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Use of Bayesian MUNE to show differing rate of loss of motor units in subgroups of ALS

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HIGHLIGHTS

- Subgroups of patients defined by clinical features have different lengths of survival and different rates of loss of motor units.
- The size of motor units can be estimated with Bayesian MUNE.
- Subgroups of patients defined on clinical grounds have different sized motor units with larger motor units found in subjects with slower progression.

ABSTRACT

Objectives: To evaluate differences among patients with different clinical features of ALS, we used our Bayesian method of motor unit number estimation (MUNE).
Methods: We performed serial MUNE studies on 42 subjects who fulfilled the diagnostic criteria for ALS during the course of their illness. Subjects were classified into three subgroups according to whether they had typical ALS (with upper and lower motor neurone signs) or had predominantly upper motor neurone weakness with only minor LMN signs, or predominantly lower motor neurone weakness with only minor UMN signs. In all subjects we calculated the half life of MUs, defined as the expected time for the number of MUs to halve, in one or more of the abductor digiti minimi (ADM), abductor pollicis brevis (APB) and extensor digitorum brevis (EDB) muscles.
Results: The mean half life of MUs was less in subjects who had typical ALS with both upper and lower motor neurone signs than in those with predominantly upper motor neurone weakness or predominantly lower motor neurone weakness. In 18 subjects we analysed the estimated size of the MUs and demonstrated the appearance of large MUs in subjects with upper or lower motor neurone predominant weakness. We found that the appearance of large MUs was correlated with the half life of MUs.
Conclusions: Patients with different clinical features of ALS have different rates of loss and different sizes of MUs.
Significance: These findings could indicate differences in disease pathogenesis.

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive loss of upper and lower motor neurones. The pathogenesis of ALS is unknown but inherited abnormalities of neuronal proteins are increasingly seen to be important (Rothstein, 2009). The clinical picture of ALS results from dysfunction of both upper motor neurons (UMNs) and lower motor neurones (LMNs). There has been debate as to whether the death of LMNs is secondary to dying back of axons or dying forward of UMNs or a combination of the processes (Dadon-Nachum et al., 2011).

ALS is diagnosed on clinical grounds for which there are accepted criteria (Brooks et al., 2000) with electrophysiological evidence supporting the clinical diagnosis and facilitating early diagnosis (de Carvalho et al., 2008; Okita et al., 2011). There are other diseases of motor neurones, where subjects have either pure UMN weakness (primary lateral sclerosis) or pure LMN weakness (progressive muscular atrophy). These other diseases do not fulfill the criteria for diagnosis of ALS.

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However, even when defined according to the standard criteria (Brooks et al., 2000), ALS itself is heterogeneous. There is heterogeneity in the site of onset of disease. There is also heterogeneity in whether patients have typical ALS with mixed upper and lower motor neurone signs or whether UMN or LMN signs are predominant (Gordon et al., 2006; Gouveia and de Carvalho, 2007; Talman et al., 2009; Beghi et al., 2011). Clinical distinctions and clinical heterogeneity are important because it is possible that subjects with different clinical features have different underlying pathophysiology.

One pathophysiological finding in ALS is that large MUs that can be demonstrated by needle EMG (Hansen and Ballantyne, 1978). This is thought to occur because after denervation of muscle, there can be re-innervation due to collateral sprouting of terminal branches of surviving axons. MU size in ALS has also been studied with decomposition-based quantitative electromyography (DQEMG) (Boe et al., 2007). However, there have been no studies of the size of the entire population of motor unit action potentials (MUAPs) in ALS and the relationship of change in size of MUs to the rate of progression of disease.

We have developed a Bayesian statistical technique of motor unit number estimation (MUNE) that gives an estimate of the number of MUs in a muscle (Ridall et al., 2007; Henderson et al., 2007). In experimental animals we have found that the number of MUs estimated with our MUNE method is proportional to the number of anterior horn cells in the spinal cord at the segments containing the cell bodies of the MU (Ngo et al., 2012). Previously we have performed serial studies of MU numbers through the course of disease, and shown that the loss of MUs is well-fitted by an exponential decay curve and also that the rate of MU loss is greatest at the site of onset of weakness (Baumann et al., 2012).

As well as estimating the number of MUs, our MUNE technique also estimates the size of all the surface-recorded MUAPs that contribute to the CMAP. We now present the results of our serial MUNE recordings from patients with ALS, to examine the rate of loss of MUs in patients grouped according to clinical criteria of upper or lower motor neurone weakness and gender, and also to evaluate the changes in size in MUs as disease progresses.

2. Methods

2.1. Subjects and clinical assessment

From 2002 to 2011 we invited consecutive unselected local ALS patients who were attending the Motor Neurone Disease multidisciplinary clinic at the Royal Brisbane and Women's Hospital (RBWH) to participate in serial MUNE studies. The study was approved by the Hospital Ethics Committee and all subjects gave written consent prior to testing. ALS patients were required to meet the modified El Escorial criteria for probable or definite ALS during the course of their disease (Brooks et al., 2000). All patients had diagnostic EMG studies, and during the course of the illness all subjects met the neurophysiological criteria for ALS (de Carvalho et al., 2008). The majority of the subjects in this study have been previously described in a study showing that the rate of loss of MUs in ALS follows an exponential decline (Baumann et al., 2012). The subjects did not have other diseases, such as diabetes mellitus, that could affect the peripheral nerves. We noted the age at onset of ALS, site of onset as bulbar, upper limb (UL) or lower limb (LL) and length of symptom duration before the first visit (in months).

On the basis of our first clinical assessment of the presence of UMN and LMN signs examination, we separated subjects into three sub-groups. Signs of UMN involvement were taken to be spastic dysarthria, increased jaw jerk, emotional lability, hyperreflexia in the limbs, increased muscle tone, clonus or extensor plantar responses. Signs of LMN involvement were taken to be muscle atrophy or fasciculation.

Patients with mixed UMN and LMN signs at the first assessment were grouped as typical ALS (ALS-typical). Patients with predominantly UMN or LMN signs were designated as UMN dominant type (UMN-D) or LMN dominant type (LMN-D) of ALS, respectively, provided they later fulfilled the clinical and electrophysiological criteria for ALS.

Patients classified as UMN-D had symptoms less than 4 years, and disability due predominantly to UMN signs of emotional lability, hyperreflexia, spasticity or extensor plantar responses. In these subjects the LMN signs were minor and signs of wasting and fasciculations were limited to one or two muscles. Denervation on EMG was limited to sparse fibrillation potentials, positive sharp waves or minor MU potential remodelling on one or two muscles. Patients with UMN-D did not meet all of the criteria for ALS at the first visit but met these criteria during the course of their disease. In assigning subject to UMN-D we excluded patients from 'clinically pure PLS' (Gordon et al., 2006).

Patients classified as LMN-D had symptoms and disability due to prominent lower motor signs (muscle atrophy or fasciculations) at the time of first study, with no or minor UMN signs. Emotional lability, hyperreflexia, spasticity or extensor plantar responses were absent. LMN-D patients were distinguished from pure adult onset LMN syndromes such as progressive muscular atrophy (PMA) patients who have disease duration of at least 4 years and absence of UMN signs (Van den Berg-Vos et al., 2009).

2.2. Neurophysiology

MUNE studies were performed in three different nerve/muscle combinations: median nerve/abductor pollicis brevis (APB) muscle, ulnar nerve/abductor digiti minimi (ADM) and peroneal nerve/extensor digitorum brevis (EDB) muscle.

Surface recordings using the belly–tendon configuration were made from APB, ADM, and EDB muscles with disposable silver pre-gelled, 20 mm diameter self adhesive electrodes (Nicolet Biomedical, Madison, Wisconsin). All studies were performed using a Nicolet Viking IV machine. The recording electrode was placed over the middle of the belly of the muscle (with attention to the muscle end plate). Before placing the electrodes, the skin was cleaned to prevent high or mismatching impedance between the electrodes. In all studies, the skin temperature was recorded with a surface probe and was maintained above 31 °C for the hand and 29 °C for the foot. The muscle under testing was restrained with a Velcro strap, and the audiometer was used to detect movement (Henderson and Daube, 2004). The active stimulating electrode was taped approximately 7 cm from the active recording electrode. The stimulus intensity was measured as current (mA) in constant voltage mode, and stimuli were 0.1 ms in duration. The frequency of stimulation was 2 Hz.

For MUNE studies, a stimulus response curve was first obtained as described previously (Henderson et al., 2006; Blok et al., 2007). The size of the stimulus required to produce a maximal CMAP was determined with standard NCS. For the stimulus response curve, the maximal CMAP was obtained with a stimulus strength sufficiently above the maximal (at least 10–20%) that small movements of stimulating electrodes would be unlikely to affect the maximal CMAP. For each study the minimum and maximum stimulus intensity was determined before commencing collection of the stimulus–response curve by gradually increasing the stimulus intensity with at least 1000 stimuli. A software modification supplied by Nicolet Biomedical (Madison, Wisconsin) was used to collect the stimulus response curves, by automatically evoked incremental stimuli. The CMAP amplitude measurements were automatically