The natural history of central motor abnormalities in amyotrophic lateral sclerosis

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Summary
Degeneration of spinal motoneurons has been well documented in amyotrophic lateral sclerosis (ALS), but the evolution of central motor abnormalities is largely unknown. It has been suggested that glutamate-mediated neuroexcitotoxicity may be involved in the pathogenesis of ALS and that this may be manifest as an increase in corticomotor excitability early in the disease. Serial measurements of corticomotor threshold, central motor conduction time (CMCT), silent period duration and the amplitude of compound muscle action potentials (CMAPs) from ulnar nerve stimulation in the right and left first dorsal interosseous muscles were made in 76 patients with idiopathic ALS, 49 of whom were followed from presentation to death. Threshold to transcranial magnetic stimulation was determined by standard methods and CMCT was measured using the F-wave method. Silent period was estimated during a small background contraction of the muscle. Patients were classified according to the region of onset and the physical signs in the hands. The region of onset was bulbar in 17 patients, lower limb in 31 patients and upper limb in 28 patients. At presentation, 23 patients had no abnormal physical signs in the hands, 25 had lower motoneuron signs only, 14 had upper motoneuron signs only and the remainder (14) had mixed upper and lower motoneuron signs in the hands. Evolution of the central conduction parameters was determined in relation to time from onset of symptoms and also as a function of normalized total disease duration in the patients who had died. Corticomotor threshold and CMCT showed no change as the disease evolved except for patients with mixed signs, who had a terminal increase in threshold and prolongation of CMCT. Silent period duration was shorter than normal early in the disease and showed progressive lengthening throughout the illness, but nevertheless remained within the normal range regardless of the region of onset. CMAP amplitude showed a linear decline over the course of the disease. There was therefore no evidence of a phase of increased corticomotor hyperexcitability at any stage of disease progression. The early shortening of silent period, however, probably represents a shift in the balance of excitatory and inhibitory inputs to the cortical output cells responsible for voluntary action, and could be a reflection of degeneration of cortical interneurons. None of the measures of central motor function in ALS are likely to be useful for monitoring patients in a clinical trial setting.

Keywords: ALS; central motor conduction; serial studies; corticomotor threshold; silent period

Abbreviations: ALS = amyotrophic lateral sclerosis; CMAP = compound muscle action potential; CMCT = central motor conduction time; MEP = motor evoked potential; TMS = transcranial magnetic stimulation

Introduction
Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of corticomotoneurons in both the cerebral cortex and the spinal cord (Lawyer and Netsky, 1953; Smith, 1960; Brownell et al., 1970). The result is a syndrome of mixed upper and lower motoneuron signs which progresses relentlessly and leads to death at a median time of 29.1 months after presentation (Munsat et al., 1988; Haverkamp et al., 1995). The lower motoneuron component, manifest as muscle wasting, weakness and fasciculation, accompanied by the compensatory changes of intramuscular reinnervation detectable on EMG, has been widely studied. Serial measurements of muscle fibre density (Yuen and Olney, 1997), motor unit number estimates (Bromberg et al., 1993; Felice, 1995) and muscle strength measurements (Pradas et al., 1993;
Reports of reduced corticomotor threshold in ALS, especially in patients early in the course of the disease, have appeared (Eisen et al., 1993; Mills and Nithi, 1997a), but there is no information as to how these abnormalities evolve. About 20% of patients with idiopathic ALS have prolonged central motor conduction time (CMCT) (Eisen et al., 1990; Mills and Nithi, 1998), but there is little information as to how these changes over time. Similarly, silent period duration has been reported to be shorter than normal in ALS, and indeed it has been suggested that this is a marker of the condition (Desiato and Caramia, 1997), but again the evolution of this abnormality as the disease progresses is not known.

It would be useful to have a measure of the number of fibres in the corticospinal tract in ALS and it has been suggested (de Carvalho et al., 1999; Triggs et al., 1999) that the ratio of the motor evoked potential (MEP) amplitude or area to that of the compound muscle action potential (CMAP) evoked by supramaximal nerve stimulation be used. However, MEP amplitude and area depend not only on the number of fibres in the corticospinal tract but also on the synchrony with which impulses arrive at the spinal motoneurons (Magistris et al., 1998). Furthermore, it is known that spinal motoneurons may fire repeatedly in response to a descending volley (Day et al., 1987; Hess et al., 1987; Kiers et al., 1995), and hence the MEP, already desynchronized by temporal dispersion in the corticospinal tract, may be rendered even more complex by multiple contributions from the same motor unit. The triple stimulation technique (Magistris et al., 1998; Rosler et al., 2000) overcomes these difficulties but was not considered suitable for repeated use on patients with ALS.

The aim of the present study was to follow up patients with ALS over the course of their disease from presentation to death to document changes in central motor conduction parameters. CMAP amplitude from peripheral nerve stimulation was used as a convenient marker of overall lower motoneuron degeneration. The study also assessed whether simple measures of central motor conduction could be used to monitor treatment in a clinical trial setting.

Methods

Patients

Patients with a potential diagnosis of ALS referred for diagnostic neurophysiology were recruited with the approval of The Oxford Research Ethics Committee and the King’s College Hospital Research Ethics Committee. An initial neurological examination was performed to classify patients as having definite, probable or possible ALS according to the El Escorial criteria (Brooks, 1994; Chaudhuri et al., 1995). Patients with a coincidental nerve entrapment, such as an ulnar nerve lesion at the elbow, were not excluded. Other signs of ALS were present. Three patients with diabetes were excluded at the outset since central motor abnormalities have been reported in this condition (Abbruzzese et al.,

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Evolution of central abnormalities in ALS

One of the theories for the pathogenesis of ALS supposes that cortical cells are the subject of neuroexcitotoxic cell death (Shaw, 1994). The glial-specific glutamate transporter GLT-1 has been reported to be markedly reduced in both the brain and the spinal cord in ALS (Rothstein et al., 1992, 1995; Rothstein, 1995; Bristol and Rothstein, 1996). The effect of excess extracellular glutamate might be to render cortical cells hyperexcitable prior to cell death. It was therefore of particular interest to determine if output cells of the motor cortex went through a phase of increased excitability during the evolution of disease.

More recently it has been shown that intracortical inhibition (Kujirai et al., 1993) is abnormal in ALS. Short-interval intracortical inhibition, in which the effects of a subthreshold conditioning stimulus on a suprathreshold test stimulus given 1–5 ms later, is less than normal in ALS (Yokota et al., 1996; Ziemann et al., 1997). Short-interval intracortical inhibition appears to become less as disease progresses, although these reports were based on small numbers of patients, usually seen only twice (Zanette et al., 2002). Long-interval inhibition, probably also of cortical origin, in which suprathreshold conditioning and test stimuli are given 100–300 ms apart, has also been shown to be abnormal in ALS (Zanette et al., 2002). These reports suggest an abnormality of GABAergic inhibitory transmission in ALS (Nihei et al., 1992; Hanajima et al., 1998).
1993). None of the patients was taking medication known to affect central motor conduction. Patients were further classified according to site of onset (bulbar, upper or lower limb) and according to the physical signs present in the hands (no signs, lower motoneuron signs only, upper motoneuron signs only or mixed signs). The group with only lower motoneuron signs had wasting with weakness and fasciculations in intrinsic hand muscles with upper limb hyper-reflexia and without impairment of discrete finger movements. The group with only upper motoneuron signs had upper limb hyper-reflexia or a positive Hoffmann sign, and/or impairment of discrete finger movements without wasting or fasciculation in intrinsic hand muscles. The group with mixed signs had both upper and lower motoneuron signs in the hand. The time of onset of the disease was estimated from the appearance of the first relevant symptom determined by the history. Follow-up of patients was at 3-month intervals for as long as the patient was willing to return for repeat neurological examination and neurophysiology. Follow-up also allowed certainty in the diagnosis to be established. From an initial sample of 98 patients, 15 were excluded because there was no progression in symptoms, three had a diagnosis of multifocal motor neuropathy with focal conduction block and four had multiple cervical radiculopathies and myelopathy.

Nerve conduction studies
Both hands were studied in all patients. CMAPs were recorded from the first dorsal interosseous muscle with chlorided silver electrodes taped over the belly and tendon. Supramaximal electrical stimuli to the ulnar nerve at the wrist were used to evoke a maximal CMAP, the peak-to-peak amplitude of which was measured. Minimal F-wave latency was determined from 20 trials.

Corticomotor threshold
A figure-of-eight coil driven by a Magstim 200 magnetic stimulator was positioned 5 cm lateral to the vertex in the interaural line and oriented at 45° to the parasagittal plane (Mills et al., 1992). Threshold was determined with the muscle at rest, confirmed by lack of EMG activity on visual and auditory monitoring. A standard procedure (Mills and Nithi, 1997b) in which the lowest intensity at which 10 consecutive trials yielded MEPs of at least 50 μV and the highest intensity at which 10 consecutive trials yielded no response was used. The mean of these upper and lower intensity levels was taken as the resting corticomotor threshold as a percentage of maximal stimulator output. If the threshold to cortical stimulation could not be determined because 10 responses were not obtained at 100% maximal stimulator output, the threshold was designated as 100%. The test–retest reliability of this method has been determined (Mills and Nithi, 1997b); a change in resting threshold of ≥13% over a period of 3 months would be significant at the 5% level.

Central motor conduction time and silent period
CMCT was determined by the F-wave method using the formula \((F + M - \mu)/2\). In five patients F waves were absent and CMCT could not be determined. Stimulus intensity was set at the resting motor threshold and the patient was asked to produce a modest background voluntary contraction of ~20% maximum force. It is known that in small hand muscles the onset latency of the MEP is stable above 10% maximum contraction levels (Hess et al., 1987; Kischka et al., 1993). The cortex-to-muscle latency was defined as the shortest in 10 trials. The normal values for this muscle have been determined using the same techniques (Mills and Nithi, 1997b). Silent period was defined as the interval from stimulus to the earliest reappearance of EMG activity in 10 trials.

Data analysis
The right and left sides were studied in all patients, but clearly values from the two sides cannot be considered as independent variables. Indeed, regression of the right- on the left-sided values of the relevant measurements revealed significant correlation for corticomotor threshold \((P < 0.0001)\), CMCT \((P < 0.0001)\), silent period \((P < 0.0001)\) and CMAP amplitude \((P < 0.0001)\). Consequently, values obtained from the right and left sides at each follow-up in each patient were averaged. In the analysis of progression in relation to physical signs present in the hands, however, the situation is more complex. The signs will change as the disease progresses and at any given time signs in the two hands may differ. As a compromise, these data were analysed without averaging the two sides.

Patients with ALS deteriorate at different rates. Two approaches have been used to investigate the evolution of the various central motor conduction parameters. First, taking all the data, the time from the onset of symptoms was split into epochs of 250 days and a mean calculated over all the available data. Secondly, taking only those patients who had died, the duration of the illness from onset to death was normalized between zero and unity and data were averaged into bins representing 20% of the total disease duration. Analysis of variance was used to determine whether the mean of data at any time point was significantly different from others; a \(P\) value of \(< 0.05\) was taken as significant. Where required, \(t\)-tests were used to determine whether a mean value differed significantly from normal. Normal data from a previously reported series of healthy controls \((n = 55, \text{age range } 23–84 \text{years})\) using the same methods (Mills and Nithi, 1997b) were used for comparison. In healthy controls, the mean (95% confidence interval) for threshold is 44.2 (27.4–60.9)% of maximal stimulator output, for CMCT it is 5.8 (3.7–7.9) ms and for silent period duration it is 77.3
(57.5–97.1) ms. CMAP amplitude in normals should exceed 5 mV.

**Results**

Data were available from 76 patients (49 males) of mean ± SD age 62.9 ± 12.6 years (median 65 years). The median time from onset to inclusion in the study was 348 days. At the time of writing 49 patients had died. The median duration of illness in these patients was 780 days. Patients were studied at intervals of ~3 months and there were between two and 14 follow-up observations on each patient; the mean number of follow up studies was 3.1. The total number of observations was 468. The region of onset was bulbar in 17 patients, lower limb in 31 patients and upper limb in 28 patients. At presentation, 23 patients had no abnormal physical signs in the hands, 25 had lower motoneuron signs only, 14 had upper motoneuron signs only and the remainder (14) had mixed upper and lower motoneuron signs in the hands.

**Evolution with respect to time from onset**

Results from the first method of analysis are seen in Fig. 1. Using analysis of variance, corticomotor threshold \((P = 0.9)\), CMCT \((P = 0.7)\) and CMAP amplitude \((P = 0.4)\) showed no significant trends with time after onset, whereas silent period duration became significantly longer as the time after onset of symptoms increased \((P = 0.01)\). After subdividing the patients according to region of onset (Fig. 2), analysis of variance showed no significant trends in the evolution of threshold \((P\) values: bulbar 0.3; upper limb 0.1, lower limb 0.4), CMCT \((P\) values: bulbar 0.7; upper limb 0.8; lower limb 0.6), silent period \((P\) values: bulbar 0.09; upper limb 0.15; lower limb 0.13) or CMAP amplitude \((P\) values: bulbar 0.08, upper limb 0.07; lower limb 0.1). There were no significant differences between the evolution of threshold, CMCT and silent period according to region of onset, but CMAP amplitude was significantly lower in patients with upper limb onset than bulbar \((P = 0.02)\) or lower limb \((P = 0.04)\) onset.

**Evolution with respect to physical signs in the hands**

Patients with upper motoneuron and mixed signs in the hands overall had significantly higher thresholds than patients with no signs or lower motoneuron signs only \((P = 0.04)\), but there were no significant trends in the evolution of threshold with time (Fig. 3). Patients with mixed signs whose disease had been present for >1200 days, however, all had thresholds of 100%. CMCT in patients with mixed signs showed a significant rise \((P = 0.003)\) 1250–1500 days after disease onset, but there were no significant changes in CMCT over time in the other groups. Silent period showed no significant trends over time with respect to signs in the hands. CMAP amplitude was overall significantly lower in patients with lower motoneuron or mixed signs than in patients with no signs or upper motoneuron signs \((P = 0.02)\). The rate of decline was faster in patients with upper than with bulbar onset \((P = 0.04)\).

**Evolution with respect to total disease duration**

Considering now the second method of analysis, in which the total course of the disease was normalized across
patients (Fig. 4), again corticomotor threshold \((P = 0.3)\) and CMCT \((P = 0.9)\) showed no significant change over the course of the disease, although threshold did show a trend towards reduction early in the course. In contrast, silent period was significantly shorter than normal early in disease evolution \((P = 0.04)\) and showed a significant prolongation \((P = 0.02)\) as the disease evolved. CMAP amplitude showed a highly significant \((P = 0.0007)\) linear decline. After subdividing the patients according to region of onset (Fig. 5), analysis of variance showed no significant trends in the evolution of threshold \((P\) values: bulbar 0.9; upper limb 0.87; lower limb 0.92), CMCT \((P\)
values: bulbar 0.77; upper limb 0.9; lower limb 0.56) or silent period (P values: bulbar 0.7; upper limb 0.6; lower limb 0.3). CMAP amplitude showed a significant decline over time in all three regions of onset (P values: bulbar 0.02; upper limb 0.007; lower limb 0.01) and patients with upper limb onset had significantly lower CMAP amplitudes than patients with either bulbar onset (P = 0.01) or lower limb onset (P = 0.03).

**Discussion**
Progression in ALS clearly differs widely between individuals and assessing the rate of progression in groups of patients with ALS presents methodological problems. Either the duration of disease from onset can be used, in which case data from patients at different stages of disease will be averaged, or the total disease duration can be normalized to unity and patients’ data can then be treated on the assumption...
that all follow a similar course, but of different durations. Both methods were used here.

Threshold
No evidence was found that corticomotor threshold to hand muscles changes significantly overall as ALS progresses. This was true in patients with upper limb, lower limb and bulbar onset and, apart from a terminally high threshold in patients with mixed signs in the hands, as has also been noted recently (de Carvalho et al., 2003), there was no influence of upper or lower motoneuron abnormalities on the evolution of threshold. Threshold measures the amount of induced current required to excite cortical output cells, but is also influenced by spinal motoneuron excitability. If spinal motoneurons were, for instance, inhibited for some reason then threshold would appear high even though cortical excitability was normal. Threshold, then, reflects a balance of cortical and spinal cord excitability which cannot easily be dissected.

It has been reported previously that threshold tends to be lower than normal in patients with no signs in the hands (Eisen et al., 1993; Mills and Nithi, 1997a, although this has not been confirmed by others (de Carvalho et al., 2002). This study has shown that patients with no signs or lower motoneuron signs only tend to have thresholds in the lower half of the normal range (Fig. 3) and remain at this level throughout the course of the disease. Similarly, patients with upper motoneuron or mixed signs in the hands tend to have a higher than normal threshold, and again this persists throughout the illness. There is thus no evidence from these studies of a phase of increased corticospinal excitability early in the disease.

Central motor conduction time
TMS probably excites large-diameter output cells contributing a small but rapidly conducting moiety to the corticospinal tract (Ranck, 1975). Previous work (Eisen et al., 1990; Desiato and Caramia, 1997; Mills and Nithi, 1998) has shown that CMCT is only modestly prolonged in ALS, but in only ~20% of cases. The present results confirm this finding, but also show that there is no overall change in CMCT as the disease progresses. Patients with mixed signs whose disease has been present for >4 years do, however, show a prolonged CMCT. There are several possible mechanisms for CMCT prolongation in ALS: impairment of excitation of cortical cells by TMS; degeneration of fast-conducting fibres in the corticospinal tract; and impairment of synaptic activation of spinal motoneurons (Thompson et al., 1987). Recently, using the triple stimulation technique (Magistris et al., 1998), it has been shown that prolonged CMCT in ALS is associated with conduction failure in the corticospinal tract (Rosler et al., 2000). Presumably, CMCT shows little change over time in the present study because sufficient fast-conducting corticospinal fibres remain functioning.

Silent period
In ALS, silent period duration has been reported to be shorter than normal (Desiato and Caramia, 1997), but this finding has not been confirmed by others (Triggs et al., 1992; Prout and Eisen, 1994). These studies are not directly comparable with the current findings because stimulus intensity was not controlled or specified. The present results show a shorter than normal silent period early after presentation, but this abnormality becomes less obvious as the disease evolves. The origin of the silent period in ongoing EMG activity when TMS is delivered is predominantly cortical, although the initial part may have a spinal origin (Uncini et al., 1993; Ziemann et al., 1993). Overall, the prevailing view is that the silent period represents a TMS-evoked intracortical inhibition of the cells engaged in voluntary action. Furthermore, studies on late intracortical inhibition (Zanette et al., 2002), which corresponds in time course to the silent period, suggest that both phenomena are related to a long inhibitory postsynaptic potential (IPSP) evoked in output cells by inhibitory cortical interneurons operating through GABA_A receptors (Sanger et al., 2001). The duration of the silent period will be determined by the depth of this inhibition and the degree of excitatory input to cortical output cells. In the present study, silent period showed a modest but significant prolongation as the disease evolved. This applied to patients with bulbar, lower or upper limb onset and there was no correlation with the signs present in the hands. It is tempting to speculate that, early in the disease, hyperexcitability of cells providing excitation to output cells leads to a shortening of the silent period, and as the disease evolves these cells degenerate, leading to a progressive lengthening of the silent period.

CMAP amplitude
As expected, CMAP amplitude, representing the volume of excitable tissue in the first dorsal interosseous muscle, declines as the disease progresses. Equally expected are the findings that CMAP amplitude is in general lower in patients with lower motoneuron findings than upper. The decline in CMAP amplitude differs depending on the region of onset. It should be recalled that the processes of denervation and reinnervation characteristic of ALS will have opposing effects on CMAP amplitude. The finding that the CMAP declines more slowly in patients with lower limb or bulbar onset may reflect less denervation or greater reinnervation in the clinically less affected hand muscles of these patients.

Conclusions
These results have implications for the use of these parameters to monitor changes during treatment. Clearly, threshold and CMCT are blunt measures of corticospinal function in ALS, showing little change as the disease evolves, and are therefore unlikely to be useful in the serial monitoring of patients in a clinical trial. Silent period lengthens progres-
sively as the disease evolves, but even so remains within the normal 95% confidence interval (Fig. 5), and so this too is unlikely to be useful in a trial setting. A recently proposed TMS index (de Carvalho et al., 2003) which combines the deviation from the mean of both threshold and CMCT may prove to be a more sensitive measure, but ultimately measurements more directly related to the pathophysiology of ALS are required. In this regard, a serial study of long- and short-interval intracortical inhibition will be of interest.

References


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