Cortical inexcitability defines an adverse clinical profile in amyotrophic lateral sclerosis

T. Dharmadasa, J. Howells, J. M. Matamala, N. G. Simon, D. Burke, S. Vucic and M. C. Kiernan

*Brain and Mind Centre, University of Sydney, Sydney, NSW; †St Vincent’s Clinical School, University of New South Wales, Sydney, NSW; ‡Sydney Medical School, University of Sydney, Sydney, NSW; §Department of Neurology, Royal Prince Alfred Hospital, Sydney, NSW; and ‡Westmead Clinical School, University of Sydney, Sydney, NSW, Australia

**Keywords:** amyotrophic lateral sclerosis, cortical inexcitability, disease progression, survival

**Received 11 September 2019**

**Accepted 2 September 2020**

**European Journal of Neurology 2021, 28: 90–97**

doi:10.1111/ene.14515

**Background and purpose:** In amyotrophic lateral sclerosis, studies using threshold-tracking transcranial magnetic stimulation (TMS) have identified corticomotoneuronal dysfunction as a key pathogenic mechanism. Some patients, however, display no motor response at maximal TMS intensities, termed here an ‘inexcitable’ motor cortex. The extent to which this cortical difference impacts clinical outcomes remains unclear. The aim of this study was to determine the clinical profile of patients with inexcitability to TMS.

**Methods:** Motor cortex excitability was evaluated using TMS. Patients in whom a motor evoked potential could not be recorded in one or more limbs at maximal TMS intensities were classified as four-limb or partially inexcitable. Demographic information, clinical variables and survival data were analysed.

**Results:** From 133 patients, 40 were identified with inexcitability. Patients with four-limb inexcitability were younger (*P* = 0.03) and had lower-limb disease onset (64%), greater functional disability (*P* < 0.001) and faster disease progression (*P* = 0.02), particularly if inexcitability developed within 1 year of symptoms (*P* < 0.01). Patients with partial inexcitability had higher resting motor thresholds compared to the excitable cohort (*P* < 0.01), but averaged short-interval intracortical inhibition was similar (*P* = 0.5). Mean survival was reduced if inexcitability involved all limbs within 12 months of symptom onset (*P* = 0.04).

**Conclusion:** Amyotrophic lateral sclerosis patients with inexcitability of all four limbs to TMS have a distinct clinical profile of younger age and lower-limb onset. Importantly, these patients display a more malignant disease trajectory, with faster progression, greater functional disability and reduced survival when occurring in early disease. This measure may provide an important prognostic marker in amyotrophic lateral sclerosis.

**Introduction**

In amyotrophic lateral sclerosis (ALS), threshold-tracking transcranial magnetic stimulation (TMS) studies have shown that inhibitory processes at the cortical level are depressed [1], which is linked to survival in early disease [2]. Some patients, however, display no motor response even at maximal TMS intensities, which is termed an ‘inexcitable’ motor cortex. The extent to which such cortical differences underlie heterogeneity of clinical outcomes remains unclear.

The minimal TMS intensity required to elicit a motor evoked potential (MEP) is represented by the resting motor threshold (RMT) [3]. Abnormalities of RMT have been inconsistently reported in ALS. In early ALS, RMT may be reduced [1], particularly before clinical involvement of intrinsic hand muscles,
but it is commonly increased when evidence of disease becomes more extensive [1,4,5]. Whilst there have been previous studies of lower-limb MEPs [6,7], they have not focused on ‘cortical inexcitability’. It is of particular interest that inexcitability has been reported in early disease [8]. Many mechanisms could contribute to this, including loss of excitatory projections onto motor cortical output neurons, degeneration of motor cortex neurons, and inability of diseased lower motor neurons (LMNs) to be activated by descending corticospinal volleys [8]. To the best of our knowledge, this group of ALS patients remains clinically uncharacterized. The aim of the present study was to define the clinical and prognostic profile of ALS patients who present with inexcitability to TMS at initial assessment.

Methods

Patients

Patients referred to the Forefront ALS Clinic (Sydney) were prospectively recruited between March 2016 and October 2018. The research was approved by the Human Research Ethics Committee, University of Sydney, and all participants gave written informed consent prior to participation. Detailed examination and neurophysiological testing were performed, with investigations undertaken where necessary to exclude mimics.

Patients were categorized according to their clinical site of onset (upper limb, lower limb or bulbar). Initial side of disease was also documented. Classification into either ‘inexcitable’ or ‘excitable’ groups was based on motor cortical testing, detailed below. Healthy control participants were subjected to identical studies.

Neurophysiological assessment

Transcranial magnetic stimulation was undertaken across all four limbs in each patient to determine cortical excitability regionally across the motor cortex. A 90-mm circular coil was used to record from the abductor pollicis brevis (APB), whilst a 110-mm double-cone coil was used for the tibialis anterior (TA) [3,9–11]. The sequence of limb testing was deliberately varied, resulting in a pseudorandom testing order. A BiStim² system was used to generate the magnetic stimuli (Magstim Co., Whitland, Wales, UK).

Resting motor threshold was defined as the lowest stimulus intensity (%) required to maintain a target MEP of 0.2 mV ± 20%, as previously described [12,13]. Whilst this target MEP is above that used with conventional methods (0.05 mV [3]), the reasons for this choice have been given elsewhere [12], based on the stimulus–response curves for APB [13] and TA [14]. The difference in MEP target may make comparison with the conventional technique problematic but does not materially affect our results, particularly those related to cortical inexcitability. Inexcitability was defined by the inability to obtain a MEP at the maximal stimulus intensity of 100% (i.e. a MEP of 0 mV at 100%) following at least three attempts. The ‘four-limb inexcitable’ cohort was characterized by absence of a MEP in all limbs at this maximum stimulus, whilst the ‘partially inexcitable’ cohort was defined by absence of a MEP in one–three limbs. Where RMT could not be calculated due to partial inexcitability, a value of 100% was assigned. The ‘excitable’ cohort represented patients in whom MEPs could be recorded in all limbs. Short-interval intracortical inhibition (SICI, %) was measured between interstimulus intervals of 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 7 ms using paired-pulse TMS [1,13]. Central motor conduction time (CMCT) was measured using F-wave methodology [15].

Peripherally, the median nerve was stimulated electrically at the wrist and the common peroneal nerve at the fibular head to record compound muscle action potentials (CMAPs) from the APB and TA muscles. Testing was occasionally undertaken over two consecutive days.

Clinical assessments

Disease duration was calculated from symptom onset to study assessment. The Medical Research Council (MRC) rating scale was used to grade muscle strength, generating subscores for upper and lower limbs (maximal sum score 90). Upper motor neuron (UMN) involvement was assessed clinically [16] (maximal limb score 36). Functional disability was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) [17]. Progression rate was determined as previously described [(48 – ALSFRS-R)/disease duration] [18,19] and categorized into slow (<0.5), moderate (0.5–0.9) and fast (≥1.0).

Statistical analysis

Statistical analysis was performed using SPSS 25 and GraphPad 7.0 (GraphPad Software Inc., California, USA). Normality was evaluated by Shapiro–Wilk testing. Student’s independent t test was used for comparison between two groups. Categorical variables were compared using chi-squared tests and Fischer’s exact tests for group comparisons. Kruskal–Wallis and
Wilcoxon rank sum tests were used to compare non-parametric data. Logistic linear regression analysis was performed to identify independent predictors of inexcitability. Survival time was estimated from date of symptom onset to either date of death or censored observations. Kaplan–Meier survival curves were used to compare the groups. Results are expressed as mean ± standard error of the mean for parametric data, and median (interquartile range) for non-parametric data. *P* values < 0.05 were considered statistically significant.

**Results**

In all, 133 ALS patients were included in the final study. MEPs could be recorded in all limbs of 93 patients, forming the ‘excitable’ cohort. The remaining 40 patients demonstrated inexcitability, with four-limb involvement being the most common inexcitability pattern (10%; Fig. 1a) compared to three, two or one limb involvement. The frequency of inexcitability was greater when recording from legs (26% of all limbs) compared to arms (19%; *P* < 0.05). For 85% of limb onset patients, inexcitability corresponded to the side of onset.

**Phenotypic profile of inexcitability**

The majority of patients with four-limb inexcitability had lower-limb disease onset (nine of 14), but there was no similar tendency in the partially inexcitable or excitable cohort (Fig. 1b–d). Considering the total ALS population studied, this translated to inexcitability in approximately 45% of patients with lower-limb disease and 29% with bulbar onset. The upper-limb onset subgroup contained a significantly smaller proportion with inexcitability (16%; upper-versus lower-limb onset: Pearson chi-squared 10.511, *P* = 0.001, effect size 0.327) (Table S1). The pattern of inexcitability also differed according to site of onset: bilateral leg involvement was most common for lower-limb onset patients (50%), whilst unilateral (asymmetric) involvement of the affected upper limb was most likely for upper-limb onset patients (67%).

![Figure 1 ALS patient proportions. (a) Proportion of patients in each cohort within the total ALS population. (b)–(d) Site-of-onset phenotype distribution within each ALS cohort.](image-url)
Clinical and demographic features

Disease duration was similar across all ALS cohorts and no patients demonstrated motor paralysis on clinical testing. The four-limb inexcitable cohort was significantly younger, with a greater degree of functional disability and faster disease progression (Table 1). These differences were not found in patients with partial inexcitability, indicating that changes were restricted to four-limb involvement. Inexcitable groups were characterized by a UMN phenotype, underscored by a higher clinical UMN score (chi-squared = 24.244, df 2, \( P < 0.001 \); mean rank inexcitable 78.72, excitable 46.43) (Fig. 2). In contrast, muscle strength (MRC) was similar between all cohorts (Table 1).

Logistic regression was performed to determine clinical predictors of inexcitability. On univariate analysis, decreasing age \( [\beta_{\text{age}} = -0.034 \pm 0.02, P = 0.04; 95\% \text{ confidence interval} (\text{CI}) -0.068, 0.00] \), ALSFRS-R \( (\beta_{\text{ALSFRS-R}} = -0.116 \pm 0.04, P = 0.003; 95\% \text{ CI } -0.196, -0.036) \) and increasing UMN scores \( (\beta_{\text{UMN}} = 0.154 \pm 0.04, P < 0.001; 95\% \text{ CI } -0.224, -0.084) \) were associated with odds (log) of inexcitability. On multivariate analyses, a higher UMN score \( (\beta_{\text{UMN}} = 0.158 \pm 0.076, P < 0.001; 95\% \text{ CI } 0.006, 0.21) \) and lower ALSFRS-R \( (\beta_{\text{ALSFRS-R}} = -0.140 \pm 0.104, P = 0.008; 95\% \text{ CI } -0.348, 0.068) \) were independent predictors of inexcitability.

Cortical and peripheral nerve function

In control subjects, there was no difference in RMT between the APB and TA muscles \( (P = 0.09) \), but RMT was significantly higher for partially inexcitable patients (Table 2), with no significant relationship between RMT and disease duration (Pearson’s \( r = 0.02, R^2 = 0.0006, P = 0.8 \)) or UMN score (Pearson’s \( r = -0.02, R^2 = 0.0004, P = 0.7 \)). In contrast, CMCT and the reduction of averaged SICI were comparable across partially inexcitable and excitable ALS groups. CMAP amplitude was universally reduced in excitable limbs.

Survival analysis

The median follow-up time from symptom onset to study end amongst censored observations was 12.5 months (range 2–132, interquartile range 2–26). 25% of patients had died by October 2018 and median survival time for the whole cohort from onset was

---

**Table 1 Clinical differences between ALS cohorts**

|                        | Four-limb inexcitable \( (n = 14) \) | Partially inexcitable \( (n = 26) \) | Excitable \( (n = 93) \) | \( P \) value |
|------------------------|--------------------------------------|--------------------------------------|--------------------------|--------------|
| Gender (M:F)           | 7.7                                  | 12.14                                | 52.41                    | NA           |
| Age (years)            | 54.7 ± 3.0                           | 60.8 ± 1.5                           | 63.3 ± 1.2               | <0.05; <0.01 |
| Disease duration (months; median, IQR) | 15 ± 9.4 (6.8–34) | 12.5 ± 4.9 (7.8–36) | 12 ± 2.4 (8–25) | n.s.         |
| ALSFRS-R (range)       | 34.1 ± 2.0 (21–44)                   | 40.9 ± 0.7 (32–46)                   | 47.1 ± 0.5 (25–47)       | <0.001; <0.0001 |
| Progression rate       | 1.33 ± 0.4                           | 0.62 ± 0.1                           | 0.59 ± 0.1               | <0.05; <0.01 |
| UMN score (/36)        | 23.2 ± 0.8                           | 16.2 ± 0.8                           | 11.3 ± 0.6               | <0.0001      |
| MRC scores             |                                       |                                       |                          |              |
| Sum score (/90)        | 75.6 ± 4.2                           | 77.7 ± 3.1                           | 81.2 ± 1.2               | n.s.         |
| UL score (/60)         | 49.4 ± 3.3                           | 54.9 ± 1.7                           | 52.9 ± 1.1               | n.s.         |
| LL score (/30)         | 24.7 ± 2.1                           | 25.1 ± 1.3                           | 27.3 ± 0.5               | n.s.         |

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; F, Female; IQR, interquartile range; LL, lower limb; M, Male; MRC, Medical Research Council; n.s., not significant; UL, upper limb; UMN, upper motor neuron. \( P \) values: *four-limb inexcitable versus partially inexcitable; †four-limb inexcitable versus excitable; ‡partially inexcitable versus excitable.

**Figure 2** UMN scores. UMN scores according to number of inexcitable limbs. ****\( P < 0.0001 \); **\( P < 0.01 \); *\( P < 0.05 \).
17 months (interquartile range 9–29). No differences in survival times were seen between ALS groups ($P = 0.7$).

**The early ALS cohort**
Given that disease duration may have an impact on the development of an inexcitable cortex, separate analyses were performed in the subgroup with ≤12 months of symptoms (four-limb inexcitable $n = 7$, partially inexcitable $n = 15$, excitable $n = 52$). The four-limb inexcitable group demonstrated the same unique clinical profile of predominantly lower-limb onset phenotype (57%), younger age (51.7 ± 3.2 years, partially inexcitable 60.8 ± 1.6, $P < 0.01$; excitable 63.6 ± 1.7, $P = 0.01$), more functional disability (ALSFRS-R 32.7 ± 3.8, partially inexcitable 40.3 ± 1.0, $P < 0.05$; excitable 42.4 ± 0.6, $P < 0.0001$) and faster disease progression (2.4 ± 0.6, partially inexcitable 0.9 ± 0.2; excitable 0.8 ± 0.2, $P < 0.01$). CMAP values were not significantly different between ALS groups.

Survival analysis revealed a significantly reduced survival time when inexcitability extended across all four limbs (15 ± 2.2, excitable 19 ± 0.8, $P = 0.04$) (Fig. 3). Of note, all patients in this group were taking riluzole.

**Discussion**
The present study has identified distinct characteristics of ALS patients with four-limb inexcitability to TMS, a group that has remained clinically undefined. It is important to clarify that the presence of inexcitability to TMS does not mean that corticospinal neurons are inexcitable by other means. Given their greater disability, faster progression and significantly reduced survival when four-limb inexcitability occurred within 12 months, these patients are likely to be at a more severe disease stage. These characteristic features were associated with younger age at presentation and predominantly lower-limb disease onset. From a clinical practice viewpoint, these findings highlight the utility of TMS studies in identifying this distinct subgroup with a more malignant disease trajectory.

**Different mechanisms may contribute to inexcitability in ALS**
The RMT reflects the ability of TMS to excite corticospinal motoneurons to produce a MEP [20]. In contrast to earlier studies which have reported higher thresholds...
for TA than APB in healthy subjects [6,7,11] no such difference was found, which may have been influenced by differences in coil-type and technique [9,21]. The need for high stimulus intensities or the inability to produce a MEP could result from failure at three main points along the corticomotoneuronal pathway: (i) insufficiency of excitatory inputs to the corticomotoneuron (failure at the interneuronal level), (ii) relative inexcitability or degeneration of corticomotoneurons (failure at the corticomotoneuron level); (iii) inability of spinal motoneurons to translate the corticospinal volley into a discharge (failure at the spinal level). Regarding the latter, CMAP values did not significantly differ between the ALS cohorts. This suggests that the LMN pool was probably not hypoexcitable and that inexcitability was not driven by major differences in LMN deficit, rendering it unlikely that failure at the spinal level contributed greatly to inexcitability. Considering mechanisms that may contribute to inexcitability at the cortical level, a decrease in glutamate has been inversely associated with increased RMT [22,23], potentially suggesting a lower level of neurotransmitter activity due to a more exhausted neuronal pool. Whilst such pathology would typically be associated with end stages of disease, the more rapid clinical disease trajectory demonstrated in the four-limb inexcitable group would be consistent with more aggressive loss of corticospinal axons earlier in disease. The density of corticomotoneuronal projections onto spinal motor neurons may also influence RMT at the cortical level [3], with the higher density of corticomotoneuronal projections from the hand region inherently rendering this pathway easier to stimulate [3,11]. Comparatively, the cortical leg region has fewer monosynaptic corticospinal projections [11], which could require higher stimulation intensities as the disease evolved through the progressive loss of corticospinal axons to a smaller motoneuron pool. This would be in keeping with the predominance of lower-limb onset patients within the inexcitable group in this study. Overall, the cortical profile of the four-limb inexcitable cohort would appear to be driven by faster, more severe involvement of the corticospinal system earlier in disease, with the phenotypic lower-limb profile influenced by proportionally greater axonal loss from this smaller cortical area.

Equally, however, the ability of patients to contract muscles for which no MEP could be recorded suggests that loss of corticomotoneurons was not the sole factor in the inexcitability. This presumes that corticomotoneurons activated in the MEP and in voluntary contractions are similar, which is likely given previous data for healthy subjects [24]. Of interest, averaged SICI was uniformly reduced in both excitable and partially inexcitable ALS cohorts. Although this phenomenon occurs at the level of the motor cortex, the mechanisms are separate from those that govern RMT: a reduction in SICI reflects a reduction in inhibitory interneuronal circuitry and GABAergic synaptic neurotransmission [1,5,23], whilst RMT reflects activity of excitatory interneuronal circuits that generate I waves. This raises the question of how much the cortical dysfunction is interneuronal rather than corticomotoneuronal, and whether interneuronal loss can explain why patients with inexcitability to TMS could still contract the target muscle. Indeed, an interneuronal hypothesis would be consistent with prior views in ALS [25], but extends the ‘interneuronopathy’ to include excitatory interneuronal circuits.

The four-limb inexcitable ALS cohort has a unique clinical profile

Although the literature on ALS focality has been largely descriptive, the clinical site of onset is relevant due to its links to disease trajectory, patterns of spread and prognosis [26,27]. The frequency between upper- and lower-limb onset has been reported fairly equally in classic ALS [28,29], contrasting the lower-limb onset predominance in the four-limb inexcitable cohort. The rapid clinical trajectory of this group also differs from classic lower-limb onset ALS, which has typically been identified as having slower disease progression [26]. Importantly, progression rate represents an independent prognostic biomarker in ALS [18,19], with faster disease progression rates at initial presentation, as seen in this study cohort, associated with a 3.7-fold increase in the risk of death [18]. This more malignant disease course in the four-limb inexcitable group is reinforced by poorer survival amongst patients who developed this involvement early. Taken together, this implies that the descriptive clinical onset phenotype alone may be insufficient when defining disease trajectory, and advocates for cortical profile to be taken into consideration when assigning nosology. Future studies exploring inexcitability from additional muscles may help clarify clinical and prognostic implications further, particularly those that define unique features such as the clinical ‘split-hand’, which may have an underlying cortical basis [5,14].

Conclusion

The presence of cortical inexcitability in all four limbs appears to define a unique clinical and prognostic profile in ALS patients, marked by a faster rate of disease progression and higher functional disability, as well as
reduced survival if present early in disease. This cohort is typically younger and has a lower-limb predominant phenotype, both features which are historically identified as having a more favourable prognosis. This suggests that cortical inexcitability may represent a separate and distinct subgroup in the ALS spectrum of disease, questioning our prior understanding of survival factors and suggesting a more reticent outlook on prognosis. In clinical practice, understanding and identifying this phenotype will allow for a more practical understanding of patient outcomes, and assist in planning multidisciplinary management.

Acknowledgements

All authors gratefully acknowledge the following. T.D. is recipient of scholarships from the University of Sydney, Rotary Club, Motor Neurone Disease Research Australia (MNDRA) and the Yulgilbar Research Foundation. J.H. is recipient of the Bill Gole Fellowship, MNDRA. J.M.M. has scholarships from the International Federation of Clinical Neurophysiology, Becas-Chile and Clinica Alemana de Santiago. M.C.K. and D.B. serve as Editors-in-Chief of the Journal of Neurology, Neurosurgery and Psychiatry and Clinical Neurophysiology Practice, respectively.

Study funding: This study was supported by funding to Forefront, a collaborative research group dedicated to the study of motor neuron disease and frontotemporal dementia, from the National Health and Medical Research Council of Australia Program Grant (#1037746).

Disclosures of conflict of interest

The authors declare no financial or other conflicts of interest.

Data Availability Statement

Data supporting the study findings are available upon reasonable request from a qualified investigator, for a period of 3 years from publication date, subject to approval from the Human Research Ethics Committee of the University of Sydney.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Phenotypic distribution of ALS groups

References

1. Vucic S, Kiernan M. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. Brain 2006; 129: 2436–2446.
2. Shibuya K, Park S, Geesinga N, et al. Motor cortical function determines prognosis in sporadic ALS. Neurology 2016; 87: 513–520.
3. Rossini P, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015; 126: 1071–1107.
4. Mills K, Nithi K. Corticomotor threshold is reduced in early sporadic amyotrophic lateral sclerosis. Muscle Nerve 1997; 20: 1137–1141.
5. Vucic S, Ziemann U; Eisen A, Hallett M, Kiernan MC. Transcranial magnetic stimulation and amyotrophic lateral sclerosis: pathophysiological insights. J Neurol Neurosurg Psychiatry 2013; 84: 1161–1170.
6. Kesar T, Stinear J, Wolf SL. The use of transcranial magnetic stimulation to evaluate the cortical excitability of lower limb musculature: challenges and opportunities. Restor Neurol Neurosci 2018; 36: 333–348.
7. Terao Y, Ugawa Y, Sakai K, Usaka Y, Kohara N, Kanazawa I. Transcranial stimulation of the leg area of the motor cortex in humans. Acta Neurol Scand 1994; 89: 378–383.
8. Mills K. Magnetic stimulation of the human nervous system. Oxford, UK: Oxford University Press, 1999.
9. Dharmadasa T, Matamala J, Howells J, Simon NG, Vucic S, Kiernan MC. The effect of coil type and limb dominance in the assessment of lower-limb motor cortex excitability using TMS. Neurosci Lett 2019; 23: 84–90.
10. Dharmadasa T, Matamala J, Howells J, Vucic S, Kiernan MC. Early focality and spread of cortical dysfunction in amyotrophic lateral sclerosis: a regional study across the motor cortices. Clin Neurophysiol 2020; 131 (4): 958–966.
11. Groppa S, Oliviero A, Eisen A, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an I.F.C.N. Committee. Clin Neurophysiol 2012; 123: 858–882.
12. Vucic S, Howells J, Trevillion L, Kiernan MC. Assessment of cortical excitability using threshold-tracking techniques. Muscle Nerve 2006; 33: 477–486.
13. Fisher R, Nakamura Y, Bestmann S, Rothwell JC, Bostock H. Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. Exp Brain Res 2002; 143: 240–248.
14. Menon P, Kiernan M, Vucic S. Cortical excitability varies across different muscles. J Neurophysiol 2018; 120: 1397–1403.
15. Claus D. Central motor conduction: method and normal results. Muscle Nerve 1990; 13: 1125–1132.
16. Turner M, Cagnin A, Turkheimer FE, et al. Evidence of wide-spread cerebral microglial activation in amyotrophic lateral sclerosis. Neurobiol Dis 2004; 15: 601–609.
17. Cedrbaum J, Stambler N, Malta Errol, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999; 169: 13–21.
18. Labra J, Menon P, Byth K, Morrison S, Vucic S. Rate of disease progression: a prognostic biomarker in ALS. J Neurol Neurosurg Psychiatry 2016; 87(6): 628–632.
19. Kimura F, Fujimura C, Ishida S, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 2006; 66: 265–267.
20. Awisus F. TMS and threshold hunting. Suppl Clin Neuropsychol 2003; 56: 13–23.
21. Niewiadomska M, Wochnik-Dyjas D, Glazowski C. Cortical excitability threshold for distal limb muscles in transcranial magnetic stimulation. Method–normative values. Neurobiol Exp (Wars) 1998; 58: 69–77.
22. Amassian V, Stewart M, Quirk GJ, Rosenthal JL. Physiological basis of motor effects of a transient stimulus to cerebral cortex. Neurosurgery 1987; 20: 74–93.
23. Zanette G, Tamburin S, Manganotti P, Refatti N, Forgione A, Rizzuto N. Different mechanisms contribute to motor cortex hyperexcitability in amyotrophic lateral sclerosis. Clin Neurophysiol 2002; 113: 1688–1697.
24. Pierrot-Deseilligny E, Burke D. The circuitry of the human spinal cord: spinal and corticospinal mechanisms of movement. New York, NY: Cambridge University Press, 2012.
25. Turner M, Kiernan M. Does interneuronal dysfunction contribute to neurodegeneration in amyotrophic lateral sclerosis? Amyotroph Lateral Scler 2012; 13: 245–250.
26. Turner M, Brockington A, Scaber J, et al. Pattern of spread and prognosis in lower-limb onset ALS. Amyotroph Lateral Scler 2010; 11: 369–373.
27. Ravits J, La Spada A. ALS motor phenotype heterogeneity, focality and spread. Neurology 2009; 73: 805–811.
28. Walhout R, Verstraete E, Van den Heuvel MP, Veldink JH, Van den Berg LH. Patterns of symptom development in patients with motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener 2018; 19: 21–28.
29. Dharmadasa T, Henderson R, Talman PS, et al. Motor neuron disease: progress and challenges. Med J Aust 2017; 206: 357–362.