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Motor-evoked potential gain is a helpful test for the detection of corticospinal tract dysfunction in amyotrophic lateral sclerosis

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HIGHLIGHTS

- Motor-evoked potential (MEP) gain is decreased in patients with amyotrophic lateral sclerosis (ALS).
- MEP gain may allow the early detection of upper motor neuron dysfunction in patients and improve the diagnosis of ALS.
- The diagnostic utility of MEP gain is equivalent to the triple stimulation technique (TST) and better than diffusion tensor imaging (DTI).

ABSTRACT

Objective: The detection of upper motor neuron (UMN) dysfunction is necessary for the diagnosis of amyotrophic lateral sclerosis (ALS). However, signs of UMN dysfunction may be difficult to establish. This study aimed to determine whether motor-evoked potential (MEP) gain (MEP area/background electromyographic activity) represents an efficient alternative to assess UMN dysfunction.
Methods: MEP area, MEP/compound muscle action potential (CMAP) area ratio, and MEP gain were tested at different force levels in healthy control subjects and ALS patients. Receiver operating characteristic (ROC) curve analyses was used to determine the diagnostic utility of MEP gain and compare it to alternative techniques, namely, diffusion tensor imaging (DTI) and the triple stimulation technique (TST).
Results: MEP gain revealed a significant difference between the patients and healthy control subjects in contrast to MEP area and MEP/CMAP area ratio. The diagnostic utility of MEP gain was comparable with that of TST and superior to that of DTI.
Conclusion: MEP gain can distinguish ALS patients from control subjects and may be helpful for the diagnosis of ALS.
Significance: MEP gain appears to be a useful adjunct test and noninvasive method for the assessment of corticospinal dysfunction.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is clinically characterized by the combination of both upper motor neuron (UMN) and lower motor neuron (LMN) symptoms. Given the need for precise diagnostic criteria, in 1990, the World Federation of Neurology Subcommittee on Motor Neuron Disease proposed a classification into degrees of diagnostic certainty depending on the presence of UMN and LMN dysfunction. However, the presence of UMN dysfunction may be difficult to establish. Therefore, tools capable of detecting UMN dysfunction are necessary. These tools may improve diagnostic certainty and allow patients with suspected ALS more timely access to treatment and clinical trials.

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In an awake human brain, the motor cortex area can be activated using noninvasive focal transcranial magnetic stimulation (TMS) (Barker et al., 1985). TMS can help to assess corticospinal dysfunction. Motor-evoked potential (MEP) normalization by compound muscle action potential (CMAP) has been proposed to consider the recorded muscular volume (de Carvalho et al., 2005). However, the increasing size of single motor units caused by the compensatory reinnervation process at the early stage of ALS can prevent the detection of CMAP alteration (Pouget et al., 1995). Therefore, compensatory plastic changes may mask structural alterations and prevent the reliable assessment of motor system integrity. Up to 30% of the single motor unit pool may be lost before the first clinical signs of muscular weakness due to LMN sprouting (Pouget et al., 1995; Aggarwal and Nicholson, 2002). The use of methods such as surface electromyography (EMG), which considers a motor unit's functional and structural alterations, would be interesting. At the early stage of the disease, reinnervation increases the size of motor units. This increase in the size of single motor units can prevent detection of the first clinical signs of muscular weakness. This observation is the reason why CMAP does not decrease at the early stage of ALS. Therefore, EMG activity better reflects the functional state of motor units than an electrical supramaximal stimulation of the axons because CMAP does not correspond to the muscular activation ability of the subject. MEP amplitude, expressed as a function of background EMG activity, was first used in 1996 (Mathis et al., 1996). This parameter is called MEP gain, and it refers to the ratio between MEP size and the mean magnitude of the smoothed rectified background EMG recorded prior to the stimulus. MEP gain can detect abnormalities earlier than the MEP/CMAP ratio. We have previously described MEP gain as a useful means of assessing UMN dysfunction in ALS patients (Attarian et al., 2006). Additionally, we have demonstrated that MEP gain decreases with time in ALS patients, whereas no change occurs in patients with Kennedy's disease in which the corticospinal pathway is spared but the spinal motoneurons are selectively affected.

Other techniques have been previously proposed for the detection of UMN impairment in ALS. Such techniques include the triple stimulation technique (TST) (Magistris et al., 1998) and diffusion tensor imaging (DTI), which is an advanced MRI technique (Basser et al., 1994; Rosler et al., 2000; Komissarow et al., 2004; Attarian et al., 2007; Filippi et al., 2010; Foerster et al., 2013; Grapperon et al., 2014). The present study aimed to analyze the diagnostic utility of MEP gain in ALS patients. We also compared the diagnostic utility of MEP gain with that of TST and DTI.

2. Methods

2.1. Subjects

We included 20 patients (17 men and 3 women), of which 14 patients had definite, probable, or possible forms of sporadic ALS according to the revised El Escorial criteria (Brooks et al., 2000) and 6 patients had progressive muscular atrophy (PMA). Twenty healthy control subjects (14 men and 6 women) were also included in the study. All subjects were recruited from the reference center for neuromuscular disorders and ALS at la Timone University Hospital of Marseille (Marseille, France). The procedure was approved by the local ethics committee. All subjects provided written informed consent to the experimental procedure as required by the Helsinki Declaration (1964).

Inclusion and exclusion criteria were selected to ensure a homogenous group of patients with ALS. Thus, only patients with recent (disease duration <2 years) spinal and sporadic forms of ALS were included. Only patients with MEPs inducible by TMS could participate in the study. Moreover, cases with any atypical findings, such as cerebellar syndrome, parkinsonism, sensory symptoms or dysautonomia, the presence of dementia, or the presence of progressive severe illness or chronic psychiatric disorders were excluded; ulnar nerve entrapment was also excluded. All patients were treated with riluzole. Treatments modulating cortical excitability were stopped 48 or 72 h before the examination.

2.2. Clinical assessment

Disease duration was calculated in months from the appearance of symptoms to the scan date. The disability level of the patients was evaluated by the revised ALS functional rating scale (ALSFRS-R), ranging from 48 (normal) to 0 (Cedarbaum et al., 1999). Muscle force was measured using the Medical Research Council (MRC) rating scale on seven muscles of the right arm ranging from 35 (normal) to 0. Furthermore, a UMN score of the right arm was used (ranging from 0 to 13, normal value: 3–6, UMN score $\geqslant 7$ was considered a clinical sign of UMN lesions) that was adapted from previous studies (Ellis et al., 1999; Iwata et al., 2011; Grapperon et al., 2014). For its calculation, right upper limb tendon reflexes were scored according to the four-point National Institute of Health myotatic reflex scale (Hallett, 1993; Litvan et al., 1996), with additional points given for Hoffman and Babinski signs and the jaw jerk reflex.

2.3. Procedures

Subjects were seated in an adjustable armchair with their right forearm held in a stereotyped position. The distal end of their forearm was immobilized in a U-shaped device, and their right hand was maintained in a perfect prone position. Their fingers were extended, and the fifth finger was permanently in contact with an isometric force transducer. The U-shaped device (Fig. 1) was used to standardize the hand position and prevent force from being exerted with another muscle than the right abductor digiti minimi (ADM). The wrist was immobilized with a strap, and the device presented a barrier to prevent abduction of the wrist. To prevent force from other fingers, there was a barrier between the 4th and 5th fingers. To record the maximum voluntary contraction (MVC), subjects were asked, with the encouragement of the experimenters, to contract their right ADM for a few seconds by pushing against the force transducer as forcefully as possible. Three measurements were conducted with a 1 min break between each MVC. CMAPs were evoked by a supramaximal stimulation of the right ulnar nerve at rest.

TMSs were performed as previously recommended (Rossini et al., 1999; Chen et al., 2008). Stimuli were delivered on the area of the left primary motor cortex innervating the right ADM using a Magstim 200 stimulator and a figure-of-eight coil (2×70 mm, Magstim, Withland, UK). All stimuli were performed at the optimal site, which is defined as the stimulation site at which MEPs with the highest amplitude were elicited with a forward anteromedial current using the lowest stimulation intensity. The resting motor threshold (RMT) was determined by increasing the maximum stimulator output in 5% steps and was taken as the minimum stimulus intensity that elicited at least 5 MEPs in 10 consecutive stimuli. This RMT value was systematically used to determine MEP gain. To stimulate precisely the same cortical site during successive stimuli, we used the eXimia Navigated Brain Stimulation system 2.3 (Nexstim, Helsinki, Finland) with a T1-weighted MRI.

Subjects were asked to produce, as steadily as possible, voluntary isometric contractions of ADM at 5%, 10%, 15%, and 20% of their MVC using force signal visual feedback on an oscilloscope screen. During each contraction, five stimuli were delivered at the RMT. The successive contraction levels were randomized and