Bangladesh Journal of Neuroscience 2021; Vol. 37 (1): 30-36

Split-hand Index in CMAP Types of Amyotrophic Lateral Sclerosis

SAHA S[1*], RAHMAN HZ[2], ALAM SKM[3], CHOWDHURY A[4], MUZAHID MAA[4], ROY U[4], KABIR MS[4], HASAN M[4], BALA CS[5], ISLAM MR[6]

Abstract:

Background: *Split hand is an early clinical sign in amyotrophic lateral sclerosis (ALS) where thenar muscles are substantially more involved than that of hypothenar muscle and Split-hand Index (SI) is the electrophysiological measurement of it.* ***Objective:*** *Our objective was to assess the utility of Split-hand Index in Amyotrophic lateral sclerosis (ALS).* ***Methods:*** *Total 56 study subjects, 28 ALS patients and 28 age & sex matched healthy controls (HCs) were enrolled after satisfying the selection criteria. According to El Escorial diagnostic criteria ALS patients were recruited. Severity and muscle strength state were assessed by ALS functional rating scale-revised (ALSFRS-R) and Medical research council (MRC) scores respectively. Then electrophysiology was done to measure SI both in ALS patients and HCs by compound muscle action potential (CMAP) based method. SI was evaluated according to CMAP types in ALS (normal CMAP and reduced CMAP). Collected data were analyzed by IBM SPSS (Statistical Package for Social Sciences) version 26 to observe relation of SI with ALS and its utility.* ***Results:*** *SI was reduced significantly both in normal CMAP and reduced CMAP ALS than Healthy controls ($SI_{Reduced\ CMAP}$ – 1.83±1.30, $SI_{Normal\ CMAP}$ – 5.59±3.72 and SI_{HCs} – 10.57±3.72; p<0.001). SI was positively correlated (r = +0.769, p<0.001) with severity status (ALSFRS-R). SI was also significantly correlated (r= +.893, p<0.001) with status of muscle strength (according to MRC score). Receiver operating characteristic (ROC) curve analysis showed that SI reliably differentiated ALS patients from healthy controls with a cut-off value 5.04 exhibiting 82.1% sensitivity and 85.7% specificity.* ***Conclusion:*** *SI was significantly related with normal CMAP and reduced CMAPALS and reliably differentiated from HCs with high diagnostic accuracy. SI also had strong positive correlation with severity and muscle strength state signifying its role in diagnosis and monitoring of ALS.*

Key word: *Amyotrophic lateral sclerosis, Split-hand Index, CMAP type of ALS*

Introduction:

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease where split hand is considered to be a specific clinical sign of it[1, 2, 3]. In 1996 Dr. Asa wilbourn used the term *split hand* where preferential wasting of thenar (lateral) hand including abductor pollicis brevis (APB) and first dorsal interosseous (FDI) occur with relative preservation of hypothenar (medial) hand including abductor digiti minimi (ADM)[4, 5, 6].

Previously researchers attempted to use this sign and its electrophysiological measure *Split-hand index (SI)* to diagnose ALS as there was no specific diagnostic test for ALS[2, 3, 7-12]. Though split hand has been reported in some other cases like spinal muscular atrophy (SMA), cervical spondylotic

1. Dr. Sujan Saha, Resident, Department of Neurology, BSMMU, Dhaka.
2. Dr. Hasan Zahidur Rahman, Professor, Department of Neurology, BSMMU,
3. Dr. SK. Mahbub Alam, Assocate Professor, Department of Neurology, BSMMU,
4. Dr. Md. Abdullah Al Muzahid, Dr. Uttam Roy, Dr. Md. Suman Kabir, Dr. Mehedi Hasan, Resident, Dept. of Neurology, BSMMU,
5. Dr. Chandra Shekhor Bala, Resident, NINS and Hospital, Dhaka,
6. Prof. Md. Rafiqul Islam, Professor And Chairman, Department of Neurology, BSMMU

amyotrophy, spinocerebellar ataxia type 3 (SCA 3) and even in normal elderly individual[13],SI may be used to in this regard differentiate ALS from those mimics[3].

The aim of the present study was to investigate split hand phenomenon in ALS by measuring SI in ALS(normal CMAP and reduced CMAP) patients and comparing the values with that of healthy controls (HCs). We also attempted to correlate SI with severity state of ALS and studied diagnostic utility of it. So that it can be established as a simple and useful electro diagnostic tool for ALS.

Materials and methods:

The study was carried out in Neuromuscular Disorder Clinic, Inpatient and Outpatient Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from September 2019 to September 2020 after being approved by Institutional review board (IRB). After meeting El Escorial diagnostic criteria as definite, probable and possible cases, 28 ALS patients were recruited along with 28 age and sex matched HCs as study subjects by convenient purposive sampling. Subjects with features suggestive of cervical cord or nerve root compression, any form of chronic neuropathy including diabetic neuropathy, hereditary sensory and motor neuropathy (HSMN), chronic inflammatory demyelinating poly neuropathy (CIDP), median and or ulnar entrapment neuropathy (based on clinical features and nerve conduction study), chronic kidney disease (CKD) were excluded from study. Patients' severity state was evaluated by ALS Functional Rating Scale-Revised (ALSFRS-R) [14]. Muscle strength was assessed using Medical Research Council (MRC) score[15]. The following muscle groups were assessed bilaterally yielding a total MRC score of 90: shoulder abduction, elbow flexion, elbow extension, wrist dorsiflexion, finger abduction, thumb abduction, hip flexion, knee extension and ankle dorsiflexion. Data were collected through face-to-face interview using semi-structured questionnaire having selected variables according to objectives. The utility of study was explained to all study subjects and written informed consent was taken. Subjects' right to withdraw from the study at any point of time was ensured and information obtained from study subjects was kept confidential except for research purpose only.

Electrophysiology was done using NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/ NCV/EP Measuring System in the department of neurology, BSMMU, Dhaka. Room temperature was maintained roughly at 22-24^0 C during procedure and skin temperature at 32-36^0 C was ensured.

In all patients median, ulnar, common peroneal and tibial motor nerves, as well as the sural, median and ulnar sensory nerves along with needle electromyographic (EMG) activity were assessed in all four regions. Routine nerve conduction studies (NCS) of median and ulnar nerve were also performed in HCs to exclude any pathology.

For SI measurement median and ulnar nerves were supramaximally (120%) stimulated at wrist and the resultant baseline-to-peak CMAP amplitude (mV) were recorded over APB, ADM and FDI muscles by positioning electrodes in a belly tendon arrangement. The G1 electrode (active) was positioned over the muscle belly of respective muscle ensuring a negative take-off of the CMAP response, while the G2 electrode (reference) was positioned over base of thumb for APB & FDI and base of digit 5 for ADM. The distance between the cathode (stimulation site at wrist) and active (G1) recording electrodes was 7 cm.CMAP amplitude was considered normal or reduced as follows[7]: APB - Normal: ≥4, Reduced: <4; ADM - Normal: ≥5.5, Reduced: <5.5; FDI – Normal: e"7.7, Reduced: <7.7.According to CMAP ALS was sub grouped as normal CMAP ALS (CMAP of APB, FDI and ADM normal) and reduced CMAP ALS (any one value of CMAP of APB/FDI/ADM reduced). Then SI was calculated using following formula: $SI = (CMAP_{APB} \times CMAP_{FDI}) / CMAP_{ADM}$.

Continuous data were presented as mean ± SD values and categorical as frequency and percentage. Comparison of continuous data and categorical data between two groups were done by unpaired t-test and chi-square tests respectively. Comparisons of continuous data among three or more groups were done by ANOVA test. Correlation

analyses were done by Pearson's correlation test. Receiver Operating Characteristics (ROC) curve analysis was done to reveal diagnostic utility of SI in ALS. The cutoff for statistical significance was set at $p < 0.05$. A statistical analysis was carried out using IBM SPSS (Statistical Package for Social Sciences) version 26.

Results:

We recruited 28 ALS patients along with 28 HCs according to selection criteria. Both ALS and HCs group were age (41.2±14.4 vs. 38.8±12.9 years, p 0.509) and sex (Male: Female = 3:1 vs. 2.5:1) matched. Limb onset ALS was 78.6% and bulbar onset 21.6%. According to El Escorial diagnostic criteria 32.1% was definite, 32.1% was probable and 35.8% was possible ALS. Majority of possible cases (80%) were normal CMAP ALS. On the other hand majority of definite and probable cases (100%, 77.8%) were reduced CMAP ALS. The mean disease duration from symptom onset were 16.1±11.0 months ranging from minimum 4 months to maximum 40 months. Majority of the patients (53.6%) were in moderate state of severity with ALSFRS-R score 36 (32-41). Median MRC of normal CMAP ALS was 70 whereas in reduced CMAP ALS it was 49.

According to CMAP amplitude of APB, FDI and ADM reduced CMAP ALS was 64% and normal CMAP ALS was 36% (Figure 1). Electrophysiological studies also revealed significant reduction of CMAP amplitude of APB, FDI and ADM both in normal and reduced CMAP ALS than that of HCs (Table 1). CMAP of APB and FDI were relatively more reduced than that of ADM in both type of ALS depicting electrophysiological correlation of split hand (Figure 2). There was also marked reduction of APB/ADM ratio in ALS patients than HCs (0.86±0.39 vs. 1.23±20, p<0.001).

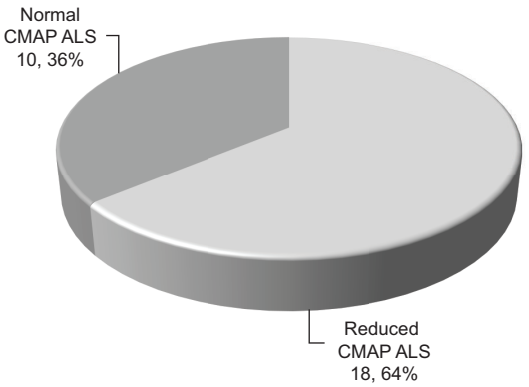

Fig.-1: *Pie diagram showing CMAP type in ALS*

SI was significantly reduced in the ALS than that of HCs (SI_{ALS} - 3.17±2.22, SI_{Hcs} - 10.57±3.72; p<0.001) (Figure 3).There was also significant difference of SI in ALS subgroup than the HCs ($SI_{Reduced\ CMAP}$ – 1.83±1.30 vs. SI_{HCs} – 10.57±3.72,

Table-I

Electrophysiological parameters in CMAP types of ALS and HCs

Parameters	CMAP types of ALS		HCs	P value
	Reduced CMAP ALS	Normal CMAPALS		
CMAP (mV)				
APB	2.49±1.57	9.46±1.95	18.71±4.22	<0.001**†
FDI	1.64±1.05	6.15±1.46	9.78±2.90	<0.001**†
ADM	3.19±2.02	10.50±2.73	15.42±3.50	<0.001**†
Split-hand Index				
SI	1.83±1.30	5.59±1.23	10.57±3.72	<0.001**†

CMAP-Compound muscle action potential, ALS-Amyotrophic lateral sclerosis, HCs-Healthy controls, APB-Abductor pollicis brevis, FDI-first dorsal interosseous, ADM-Abductor digiti minimi, SI-Split-hand Index, * Significant (p'CO.O'i), ** p<0.001 (Compared with HCs), ^0.001 (Compared with normal CMAP ALS)

$p<0.001$; $SI_{Normal\ CMAP}$ – 5.59±3.72 vs. SI_{HCs} – 10.57±3.72, $p<0.001$) (Figure 4).

There was strong positive correlation ($r = +0.769$, $p<0.001$) of SI with severity state of disease (according to ALSFRS-R score) (Figure 5). SI was also significantly correlated ($r= +.893$, $p<0.001$) with status of muscle strength (according to MRC score).

We performed Receiver Operating Characteristic (ROC) curve analysis to see diagnostic utility of SI in ALS. ROC revealed that SI reliably differentiated ALS from HCs with a cut off value 5.04, AUC = 0.945, $p<0.0001$, Sensitivity = 82.1%, Specificity = 85.7% (Figure 6).

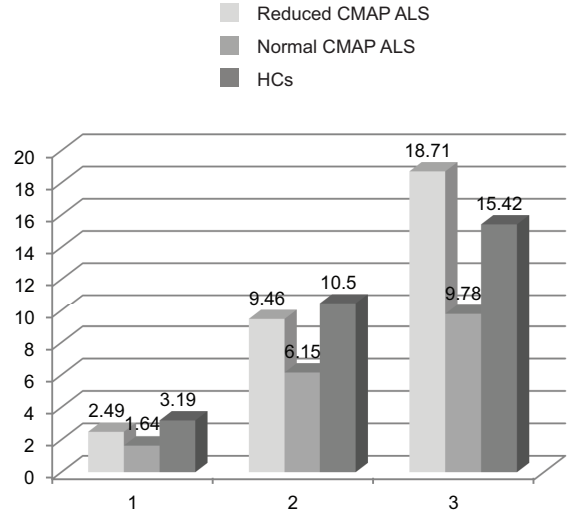

Fig.-2: *Bar diagram showing comparison of CMAP (mV) of APB, FDI and ADM among reduced CMAP ALS, normal CMAP ALS and HCs*

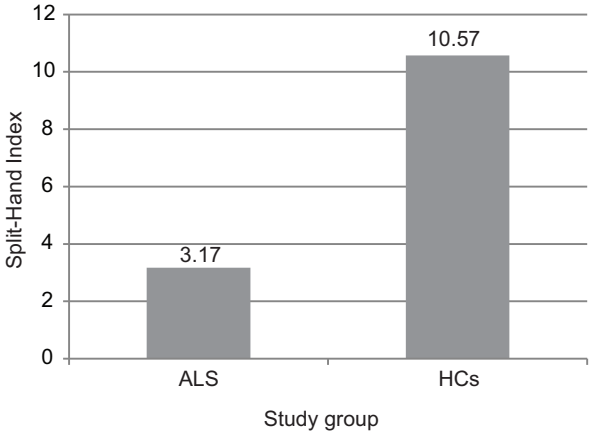

Fig.-3: *Bar diagram showing SI in ALS and HCs*

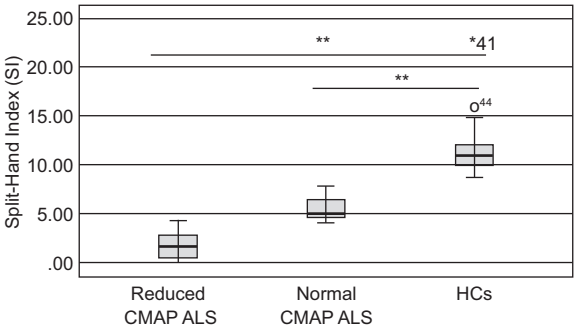

Fig.-4: *Box-Whisker plot showing the split-hand index (SI) of reduced CMAP ALS, normal CMAP ALS and Healthy controls (HCs), *Significant ($p<0.05$), **$p<0.001$ (compared with HCS), †$p<0.001$ (compared with normal CMAP ALS)*

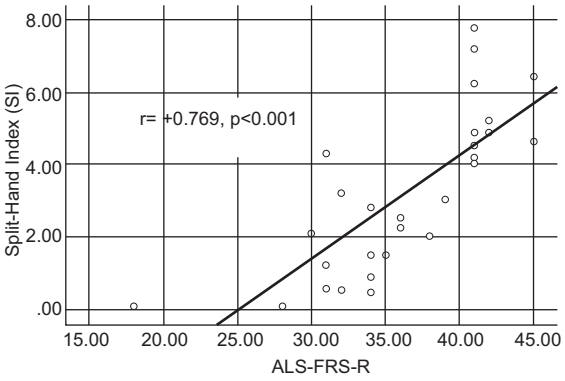

Fig.-5: *Scatter diagram showing strong positive correlation of split-hand index (SI) with severity of ALS (ALSFRS-R)*

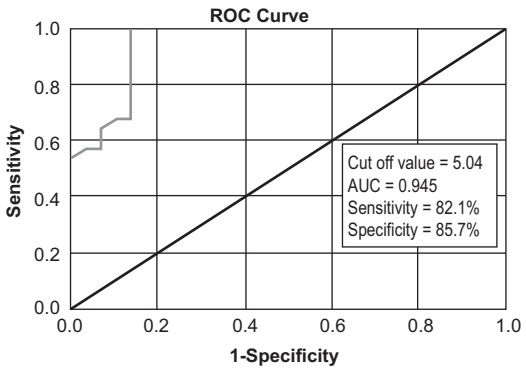

Fig.-6: *Receiver operating characteristic (ROC) curve analysis of Split-hand Index (SI) ALS*

Discussion:

In the current study we observed SI as a potential neurodiagnostic tool as it reliably differentiates ALS from HCs. The results obtained from this CMAP based study indicates that SI can reflect the dissociated involvement of small hand muscles, even in ALS patients with normal CMAP. In earlier stage of disease CMAP remains normal. When 50% motor neurons are involved, CMAP of those innervating muscles start to decline[10]. So we have taken into account the CMAP type of ALS, normal CMAP ALS and reduced CMAP ALS, to assess reliability of SI in diagnosing the earlier stage of disease. We observed that CMAP of APB, FDI and ADM were normal in normal CMAP ALS still they were significantly reduced than that of HCs. Though SI of normal CMAP ALS was higher than reduced CMAP ALS, still there remained significant difference from that of HCs. Previously wang et al. 2019 and Kim et al. 2016 also found same significant result[9,10].

A reduced APB/ADM ratio was observed in patients with ALS which demonstrates a clear difference in dysfunction between the spinal motor neurons and cortico-motor-neuronal innervating the APB and ADM in ALS disease. Kuwabara et al. 2008 also found same significant finding during electrophysiological evaluation of split hand[16].

Besides SI had strong positive correlation with severity state (according to ALSFRS-R score) and muscle strength status (according to MRC score) reflecting the fact along with decline of functional status and muscle strength SI also reduces. Menon et al. 2013, 2014 also showed same relations[3, 7].

In this study, Receiver operating characteristic (ROC) curve analysis showed that SI reliably differentiated ALS patients from healthy controls with a cut-off value 5.04 exhibiting 82.1% sensitivity and 85.7% specificity. Previously Menon et al. (2011) performed ROC analysis and found that SI reliably differentiated ALS from Non ALS with a cut off value <5.2, AUC = 0.90, p<0.0001, Sensitivity = 81%, Specificity = 82%.By ROC analysis Kalita et al. (2017) also showed SI of ≤5.2 had 82% sensitivity and 88.8% specificity with AUC=0.92 in diagnosis of ALS[2, 8].

Till now there is no specific diagnostic test for ALS. Diagnosis mainly relies on combination of upper and lower motor neuron dysfunction along with progressiveness of the disease[17]. In absence of diagnostic test clinical criteria were developed for earlier diagnosis but found to be less sensitivity resulting diagnostic delay[18, 19, 20]. Then, a modification was done to include EMG findings along with clinical features for delineating lower motor neuron (LMN) dysfunction[21]. Awaji-Shima criteria increased the diagnostic sensitivity[22, 23, 24] but extensive EMG samplings are required. Besides EMG findings of lower motor neuron dysfunction are not specific for ALS.

In this regard SI can be a simple electrophysiological test which can be done in basic electrophysiological setting without any sophisticated technique. Besides this study may also reflect the underlying pathophysiology of ALS where thenar complex group of muscles (APB and FDI) have greater cortical representation[2] and split hand sign may suggest a cortical onset of ALS[1, 13, 14]. As preferential atrophy of APB and FDI muscles was a specific feature of ALS, measured by the split-hand index, it supports the cortical origin of ALS.

Conclusion, limitations and recommendations

We observed significant reduction of SI in ALS than HCs despite normal CMAP in ALS subgroup. It may have diagnostic and prognostic utility in ALS. But the sample size was small, study was single centered and follow up was not done. Future multicentered, follow up study should be done with large sample size.

Ethical issue

All study subjects gave written informed consent and clearance for study was given by IRB, BSMMU (Memo No. BSMMU/2019/12264, Date: 07-11-2019).

Conflicts of interest

The authors declare no conflict of interest

Acknowledgements

We acknowledge all the respondents as well as Department of Neurology, BSMMU.

Abbreviations

ALS: Amyotrophic lateral sclerosis, **ADM:** Abductor digiti minimi, **ALSFRS-R:** ALS functional rating

scale-revised, **APB**: Abductor pollicis brevis, **CMAP:** Compound muscle action potential, **EMG:** Electromyogram, **FDI:** First dorsal interosseous, **MND:** Motor neuron disease, **MRC:** Medical research council, **SI:** Split-hand Index, **ROC:** Receiver operating characteristic

References

1. Weber M, Eisen A, Stewart H, Hirota N. The split hand in ALS has a cortical basis. Journal of the neurological sciences. 2000 Nov 1;180(1-2):66-70.
2. Menon P, Kiernan MC, Vucic S. Appearance, phenomenology and diagnostic utility of the split hand in amyotrophic lateral sclerosis. Neurodegenerative Disease Management. 2011 Dec;1(6):457-62.
3. Menon P, Kiernan MC, Yiannikas C, Stroud J, Vucic S. Split-hand index for the diagnosis of amyotrophic lateral sclerosis. Clinical neurophysiology. 2013 Feb 1;124(2):410-6.
4. Kuwabara S, Mizobuchi K, Ogawara K, Hattori T. Dissociated small hand muscle involvement in amyotrophic lateral sclerosis detected by motor unit number estimates. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 1999 Jul;22(7):870-3.
5. Wilbourn AJ. The “split hand syndrome”. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000 Jan;23(1):138.
6. Wilbourn AJ, Sweeney PJ. Dissociated wasting of medial and lateral hand muscles with motor neuron disease. Can J Neurol Sci. 1994;21(Suppl 2):S9.
7. Menon P, Kiernan MC, Vucic S. ALS pathophysiology: insights from the split-hand phenomenon. Clinical Neurophysiology. 2014 Jan 1;125(1):186-93.
8. Kalita J, Kumar S, Misra UK, Neyaz Z. Split hand index and ulnar to median ratio in Hirayama disease and amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2017 Oct 2;18(7-8):598-603.
9. Kim DG, Hong YH, Shin JY, Park KH, Sohn SY, Lee KW, Park KS, Sung JJ. Split hand phenomenon in amyotrophic lateral sclerosis: a motor unit number index study. Muscle & Nerve. 2016 Jun;53(6):885-888.
10. Wang ZL, Liu M, Ding Q, Hu Y, Cui L. Split-hand index in amyotrophic lateral sclerosis: an F-wave study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2019 Oct 2;20(7-8):562-567.
11. Mohammed NH, Hamdan FB, Al-Mahdawi AM. Evaluation of F wave and split hand index in patients with amyotrophic lateral sclerosis. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2020 Dec;56(1):1-8.
12. Shaw PJ, Wood-Allum C. Motor neurone disease: a practical update on diagnosis and management. Clinical Medicine. 2010 Jun;10(3):252.
13. Eisen A, Kuwabara S. The split hand syndrome in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2012 Apr 1;83(4):399-403.
14. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A, Bdnf Als Study Group, 1A complete listing of the BDNF Study Group. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. Journal of the neurological sciences. 1999 Oct 31;169(1-2):13-21.
15. O’Brien MD. Aid to the examination of the peripheral nervous system. 5th ed. Edinburgh: Saunders; 2010. p. 2.
16. Kuwabara S, Sonoo M, Komori T, Shimizu T, Hirashima F, Inaba A, Misawa S, Hatanaka Y, Tokyo Metropolitan Neuromuscular Electrodiagnosis Study Group. Dissociated small hand muscle atrophy in amyotrophic lateral sclerosis: frequency, extent, and specificity. Muscle & nerve. 2008 Apr;37(4):426-30.
17. Vucic S, Nicholson GA, Kiernan MC. Cortical hyperexcitability may precede the onset of

familial amyotrophic lateral sclerosis. Brain. 2008 Jun 1;131(6):1540-50.

18. Chiò A. ISIS Survey: an international study on the diagnostic process and its implications in amyotrophic lateral sclerosis. Journal of neurology. 1999 Nov 1;246(3):III1-5.
19. Traynor B, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Amyotrophic lateral sclerosis mimic syndromes: a population-based study. Archives of neurology. 2000 Jan 1;57(1): 109-13.
20. Turner MR, Kiernan MC, Leigh PN, Talbot K. Biomarkers in amyotrophic lateral sclerosis. The Lancet Neurology. 2009 Jan 1;8(1):94-109.
21. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, Mills K, Mitsumoto H, Nodera H, Shefner J, Swash M. Electrodiagnostic criteria for diagnosis of ALS. Clinical neurophysiology. 2008 Mar 1;119(3):497-503.
22. Douglass CP, Kandler RH, Shaw PJ, Mcdermott CJ. An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease. Journal of Neurology, Neurosurgery & Psychiatry. 2010 Jun 1;81(6):646-9.
23. Schrooten M, Smetcoren C, Robberecht W, Van Damme P. Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: a prospective study. Annals of neurology. 2011 Jul;70(1):79-83.
24. Noto YI, Misawa S, Kanai K, Shibuya K, Isose S, Nasu S, Sekiguchi Y, Fujimaki Y, Nakagawa M, Kuwabara S. Awaji ALS criteria increase the diagnostic sensitivity in patients with bulbar onset. Clinical neurophysiology. 2012 Feb 1;123(2):382-5.
25. Lemon RN, Griffiths J. Comparing the function of the corticospinal system in different species: organizational differences for motor specialization?. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2005 Sep;32(3):261-79.