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Does the motor cortex influence denervation in ALS? EMG studies of muscles with both contralateral and bilateral corticospinal innervation

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ABSTRACT

Objectives: To evaluate the pattern of degeneration of lower motor neuron progression in ALS in relation to the contralateral and ipsilateral corticospinal innervation of the tested muscles.
Methods: EMG evaluation of the sternomastoid and trapezius muscles on one or both sides, and transcranial magnetic stimulation to record motor evoked responses from these muscles after ipsilateral and contralateral cortical stimulation. The sternomastoid muscle receives corticospinal input from both hemispheres, but the trapezius only a contralateral corticospinal innervation; however the power motor innervation of both these muscles is derived from the same spinal nucleus, and the same motor nerve. Seventy-five patients with ALS were studied at the time of diagnosis, and 54 control subjects, consisting of normal subjects and disease control subjects. MUP analysis and spontaneous activity were assessed.
Results: We confirmed that the sternomastoid receives both contralateral and ipsilateral corticospinal innervation, and the trapezius usually only contralateral innervation. The MUP analysis revealed symmetric changes in sternomastoid and trapezius muscles, and both muscles were equally affected.
Conclusions: Our findings are in accord with the concept that LMN degeneration in ALS is related to local factors in the spinal cord.
Significance: Our findings suggest that local factors in the spinal grey matter are important in causing LMN degeneration in ALS, but they do not rule out a corticomotoneuronal contribution.
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1. Introduction

There is uncertainty regarding the primary process of degeneration of the motor system in amyotrophic lateral sclerosis (ALS). In particular, there is controversy as to whether the disease begins independently in upper motor neurons (UMN) and lower motor neurons (LMN) (Ravits and LaSpada, 2009) or whether it is initiated primarily in the motor cortex, involving the LMNs as a later phenomenon – a process termed the "dying forward hypothesis" (Eisen et al., 1992; Eisen, 2009; Vucic and Kiernan, 2006). Vucic et al. (2008) noted that in familial ALS cortical hyperexcitability seemed to precede the clinical onset of the disease, but this study did not include needle EMG examination. The long-held view that ALS becomes clinically evident as a result of dying-back change at the motor end plate associated with axonal degeneration associated with axonal transport abnormalities and microtubular dysfunction with proximal accumulation of neurofilaments (Breuer et al., 1987; Leigh et al., 1989; Cleveland and Rothstein, 2001) is supported by histological studies in transgenic SOD1^{G93A} mice (Kennel et al., 1996; Narai et al., 2009) and in human ALS (Fischer et al., 2004). ALS presents only after loss of sufficient functioning motor units to cause weakness (Wohlfart, 1957; Aggarwal and Nicholson, 2002). However, none of these studies have evaluated patients with sporadic ALS at disease onset, a limitation inevitably imposed by patient presentation some months after the onset of the first symptom. In neuropathological studies Pamphlett et al.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FRS, amyotrophic lateral sclerosis-functional rating score; AMAN, acute motor axonal neuropathy; EMG, electromyography; Fibs-sw, fibrillations/positive sharp waves; FPs, fasciculation potentials; LMN, lower motor neuron; MEP, motor evoked potential; MUP, motor unit potential; TMS, transcranial magnetic stimulation; UMN, upper motor neuron.

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(1995) found that UMN and LMN degeneration could occur independently, an observation confirmed by Ravits and LaSpada (2009). However, a possible relationship between UMN and LMN degeneration in ALS cannot be discarded since Ince et al. (2003) noted UMN degeneration in about half of their patients who had presented with progressive muscular atrophy, a disorder that is clinically limited to the LMN involvement, at least at its onset (de Carvalho et al., 2008c).

Unfortunately, testing the concept of primacy of motor cortex abnormality in the pathogenesis of ALS is not feasible by clinical evaluation of UMN signs, since in ALS the LMN features tend to mask signs of UMN abnormality (Rowland, 1998; Rowland and Schneider, 2001). Ravits et al. (2007a), in careful clinical studies of patients with ALS showed that LMN involvement was more severe ipsilateral to the more prominent UMN signs. In a pathological study of spinal cords of ALS patients they concluded that both UMN and LMN degeneration developed independently and that degeneration of either one alone is sufficient to lead to progressive deterioration (Ravits et al., 2007b). Ravits and LaSpada (2009) stressed the distinctive pattern of clinical spread to involve contiguous anatomical regions over time. These different concepts of the mode of onset and spread of ALS within the motor system can be best studied using neurophysiological methods, especially needle EMG combined with transcranial magnetic stimulation (TMS) of the motor cortex, as early in the disease course as possible, and closely linked to clinical data.

We have taken a slightly different approach to the investigations described above. The major question that remains undetermined is the relation between EMG changes in different muscles or groups of muscles in ALS. For example, we found in an earlier study that in ALS paraspinal muscles and limb muscles innervated by the same spinal roots, both in the cervical and lumbar regions, were similarly affected (de Carvalho et al., 2008b). Kiernan (2008), in a commentary on this work, suggested that these results supported the cortical-onset hypothesis. However, it seemed to us that, if this was so, the whole motor cortex must be diffusely hyperexcitable, since paraspinal and limb cortical representations are widely separated in the cortical motor strip (Penfield and Jasper, 1954; Porter and Lemon, 2007). One should also note, following Hughlings Jackson's insight from his studies of focal epilepsy (Hitzig, 1900) that in the primary motor cortex it is movements that are represented, rather than individual muscles, as in the spinal segments, so that in ALS any relationship between LMN abnormality and cortical pathology or hyperexcitabiity, if indeed there is such an interactive relationship, is likely to be complex. We reasoned, therefore, that the corticomotoneuronal hypothesis predicts that muscles innervated by the same motor nerve derived from the same spinal segment(s) *but dependent on different representations in the motor cortex* would be affected differently.

We decided to address this question studying the sternomastoid component of the sternocleidomastoid muscle, and the trapezius muscle, using concentric needle EMG and TMS. We chose these two muscles because they receive different patterns of crossed (contralateral) and uncrossed (ipislateral) corticospinal innervation. In hemiplegia due to hemispheric lesion, there is weakness of head turning to the side of the paralysis, a feature that has led to the concept that the sternomastoid motor nucleus in the cord receives a predominantly ipsilateral cortical innervation (Balagura and Katz, 1980; Geschwind, 1981; Mastaglia et al., 1986). This has been confirmed by TMS and deep brain stimulation (Berardelli et al., 1991; Thompson et al., 1997; Costa et al., 2007). In contrast, the trapezius muscle receives only a contralateral corticospinal innervation (Berardelli et al., 1991; Thompson et al., 1997; Costa et al., 2007). Both these two muscles are innervated by motor cells in the spinal grey matter at the C1–C4 level. The neurons in the cranial part of this spinal nucleus innervate the sternocleidomastoid muscle and those in the caudal part innervate the upper portion of the trapezius muscle (Routal and Pal, 2000). These motor cells are located in the spinal cord close to the midline. Since the upper trapezius and the sternomastoid muscles are innervated by the same spinal accessory nerve, derived from the same motor neuron pool, it is only in terms of cortical drive that these two muscles differ in their motor innervations (DeToledo and David, 2001; DeToledo and Dow, 1998).

Therefore, in patients with ALS, we have examined needle EMG changes in the sternomastoid muscle, which receives both contralateral and ipsilateral corticospinal innervation at medullary level, and compared them with EMG changes in the upper part of the trapezius muscle, which receives only a contralateral corticospinal innervation. In addition we have directly tested the extent of the contralateral and ipsilateral corticospinal innervation in these two muscles using TMS.

2. Patients and methods

We studied 75 patients (Fig. 1) with ALS, 32 of whom were women, mean age 63.5 years (range 29–80 years) with a clinical diagnosis of ALS, at the time of their referral for diagnostic neurophysiological evaluation. The mean disease duration from symptom onset was 12.8 months (range 2–30 months). The disease was of bulbar-onset in 27 patients (disease duration 10.5 months; SD ± 7.1), upper-limb onset in 25 (disease duration 14.4 months; SD ± 6.0) and lower-limb onset in 23 (disease duration 14.6 months; SD ± 8.0). The differences between the disease durations, mean age and sex distribution in the three groups were not statistically significant. Twenty had definite ALS, 26 clinically probable ALS and the remainder had probable-laboratory supported ALS, based on the revised El Escorial criteria (Brooks et al., 2000). All the patients had an ALS-FRS score greater than 25/40 (mean 32.6 SD ± 4.3) at the time of investigation and no patient had clinical signs or symptoms of respiratory distress at rest. All had full neurological and neuroradiological, haematological and biochemical investigations. Routine nerve conduction studies ruled out polyneuropathy, and patients with diabetes mellitus or other conditions potentially associated with neuropathy were excluded. Patients with clinical signs of cognitive impairment were not included in this study for ethical reasons, since we required informed consent from all participating subjects.

We studied three groups of control subjects. The *first control group* consisted of 27 healthy controls (mean age 61.8 years, range 42–75 years). Twelve were women. Seven were relatives of patients with ALS, some were friends, and others were volunteers among hospital staff. The relatives of ALS patients did not show signs of ALS for a period of at least 18 months after neurophysiological testing. The *second control group* consisted of 27 patients referred for neurophysiological study for other reasons; six had a final diagnosis of Parkinson's disease, three had multiple strokes, two had multiple sclerosis, two had bilateral ulnar nerve lesions at the elbow, two had isolated phrenic nerve lesions, two had dorsal cord lesions, two had severe lumbar radiculopathy, two had chronic polyarthritis, one had multiple system atrophy, one had idiopathic cerebellar ataxia, one had an isolated hypoglossal nerve lesion, one had an uncharacterised glossal tremor, one had fibromyalgia, and one had obstructive pulmonary disease. This second grouped was investigated to add a sample of patients with non-ALS disease to our normative data. A *third control group* of eight non-ALS patients with neurological disorders was studied; five of these had chronic axonal neuropathy, associated with an acute AMAN-like onset in four and with hepatitis C virus infection with cryoglobulinaemia in one; three had severe cervical myelopathy. The mean age in this group was 62.1 years (range 40–80 years).

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