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ORIGINAL ARTICLE

The cutaneous silent period as a measure of upper motor neuron dysfunction in amyotrophic lateral sclerosis

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Upper motor neuron

Abstract
Objectives: We investigated the cutaneous silent period (CutSP) as a measure of upper motor neuron (UMN) dysfunction in amyotrophic lateral sclerosis.
Methods: The onset latency, duration, and amount of EMG suppression of the CutSP were compared with clinical UMN signs in 24 patients with amyotrophic lateral sclerosis (ALS). UMN signs were quantified using a clinical index and transcranial magnetic stimulation (TMS). Central motor conduction time (CMCT), cortical motor threshold and motor evoked potential amplitudes were assessed as measures of UMN dysfunction. CutSP was studied in abductor digit minimi (ADM) and tibialis anterior (TA) EMG recordings following stimulation of the 5th finger and sural nerves respectively. Non-parametric tests and binomial logistic regression were applied to evaluate the data.
Results: CutSP onset latency was increased in ALS patients, compared to healthy controls, both for ADM and TA muscles. In limbs with clinical UMN signs or abnormal TMS findings, the CutSP onset latency was particularly increased. There was a significant positive correlation between CutSP onset latency and the UMN score in both upper and lower limbs. In TA muscles there was also a negative correlation between CutSP onset latency and EMG suppression. The logistic regression model based on CutSP parameters correctly classified more than 70% of the cases regarding the presence of clinical signs of UMN lesion, in both upper and lower limbs. The results were not significant for TMS.

Cutaneous silent period and UMN dysfunction in ALS.

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Conclusion: We conclude that upper limb CutSP changes associates with UMN lesion in ALS. This neurophysiological measurement merits further investigation in ALS.

Introduction

Electrical stimulation of sensory nerve fibers in skin innervated by the same spinal segment as a tested limb muscle can briefly suppress voluntary contraction of the muscle [31,34]. The longest duration of this electromyographic (EMG) signal interruption is caused by a stimulus intensity about 8 to 15 times greater than the sensory threshold [11,19]. This phenomenon is known as the cutaneous silent period (CutSP). Its afferent arc results from A-delta fiber activation, which causes brief reflex suppression of lower motoneuron activity [19,11,21].

Presynaptic and postsynaptic inhibitory synapses may be involved [19] in the CutSP, but a predominant post-synaptic inhibition is likely [19,21,11,4,15]. Although the CutSP is a spinal segmental inhibitory phenomenon, it is also influenced by supraspinal pathways. For example, delayed CutSP onset latency has been reported in stroke [14]. In patients with amyotrophic lateral sclerosis (ALS) an increased CutSP onset latency has been reported [14,4,17,6], without a significant change in CutSP duration. This occurred independently of disease phenotype [4], including patients with progressive muscular atrophy (PMA), in whom there were no clinical signs of upper motor neuron (UMN) dysfunction. Corticospinal tract degeneration has been reported in about half of PMA patients at autopsy, despite the absence of UMN signs in upper and lower limbs in life [16]. In patients with PMA, the CutSP onset latency in the upper limb shortened with contralateral hand contraction [4]. It has been suggested that activation of the ipsilateral cortex associated with reduced transcallosal inhibition in ALS [35] might compensate for the impact of a subclinical UMN lesion. As a consequence, it has been proposed that a delayed CutSP might be useful to detect UMN lesion in ALS [10], at least in upper limbs. Here, we explore the statistical relation between features of UMN lesion as detected by clinical examination and by transcranial magnetic stimulation (TMS) of the brain, and CutSP changes in upper and lower limbs of patients with ALS.

Methods

Participants

Patients with probable or definite ALS defined by the Awaji criteria [8] were recruited from the ALS clinic in Lisbon. These diagnostic criteria require progressive neurogenic weakness shown by clinical and/or EMG analysis and exclusion of other potential diagnoses. We required abductor digiti minimi (ADM) and tibialis anterior (TA) strength $\geq$ 4 on the MRC scale on at least one side of the body, normal nerve conduction studies in ulnar and peroneal nerves (motor conduction studies and sensory nerve action potentials) and normal sural nerve sensory nerve action potentials. Patients incapable of giving informed consent, or with other neurological diseases especially peripheral neuropathy and epilepsy, or with metallic brain implants and pacemakers, and those taking drugs that could affect cortical excitability were excluded. All the patients were stabilized on riluzole at the time of the assessments, with a treatment duration greater than 1 month for every patient.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Lisbon Academic Medical Center. The study was performed according to the Declaration of Helsinki, and written informed consent was obtained from all participants.

Clinical assessment

Full clinical and electromyographic (EMG) assessment (MdeC) was completed before neurophysiological investigation, which was always arranged within one month following first clinical evaluation. An UMN score, as described by Geraldo et al. [13], was calculated. In each limb this score rated, tendon reflexes as 0 (absent or very weak) to 3 (very brisk), spasticity as 0 (no spasticity) to 3 (corresponding to a 3 or 4 on modified Ashworth scale), plus Hoffmann sign for upper limbs (0 or 1 if present), and plantar response as 0 or 1 (if present) - (maximum score 7 per limb). The bulbar region was scored from 0 to 3 (tongue spasticity, absent 0, present 1; jaw jerk, absent 0, brisk 1, clonus 2). The total UMN score for each patient therefore ranged from 0 to 31. A limb with very brisk reflexes (score $>$ 3), or spasticity, or abnormal reflex Hoffman, or extensor plantar response was considered as having UMN signs [3]. Functional disability was assessed on the same day using the ALSFRS-R (maximum healthy score 48) [5].

Cutaneous silent period

We have described our protocol for study of the CutSP in detail in a previous report [4]. Surface electrodes (reference 9013L0203, Natus Inc) were used for recording EMG activity and nerve action potentials. Eligible muscles (ADM and TA strength $\geq$ 4 on the MRC scale) from limbs on both sides were investigated. For the upper limb, recordings were made with the active electrode over the belly of the ADM muscle, and the reference electrode on the dorsum of the hand (in order to avoid artefact stimulation originating from the proximal ring electrode). Ground electrode (reference 9013L0862, Natus Inc) was placed on the wrist. For the lower limbs, recordings were made with the active electrode over the belly of the TA muscle (7—8 cm below the lower extremity of the ipsilateral patella) and the reference electrode 5—7 cm distally to the active electrode, over the tibial bone. The ground electrode (reference 019—400,500, Natus Inc) was placed over the patella. Adhesive tape was used to

secure the electrodes. Standard amplifier filter settings of 30-Hz and 10-kHz were used, and signals were digitized at a sampling frequency of 3 kHz.

Sensory orthodromic stimulation, using a constant current square wave of 0.2 ms duration, was applied by ring electrodes (reference 9013S0302, Natus Inc) on the Vth finger for the upper limbs; and using a conventional superficial bipolar bar stimulating electrode (reference 9013L0362, Natus Inc) over the sural nerve (cathode posterior to the lateral malleolus and anode 2 cm distally) for the lower limbs. Sensory threshold was tested by applying progressively greater stimuli intensities from 0 mA to the moment subject could identify 3 of 6 randomly timed stimuli, increasing stimulus intensity by steps of 0.1 mA. Subjects were blind to the stimulus intensity used. When necessary, threshold determination was repeated. For studies of the CutSP the stimulus intensity was then set to 15x the sensory thresholds in upper and lower limbs. Skin temperature was maintained >30 °C in each tested limb.

Since CutSP parameters are not influenced by muscle activation in the range of 10−60% of maximum voluntary contraction [18,27], patients were asked to maintain a stable contraction of the target muscle of around 50% of maximum force, monitored by audio feedback of their EMG activity. Electrical stimulation was delivered at irregular intervals, in order to avoid fatigue [19]. Recordings for analysis were made in a 1 s window, with a period of 100 ms prestimulus signal. Ten consistent responses, recorded from each muscle [4], were rectified, averaged, and analyzed offline, using custom MatLab functions (MatLab R2018a, The Mathworks, Inc.,Natick, Massachusetts). CutSP onset latency was defined as the onset of a fall in the amplitude of the EMG trace to less than 80% of the baseline signal preceding the peripheral stimulus [4]. The duration of the CutSP was calculated from its onset latency to the return of the EMG signal to 80% of baseline [4].

EMG signal from studied muscles was quantified for testing differences between groups.

Transcranial magnetic stimulation (TMS)

A Magpro x100 (MagVenture, Inc, Alpharetta, Georgia) was used for TMS. Stimulation was performed over the contralateral hand and lower limb muscle cortical areas, defined in preliminary recordings by the lowest resting motor threshold (RMT), using a round coil (inner diameter 35 mm; outer diameter 121 mm). Motor evoked potentials (MEP) were obtained using the recording settings described above. RMT was calculated for each muscle, defined as the minimum stimulus intensity needed to elicit at least 50% of responses with a minimum amplitude of 0.1 mV [28]. Stimulation was then performed at 20% above the RMT. Ten consecutive traces were recorded in each muscle, separated by more than 30 s interval, with the target muscle at rest, defined by audio monitoring. Recordings with artefact or noise from adjacent muscle contraction were discarded. The MEP with highest peak-to-peak amplitude was selected to define motor latency and motor evoked amplitude. Central motor conduction (CMCT) was calculated using the F-wave method [26], by stimulating the ulnar nerve at wrist and the peroneal nerve at fibula (20 supramaximal stimuli,1 Hz). Taking into account normative data from our laboratory [9], TMS was considered abnormal when there was no clear reproducible MEP, when MEP amplitude was below 5% of CMAP peak-to-peak amplitude, or the CMCT time was greater than 8 ms for the ADM and 16 ms for the TA.

Statistical analysis

Neurophysiological data are shown with median values, and first and third interquartile ranges (1st and 3rd IQR). Gender differences were analyzed with $\chi 2$ test. The Shapiro-Wilk test was applied to test for the data distribution and, since most neurophysiological results did not follow a normal distribution, we applied non-parametric tests. Correlations between variables were tested using the Spearman correlation coefficient. Comparisons between two groups were performed using the Mann-Whitney U test. The Kruskal-Wallis H test was used for multiple group comparisons. Post-hoc pairwise comparisons were performed using Dunn's procedure, with a Bonferroni correction for multiple comparisons. A p value < 0.05 was considered statistically significant.

Two binomial logistic regression analyses were performed, one for the upper limb and one for the lower limb studies, to ascertain the effects of CutSP and TMS on the likelihood of patients having UMN signs (dependent variable). CutSP parameters of ADM and TA muscles included in the models were: onset latency, duration and amount of EMG suppression. TMS was included as a dichotomous variable (normal vs abnormal, see Methods). Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure [1]. A Bonferroni correction was applied using all eight terms in both models, resulting in statistical significance being accepted when $p < 0.00625$. All analyses were performed in IBM SPSS for Microsoft Windows, Version 26.0 (Armonk, NY: IBM Corp).

Results

Twenty-four ALS patients, 7 women (29%; median age 59.5 years, IQR 52.5−69.0) were studied. They were consecutively observed patients respecting inclusion and exclusion criteria and consenting.

CutSP measurements

Measurements of the CutSP were obtained in a total of 74 muscles, 45 ADM and 29 TA, after excluding results from weak muscles (MRC <4, see methods) or those with an absent CutSP (7 TA muscles). CutSP onset latency was longer in TA (median 103.3 ms, IQR 89.0−108.3) than in ADM (median 77.0 ms, IQR 72.7−80.3) ($p < 0.001$). But CutSP duration (TA, median 58.3 ms, IQR 45.0−72.0; ADM, median 64 ms, IQR 52.3−75.7) and EMG suppression (TA, median 77.1%, IQR 70.7−81.4; ADM, median 75.1%, IQR 72.1−78.2) were similar ($p = 0.71$ and 0.65, respectively).

The CutSP measurements were also obtained in healthy subjects. For the ADM muscles, we used the values of 27 muscles from 28 healthy subjects (16 women; median age 63.5, IQR 52.5−69.0), reported from our previous study [4]. For the TA muscles, values were obtained in 26 TA muscles from 13 healthy subjects (7 women; median age 57.0 years,

IQR 39.0—62.0). CutSP was absent in one ADM from a healthy control subject.

Comparison of ALS and healthy subjects groups, disclosed a marginal difference in gender in the ADM groups ($p = 0.043$), since the control group had a higher number of females. Nevertheless, there was no difference between men and women in our healthy control group ($p > 0.05$), and gender does not seem to influence CutSP [11]. There were no significant differences in age between groups, for both ADM and TA sets. Regarding CutSP measurements, ALS patients had significantly higher onset latencies, for both ADM ($p = 0.006$) and TA ($p = 0.005$) muscles, compared to healthy controls (Table 1).

Clinical UMN signs

Since abnormalities in CutSP could be explained by inhibitory effects at segmental spinal levels, we categorized the tested muscles into 2 groups, according to the presence, or absence of clinical UMN signs in the respective spinal segment (see Methods). From the set of 45 ADM and 29 TA muscles from ALS patients, 27 ADM and 21 TA had clinical signs of UMN involvement in the respective limb. We compared CutSP measurements in limbs with and without UMN signs (Figure 1), and each of these subgroups with values from healthy subjects. The Kruskal-Wallis H test showed statistically significant differences between the above 3 subgroups for ADM ($p = 0.004$) and TA ($p = 0.004$) regarding CutSP onset latency. There were also significant differences in the amount of EMG suppression for the TA muscles ($p = 0.022$). Pairwise comparisons are shown in Table 2. Onset latencies were significantly higher in muscles with UMN signs when compared to controls (ADM and TA, $p = 0.001$). There was a significant decrease in the amount of EMG suppression in muscles with UMN signs when compared to muscles without UMN signs, $p = 0.08$ (Fig. 2). There were no significant differences between muscles without UMN signs and control subjects. In the 7 TA muscles with no CutSP, clinical signs of UMN lesion were positive in 4 legs ().

In every studied muscle the needle EMG changes were mild or moderate according to the inclusion criteria. Nevertheless, in order to assess a possible influence of lower motor neuron (LMN) degeneration in the CutSP findings, we analyzed neurophysiological data that evaluates LMN function. The degree of muscle contraction, evaluated by the envelope EMG signal, and ADM and TA CMAP amplitudes, following nerve stimulation, were similar between muscles with vs without CutSP, as well as between muscles in limbs with vs without clinical UMN signs ($p > 0.05$).

TMS studies

TMS recordings were investigated, as a further measure of UMN dysfunction, in the spinal segments. A reproducible motor evoked response was absent in 2 ADM and 7 TA muscles. Abnormal TMS responses were found in 73% of ADM and 42% of TA muscles (absent responses in eligible muscles was considered an abnormal result). RMT for ADM recordings (median 50.0%, IQR 50.0—58.0) was lower than in the TA recordings (median 75.0%, IQR 65.0—80.0). In addition, the MEP latency (median 23.3.0 ms, IQR 22.6—24.7) and CMTC (median 8.5 ms, IQR 7.4—9.2) were shorter in ADM than in TA recordings (median 32.2 ms, IQR 31.3—35.7 and median 14.4 ms, IQR 13.3—116.0, respectively) ($p < 0.001$). Median motor amplitude recorded in ADM (median 1.3 mV, IQR 0.7—2.3) was similar to TA (median 0.7 mV, IQR 0.5—1.2) ($p = 0.36$). We compared TMS results in muscles with vs without UMN signs (Table 2). There were no significant differences between groups ($p > 0.005$).

We also categorized muscles into 2 groups, according to the presence or absence of TMS abnormalities in the respective limb. From the set of 45 ADM and 29 TA muscles from ALS patients, 33 ADM and 10 TA had abnormal TMS results, as defined in the methods. We compared CutSP measurements in limbs with normal and abnormal TMS results. The Kruskal-Wallis H test comparing limbs with and without UMN signs in ALS patients, and with controls, showed statistically significant differences between groups for ADM ($p = 0.022$) and TA ($p < 0.001$) CutSP onset latency. Pairwise comparisons are shown in Table 3. In ADM muscles with abnormal TMS results, CutSP onset latencies were prolonged when compared with healthy subjects ($p = 0.007$). In TA muscles with abnormal TMS, CutSP onset latencies were significantly prolonged when compared either with muscles with normal TMS results ($p = 0.004$) or with healthy controls ($p < 0.001$).

Correlation analysis

The median total UMN score and ALSFRS-R score were 10.5 (IQR 6.5—14.0) and 45.0 (44.0—45.5), respectively. No significant correlations were found between these scores and CutSP parameters ($p > 0.05$ for all tests).

As previously done, we considered the UMN score in each specific anatomical region. For the cervical region, we

Table 1 CutSP measurements in ALS patients and healthy subjects.

	ADM		TA	
	ALS patients ($n = 45$)	Healthy subjects ($n = 27$)	ALS patients ($n = 29$)	Healthy subjects ($n = 26$)
CutSP onset latency (ms)	77.0* (72.7—803)	71.3 (68.7—76.7)	103.3** (89.0—108.3)	87.2 (78.7—99.0)
CutSP duration (ms)	64.0 (52.3—75.7)	65.3 (54.7—74.7)	58.3 (45.0—72.0)	61.5 (49.3—74.0)
EMG suppression (% amplitude)	77.1 (70.7—81.4)	75.7 (71.0—78.6)	75.1 (72.1—78.2)	75.5 (72.9—79.8)

All values represented are Median (IQR); n — number of muscles included; ADM — abductor digit minimi; TA — tibialis anterior; *$p = 0.006$ (Mann-Whitney test); ** $p = 0.005$ (Mann-Whitney test); *** $p = 0.007$ (Mann-Whitney test).

Table 2 CutSP measurements and TMS results in healthy subjects and in muscles with or without UMN clinical signs.

	ADM			TA		
	UMN signs (n = 27)	No UMN signs (n = 18)	Healthy subjects (n = 27)	UMN signs (n = 21)	No UMN signs (n = 8)	Healthy subjects (n = 26)
CutSP onset latency (ms)	78.0* (73.0–87.7)	75.2 (71.3–78.0)	71.3 (68.7–76.7)	104.3* (91.3–109.7)	91.3 (81.5–103.5)	87.2 (78.7–99.0)
CutSP duration (ms)	70.0 (53.3–83.7)	61.5 (51.3–66.0)	65.3 (54.7–74.7)	58.3 (43.0–71.0)	65.5 (50.7–75.2)	61.5 (49.3–74.0)
EMG suppression (% amplitude)	78.7 (69.8–82.9)	74.6 (71.4–81.3)	75.7 (71.0–78.6)	72.8** (70.4–75.6)	78.7 (77.1–80.1)	75.5 (72.9–79.8)
	UMN signs (n = 25)	No UMN signs (n = 18)		UMN signs (n = 18)	No UMN signs (n = 11)	
TMS threshold (%)	53.0 (50.0–65.0)	50.0 (45.0–55.0)		72.5 (65.0–80.0)	75.0 (65.0–90)	
TMS latency (ms)	24.0 (22.7–24.3)	23.0 (22.6–24.7)		32.7 (31.4–35.7)	32.1 (30.9–36.6)	
TMS amplitude (mV)	1.3 (0.5–2.3)	1.3 (1.0–2.0)		0.9 (0.6–1.2)	0.6 (0.5–1.3)	
TMS CMCT (ms)	8.6 (7.4–9.4)	8.5 (7.9–9.2)		14.6 (12.8–16)	14.2 (13.4–17.2)	

A limb with very brisk reflexes (score > 3), or spasticity or abnormal reflex Hoffman or extensor plantar response) was considered as having UMN signs [3]. All values represented are Median (IQR); n – number of muscles included; ADM – abductor digit minimi; TA – tibialis anterior; UMN signs – clinical signs of upper motor neurons lesion (see methods for definition); *p = 0.001 (post-hoc comparison UMN signs – healthy subjects); ** p = 0.008 (post-hoc comparison UMN signs – No UMN signs).

identified a significant correlation between upper limb UMN score and CutSP duration in the ADM muscles (r_s=0.30, p=0.045). For the lumbosacral region, there was a significant correlation between lower limb UMN scores and CutSP onset latency (r_s= 0.54, p = 0.002) and also with EMG suppression (r_s= −0.40, p = 0.031) in TA muscles. There were no significant correlations between TMS parameters and UMN score in both anatomical regions.

We also investigated correlations between TMS parameters and CutSP findings. For the ADM, we found a significant correlation between CutSP onset latency and CMCT (r_s=0.36, p = 0.018) and RMT (r_s=0.34, p = 0.025). For the TA there was no significant correlation between CutSP measurements and TMS findings.

Binomial logistic regression analyses

All continuous independent variables were found to be linearly related to the logit of the dependent variable (clinical UMN signs), and there were no significant outliers (standardized residuals < 2.0 standard deviations).

For the upper limb, the logistic regression model was statistically significant, $\chi^2(4)$ = 18.198, $p < 0.05$. Using the Nagelkerke R^2 to evaluate the goodness of fit of the logistic regression model, this model explained 45.0% of the variance in the presence of clinical UMN signs and correctly classified 73.3% of cases [23]. Of the four variables included, only two were statistically significant: CutSP onset latency and CutSP duration (Table 4). Increasing onset latency and duration were associated with an increased likelihood of having clinical UMN signs in upper limbs. For the lower limb, the logistic regression model was statistically significant, $\chi^2(4)$ = 11.035, $p < 0.05$. Using the Nagelkerke R^2 to evaluate the goodness of fit of the logistic regression model, this model explained 45.7% of the variance in the presence of clinical UMN signs and correctly classified 79.3% of cases [23]. Despite this, none of the four variables included achieved statistical significance. There was, however, a trend (p = 0.082) for the decrease in the amount of EMG suppression to be associated with an increased likelihood of having clinical UMN signs.

In this model, TMS defined as normal vs abnormal was not predictive of the clinical UMN signs for both upper and lower limbs. We tested an additional model, which included TMS threshold, MEP amplitude and CMCT. The results of this model were similar to the ones described above.

Discussion

We investigated a group of 24 ALS patients at their first assessment in our clinic. All were in good functional status (median ALSFRS-R = 35). Peripheral nerve conduction studies were within normal limits in all our patients, ruling out any peripheral effect in our findings. Additionally, EMG changes in the studied muscles were mild to moderate, and the CMAP amplitudes and the amount of muscle contraction, as determined by the EMG signal envelope, was not different between limbs with vs without UMN signs, or with vs without CutSP changes. In patients with ALS, CutSP was detected in all the ADM muscles and in 81% of TA muscles. The CutSP onset latency was increased in TA recordings consistent with

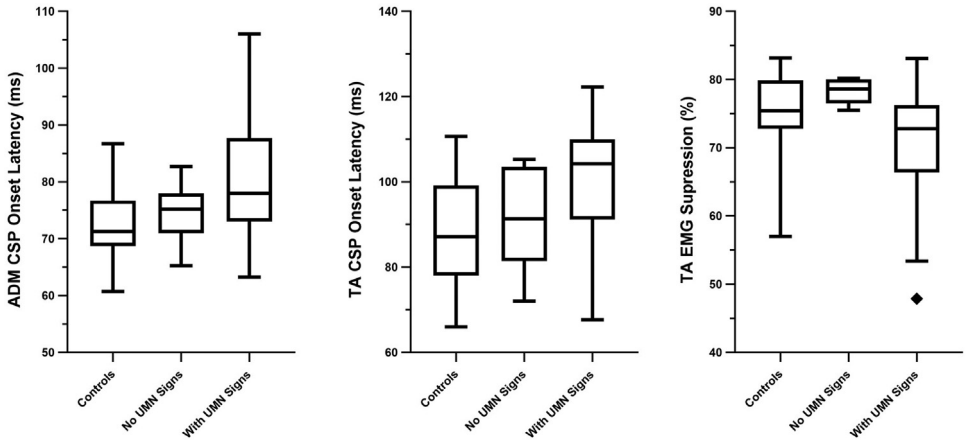

Fig. 1 Cutaneous silent period examples for each muscle studied, with and without UMN signs in the respective limb. A — ADM without UMN signs; B — ADM with UMN signs; C — TA without UMN signs; D — TA with UMN signs; Horizontal arrows — electrical stimulus; Vertical arrows — CutSP start latency; Dotted horizontal line - 80% of pre-stimulus average EMG signal.

longer spinal cord and nerve length, but no other specific differences were found between CutSP derived from these two anatomical regions.

The CutSP onset latency was significantly increased in ALS patients, when compared to controls, in both ADM and TA muscles.

Further analysis disclosed that the CutSP onset latency was significantly increased in limbs with UMN signs, or with abnormal TMS results, both in upper and lower extremities. These findings are consistent with our previous report [4] in which we demonstrated higher CutSP onset latencies in the ADM, in patients with ALS, including those without clinical signs of corticospinal dysfunction (PMA). We observed reduced EMG suppression during CutSP in TA in lower limbs with UMN signs. CutSP onset latency was also significantly increased in lower limbs of patients with abnormal TMS results. We found moderate but significant correlations between upper limb UMN score and CutSP duration in the ADM muscles, and for CutSP onset latency and EMG suppression in TA muscles. Furthermore, in the binomial logistic regression model, CutSP onset latency and duration were strong predictors of clinical signs of UMN lesion in upper limbs in ALS. For the lower limbs this binomial logistic regression disclosed a trend for a reduced EMG suppression to predict clinical UMN signs. Indeed, in 7 TA muscles EMG suppression was so slight that CutSP was considered absent (methods). The results from the lower limbs are, however, influenced by the smaller number of eligible TA muscles with CutSP response (29 muscles).

The lack of correlation between CutSP parameters and the total ALSFRS-R is not unexpected given the lack of sensitivity and specificity of the latter scale for the evaluation of UMN functional abnormality. In addition, there were no differences in TMS findings between limbs with and without

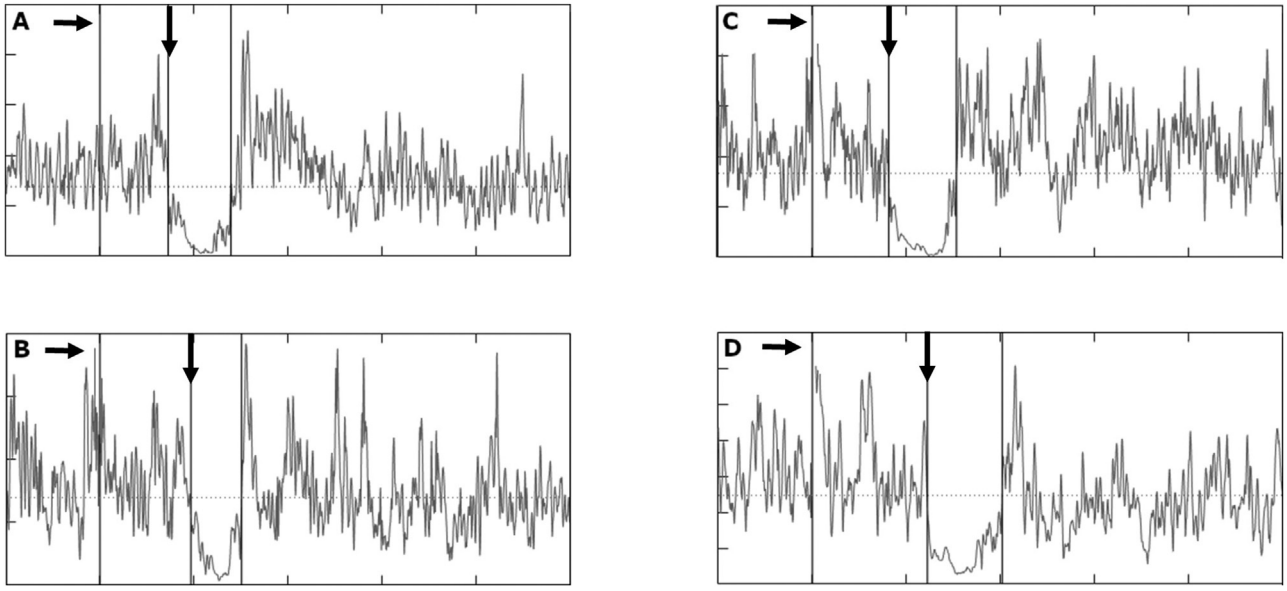

Fig. 2 Distribution of CutSP parameters in healthy subjects and in patients with or without UMN clinical signs. ADM — abductor digit minimi; TA — tibialis anterior; UMN — Upper motor neuron; CutSP — Cutaneous Silent Period; ms — milliseconds.

Table 3 Results from healthy subjects and limbs with vs without TMS changes.

	ADM			TA		
	Abnormal TMS# (n = 33)	Normal TMS (n = 12)	Healthy subjects (n = 27)	Abnormal TMS# (n = 10)	Normal TMS (n = 19)	Healthy subjects (n = 26)
CutSP onset latency (ms)	77.3* (72.7–80.3)	75.2 (72.2–80.9)	71.3 (68.7–76.7)	107.5** (103.7–112.3)	91.3 (82.3–105.3)	87.2 (78.7–99.0)
CutSP duration (ms)	66.7 (52.3–78.0)	61.5 (53.7–67.4)	65.3 (54.7–74.7)	52.5 (42.7–65.0)	66.0 (45.0–78.0)	61.5 (49.3–74.0)
EMG suppression (% amplitude)	77.2 (72.2–80.9)	73.5 (68.8–83.2)	75.7 (71.0–78.6)	72.7 (71.7–75.6)	76.0 (72.2–79.1)	75.5 (72.9–79.8)

All values represented are Median (IQR). Absent responses in eligible muscles were considered an abnormal result. n – number of muscles included; ADM – abductor digit minimi; TA – tibialis anterior; # - including absent responses; TMS – transcranial magnetic stimulation changes (see methods for definition); *p = 0.007 (post-hoc comparison Abnormal TMS – Healthy subjects); **p = 0.004 (post-hoc comparison Abnormal TMS – Normal TMS) and $p < 0.001$ (post-hoc comparison Abnormal TMS – Healthy subjects).

UMN signs, and there was no correlation between our TMS findings and the UMN scores (Table 1).

In our statistical model CutSP predicted UMN signs in upper limbs. TMS tests the function of the strong corticomotoneuronal connections [25], which are critical to rapid discrete digital movements. However, the UMN syndrome in ALS is physiologically complex [32], affecting the central nervous system beyond the classical "corticospinal" syndrome [33]. The direct pathway between Betz cells and the spinal motor neurons represents less than 5% of the corticospinal tract [2], while other projections forming the propriospinal motor system [24] are crucial to the modulation of other inputs (vestibular, cerebellar, sensory) to the spinal command motor systems [33]. Thus, although changes in UMN function can have unexpected clinical impact on motor function, the propriospinal input from the motor command signal can be estimated from CutSP studies.

Three mechanisms can explain possible EMG suppression after A-delta fiber activation. Presynaptic inhibition, in which afferent impulses excite inhibitory interneurons able to modulate UMN synaptic connections with LMNs, or interfere with la afferent synapses to LMN; postsynaptic inhibition, in which afferent impulses excite inhibitory interneurons that directly inhibit LMN; or a combined mechanism, in which afferent impulses cause a presynaptic inhibition of LMN by interfering with la afferents, and a postsynaptic inhibition onto LMN [11,19]. Some studies favor a predominant post-synaptic mechanism [4,11,15,19,21]. Our results are in agreement that the polysynaptic spinal circuits activated by A-delta fiber stimulation can be facilitated by UMN dysfunction [14,15], although we could not identify the role of each descending tract. In ALS there is abnormal sensorimotor processing in the damaged segmental ventral horn gray matter, further supporting the role of UMN dysfunction in the changes of CutSP response in these patients [29,30].

A possible effect of partial denervation of the muscles studied, due to anterior horn cell degeneration, a characteristic feature of ALS, needs consideration. We observed abnormalities in the CutSP even when there were no clinical or TMS UMN abnormalities. This is consistent with the neuropathological observations in PMA [16], in which degeneration of the corticospinal tract was found in the absence of any clinically detectable dysfunction. The physiological disturbances underlying the classical features of the UMN syndrome are complex and include the effects of propriospinal pathway damage [20]. Not all need be present in any individual with the UMN syndrome [32,33]. The CutSP is particularly sensitive to propriospinal damage. It is therefore likely, as suggested by Pierrot-Deseilligny [24], that this technique can be used to detect specific aspects of abnormality in fragments of descending motor pathways in ALS syndromes.

Our study has some limitations. The number of ALS subjects included is not large. It could be argued that we stimulated an S1 sensory nerve, the sural nerve, to record the motor response from a muscle predominantly innervated by the L5 myotome; however, this should not be a problem since the afferent volley reaching one spinal segment descends and ascends through several spinal cord segments [22]. All ALS patients were taking riluzole at the time of the assessment, a drug which is known to decrease persistent inward sodium currents in motor neurons and interneurons

Table 4 Logistic regression analysis for the presence of UMN signs in the upper limb.

	B	SE	Wald	*df*	*p*	Odds Ratio	Lower 95% CI	Upper 95% CI
CutSP onset latency	0.194	0.068	8.215	1	0.004	1.214	1.063	1.387
CutSP duration	0.086	0.036	5.814	1	0.016	1.089	1.016	1.168
EMG suppression	0.023	0.066	0.122	1	0.727	1.023	0.899	1.164
TMS	0.310	0.831	0.139	1	0.709	1.364	0.268	6.948
Constant	−21.998	8.487	6.718	1	0.010	0.000		

Note: TMS is for abnormal compared to normal. ADM − abductor digit minimi; UMN − clinical signs of upper motor neurons lesion (see methods for definition); TMS − transcranial magnetic stimulation changes (see methods for definition); 95% CI: confidence interval for odds ratio.

of the spinal cord [7]. However, the physiological effects of riluzole are considered to be limited to a brief period of a few weeks at most [12].

Although our results highlight the role of the UMN pathway in modulating segmental spinal cord inhibition mechanisms [33,30], and indicate an association between the UMN deficits and CutSP changes, the large clinical variability of the patients might have influenced our results. Some caution in interpretation is required.

Declaration of Competing Interest

The authors report no conflicts of interest

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References

[1] Box GEP, Tidwell PW. Transformation of the Independent Variables. Technometrics 1962;4:531–50.
[2] Brodal A. Neurological anatomy in relation to clinical medicine. Oxford: Oxford University Press; 1981.
[3] Escorial Brooks BREl. World federation of neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on motor neuron diseases/amyotrophic lateral sclerosis of the world federation of neurology research group on neuromuscular diseases and the El Escorial "clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 1994; 124:96–107.
[4] Castro J, Swash M, de Carvalho M. The cutaneous silent period in motor neuron disease. Clin Neurophysiol 2021;132:660–5.
[5] Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci 1999;169:13–21.
[6] Cengiz B, Mercan M, Kuruoglu R. Spinal excitability changes do not influence the mechanisms of split-hand syndrome in amyotrophic lateral sclerosis. Muscle Nerve 2018;58:503–8.
[7] Cifra A, Mazzone GL, Nistri A. Riluzole: what it does to spinal and brainstem neurons and how it does it. Neuroscientist 2013;19:137–44.
[8] de Carvalho M, Dengler R, Eisen A, England J, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008;119:497–503.
[9] de Carvalho M, Turkman A, Swash M. Motor responses evoked by transcranial magnetic stimulation and peripheral nerve stimulation in the ulnar innervation in amyotrophic lateral sclerosis: the effect of upper and lower motor neuron lesion. J Neurol Sci 2003;210:83–90.
[10] Dengler R. Upper motor neuron involvement in amyotrophic lateral sclerosis. Do we have a new diagnostic tool? Clin Neurophysiol 2021;132:618–9.
[11] Floeter MK. Cutaneous silent periods. Muscle Nerve 2003; 28:391–401.
[12] Geevasinga N, Menon P, Ng K, Van Den Bos M, Byth K, Kiernan MC, et al. Riluzole exerts transient modulating effects on cortical and axonal hyperexcitability in ALS. Amyotroph Lateral Scler Front Degener 2016;17:580–8.
[13] Geraldo AF, Pereira J, Nunes P, Reimao S, Sousa R, Castelo-Branco M, et al. Beyond fractional anisotropy in amyotrophic lateral sclerosis: the value of mean, axial, and radial diffusivity and its correlation with electrophysiological conductivity changes. Neuroradiology 2018;60:505–15.
[14] Gilio F, Bettolo CM, Conte A, Iacovelli E, Frasca V, Serrao M, et al. Influence of the corticospinal tract on the cutaneous silent period: a study in patients with pyramidal syndrome. Neurosci Lett 2008;433:109–13.
[15] Guzulaitis R, Hounsgaard J, Alaburda A. Inhibition of motoneurons during the cutaneous silent period in the spinal cord of the turtle. Exp Brain Res 2012;220:23–8.
[16] Ince PG, Evans J, Knopp M, Forster G, Hamdalla HH, Wharton SB, et al. Corticospinal tract degeneration in the progressive muscular atrophy variant of ALS. Neurology 2003;60:1252–8.
[17] Kim WK, Kwak YT. Preservation of motor neuron excitability during the cutaneous silent period in amyotrophic lateral sclerosis. J Neurol 2010;257:92–3.
[18] Kofler M, Kumru H, Stetkarova I, Schindler C, Fuhr P. Muscle force up to 50% of maximum does not affect cutaneous silent periods in thenar muscles. Clin Neurophysiol 2007;118:2025–30.
[19] Kofler M, Leis A, Valls-Solé J. Cutaneous silent periods - Part 1: update on physiological mechanisms. Clin Neurophysiol 2019;130:588–603.
[20] Kuypers H.G.J.M. The anatomical organization of the descending pathways and their contributions to motor control especially in primates. In: Desmedt JE, editor. Human reflexes, pathophysiology of motor systems, Methodology of Human Reflexes, vol 3. Basel: Karger; 1973. p. 38—68.
[21] Leis A, Ross M, Emori T, Matsue Y, Saito T. The silent period produced by electrical stimulation of mixed peripheral nerves. Muscle Nerve 1991;14:1202–8.
[22] Logigian EL, Plotkin GM, Shefner JM. The cutaneous silent period is mediated by spinal inhibitory reflex. Muscle Nerve 1999;22:467–72.

[23] Nagelkerke NJD. A note on a general definition of the coefficient of determination. Biometrika 1991;78:691–2.
[24] Pierrot-Deseilligny E. Propriospinal transmission of part of the corticospinal excitation in humans. Muscle Nerve 2002;26:155–72.
[25] Porter R. The corticomotoneuronal component of the pyramidal tract: corticomotoneuronal connections and functions in primates. Brain Res 1985;10:1–26.
[26] Robinson LR, Jantra P, MacLean IC. Central motor conduction times using transcranial stimulation and F wave latencies. Muscle Nerve 1988;11:174–80.
[27] Rodi Z, Springer C. Influence of muscle contraction and intensity of stimulation on the cutaneous silent period. Muscle Nerve 2011;43:324–8.
[28] Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W. Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999;52:97–103.
[29] Sangari S, Iglesias C, El Mendili MM, Benali H, Pradat PF, Marchand-Pauvert V. Impairment of sensory-motor integration at spinal level in amyotrophic lateral sclerosis. Clin Neurophysiol 2016;127:1968–77.
[30] Sangari S, Peyre I, Lackmy-Vallee A, Bayen E, Pradat PF, Marchand-Pauvert V. Transient increase in recurrent inhibition in amyotrophic lateral sclerosis as a putative protection from neurodegeneration. Acta Physiol (Oxf) 2022:e13758.
[31] Shahani BT, Young RR. Studies of the normal human silent period Desmedt JE, editor. New developments in electromyography and clinical neurophysiology. Basel: Karger; 1973. p. 589–602.
[32] Swash M. Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? J Neurol Neurosurg Psychiatry 2012;83:659–62.
[33] Swash M, Burke D, Turner MR, Grosskreutz J, Leigh PN, deCarvalho M, et al. Occasional essay: upper motor neuron syndrome in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2020;91:227–34.
[34] Uncini A, Kujirai T, Gluck B, Pullman S. Silent period induced by cutaneous stimulation. Electroencephalogr Clin Neurophysiol 1991;81:344–52.
[35] Wittstock M, Wolters A, Benecke R. Transcallosal inhibition in amyotrophic lateral sclerosis. Clin Neurophysiol 2007; 118:301–7.