Neurophysiological features of fasciculation potentials evoked by transcranial magnetic stimulation in amyotrophic lateral sclerosis

Abstract We report 13 patients with amyotrophic lateral sclerosis in whom fasciculation potentials (FPs) driven by transcranial magnetic stimulation (TMS) were recorded. A total of 18 different FPs were analyzed. TMS-driven fasciculations had a simple morphology and were stable. Complex potentials were never cortically driven. Recruitment by a slight voluntary contraction was verified in 7 of 13 tested FPs. FPs were driven by threshold stimuli in 7 of 10 patients and by stimuli 5% below threshold in 3 of 6. Mapping demonstrated that FPs were driven in an area close to the center of gravity of the muscle cortical area. In one case FPs were evoked from most of the cortical representation area of a very weak muscle. Three other patients with profuse fasciculations associated with other clinical conditions were also studied. No TMS evoked fasciculation was observed in this group. The results of this systematic study suggest that cortically evoked FPs arise centrally, at spinal cord or even more proximally, and can represent a marker of increased corticomotor excitability, which is predominant at an earlier phase but can persist as the disease progresses.

Key words Fasciculation . Amyotrophic lateral sclerosis . Transcranial magnetic stimulation

Introduction

In amyotrophic lateral sclerosis (ALS) interest has long focused on the significance and origin of fasciculations [6]. The clinical importance of fasciculations is stressed by the fact that neurologists do not feel confident in diagnosing ALS in a patient lacking this sign [13]. From a pathogenic point of view, fasciculations may be related to the excitotoxic hypothesis [4], at least early in the disease. The question of their origin has been a subject of some disagreement, with some arguing for a proximal origin [17], most for a distal origin [8, 19], and some for both distal and proximal origins [20] probably changing over the course of the disease evolution [4].

Fasciculation potentials (FPs) evoked by transcranial magnetic stimulation (TMS) have been reported by a few authors. To our knowledge, Caramia et al. [3] were the first to describe driven fasciculations in ALS, showing a figure of a FP of simple morphology obtained in a patient with low stimulation threshold. Later Kaji et al. [12] described three ALS patients with cortical evoked fasciculations, observed in muscles with only slight denervation. Their attempts at voluntary recruitment of these FPs were unsuccessful. Mills [14] also noted this same aspect of simple waveform FPs recruited by TMS in three ALS patients with a predominant lower motoneuron lesion, in two of whom the threshold was particularly low. The recruitment of the potentials by a slight voluntary contraction was attempted but not achieved. Desiato and Caramia [7] described 18 ALS patients with a short evolution time who had a very low threshold for TMS. Driven FPs were observed in some of these, but no further information was given. Recently Mills and Nithi [15] reported two new cases of ALS patients with low threshold and evoked fasciculations, but the neurophysiological features of the FPs...
were not described in detail, although some comments on a simple morphology of these potentials were presented. The significance of these findings is not completely established, but they may indicate a proximal origin of some fasciculations, particularly in patients with increased corticomotor excitability.

We report our systematic observation of fasciculations driven by TMS in 13 ALS patients, document their neurophysiological features, and discuss the results in terms of the possible origin and significance of these fasciculations. Attempts were also made to evoke FPs by TMS in three other patients, with abundant fasciculations associated with various clinical conditions other than ALS.

**Population and methods**

Thirteen ALS patients (ten men, three women; aged 42–74 years; a mean disease duration of 21 months, range 6–48) underwent TMS as part of their neurophysiological evaluation. At the time of this investigation the patients had possible (n = 4), probable (n = 8), or definite (n = 1) disease, as defined by the El Escorial criteria [2]. The following tests were performed on all patients: Conduction velocities were obtained at least at one motor and one sensory nerve in each limb, ruling out peripheral neuropathy and conduction block. F-waves were investigated in both peroneal and ulnar nerves: their frequency, minimal, mean and maximal latencies were recorded for 20 stimuli applied at a rate of 1 Hz, at ankle and wrist. Needle examination was performed in two muscles innervated by different nerves and roots at each limb, as well as in two muscles innervated by cranial nerves. This confirmed diffuse active denervation in at least two regions. The patients were subjected to the usual laboratory tests to rule out other diseases. Radiological investigation and cerebral spinal fluid analysis were performed as necessary to exclude other conditions. The same neurologist followed all patients and confirmed the clinical evolution of ALS. In subsequent follow-up six patients died after reaching a phase of definite criteria, four have definite criteria but are still alive, and three are now classified as probable disease.

Three patients with abundant fasciculations associated with other conditions were also investigated. Patient A was a 68-year-old man with cervical spondylotic myelopathy and fasciculations in left biceps and triceps, patient B was a 55-year-old man with bilateral L5–S1 radiculopathy and fasciculations in both gastrocnemii, and patient C was a 61-year-old man with a right C7–C8 lateral L5–S1 radiculopathy and fasciculations in both gastrocnemius. The clinical data relative to the ALS patients and the neurophysiological features of their FPs are summarized in Table 1. Table 2 shows the results of a systematic search for TMS evoked fasciculations that was carried out in six ALS patients using a needle electrode. All investigated muscles had frequent visible fasciculations.

In two patients who were studied using a needle electrode it was verified that either the round coil or the eight-shaped coil could drive the same FP. Another three patients were examined twice, first using a round coil and surface electrodes (2A, 6A, and 9A) and a second time 6–8 months later, using a round coil and either surface

**Results**

Patient A was sampled in four different sites on the left biceps and triceps, patient B was investigated on both gastrocnemius medial heads (three different sites in each), and in patient C a needle was inserted on right triceps, extensor digitorum brevis, and first dorsal interosseous (three different sites in each). Despite the abundant spontaneous fasciculations no TMS-driven fasciculations were recorded in these patients.

Two and, rarely, three phases, were stable, had a short duration (only three potentials had duration above 10 ms), and a low amplitude (only one potential recorded with surface electrodes and one recorded with a needle had amplitudes above 0.4 mV). The latency showed a short jitter, typically of about 1–1.5 ms in at least five consecutive responses, but in patient 1 a larger variation was observed.

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