Ashworth scale ≤ 3), since very marked spasticity would preclude a proper constant mild contraction (de Carvalho et al., 2012).

2.4. Normal and disease controls

We studied two groups of control subjects. There were 30 control subjects without neurological disease, and a second 'disease control' group of 13 patients with spasticity and weakness in the legs due to acquired cord lesions at cervical or thoracic levels associated with multiple sclerosis (3 subjects), to cord compression due