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REVIEW ARTICLE

Utility of Split-hand Index in Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS), a neurodegenerative disorder, is the most common type of motor neuron disease (MND). Split-hand is considered to be an early and specific clinical sign in ALS where lateral hand (thenar muscles) is more affected than medial hand (hypothenar muscles). Split-hand index (SI) is an electrophysiological measure to see split-hand and its extent which is simple and can be done in basic electrophysiological setting. It can also differentiate ALS from other mimic disorders. It can be used as a diagnostic as well as prognostic marker of ALS so that patient can undergo an early therapeutic trial.

Key words: *Amyotrophic lateral sclerosis, Split-hand Index, Compound muscle action potential, Motor unit number index, F wave persistence*

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease (MND) which is relentlessly progressive neurodegenerative disease where involvements of both upper motor neurons (UMN) and lower motor neurons (LMN) manifest asymmetrically[1, 2]. It typically involves motor neurons in cerebral cortex, brain stem and spinal cord[3]. Diagnosis of ALS is based on progressive asymmetric motor weakness involving specific body region with combination of upper and lower motor sign in absence of sensory and sphincter disturbance. There is no definitive diagnostic test. Electrophysiology supports the clinical diagnosis while other investigations are done to exclude the ALS mimics[4]. Diagnostic criteria have been developed like El Escorial criteria[5], Awaji-Shima criteria[6], but they are less sensitive for diagnosis of ALS in early stage[7] and initiation of neuroprotective therapies like riluzole are delayed. In this regard Split-hand Index (SI), an electrophysiological measure of split hand, can be a simple and very useful neurodiagnostic test for ALS[8].

Split-hand

Hand muscle wasting is a common clinical presentation in ALS. During 1990s Dr. Asa Wilbourn observed a peculiar pattern of wasting of intrinsic muscles of hand – thenar muscle (lateral hand) including abductor pollicis brevis (APB) and first doral interosseous (FDI) are more wasted when compared to hypothenar muscle (medial hand) including abductor digiti minimi (ADM). This dissociated pattern of involvement between lateral and medial hand was first then termed as *Split hand* [9, 10].

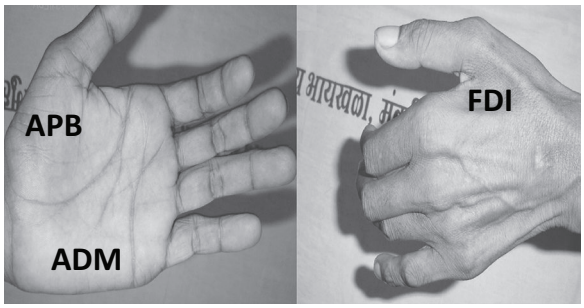

Fig.-1: *Split hand. Wasting of APB and FDI (thenar) with relative sparing of ADM (hypothenar)* [11]

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Mechanism of Split-hand

Muscles of split hand are innervated through same spinal segment (C8 and T1) but FDI and ADM are both ulnar innervated but differentially affected[12]. So, the mechanism underlying the split hand in ALS is complex [13]. However three following mechanisms have been proposed[8,14,15].

Cortical based Mechanism

Thenar muscles have greater cortical representative area than hypothenar muscle (Figure 2) and anterior horn cells (AHCs) innervating thenar muscles receive more corticomotoneuronal input which makes them vulnerable to hyperexcitability induced motor neuron degeneration via an anterograde glutamate mediated excitotoxic process[16].

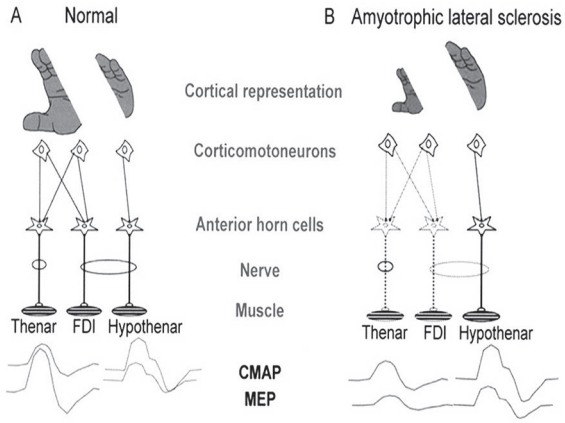

Fig.-2: *Cortical mechanism in split hand*

(A) Cortical representation of the thenar hand is larger than hypothenar & MEP is larger than the CMAP activated by TMS. Hypothenar motor evoked potential (MEP) is smaller than the CMAP.

(B) Reversal of the normal situation. Cortical representation 'shrinks' and the thenar MEP is smaller than the thenar CMAP[16].

Peripheral mechanism

Peripheral mechanism (Figure 3) for split hand suggested upregulation of persistent nodal sodium conductance as evidenced by increased strength duration time constant (SDTC) of motor axons innervating the thenar muscles causing neurodegeneration[15].

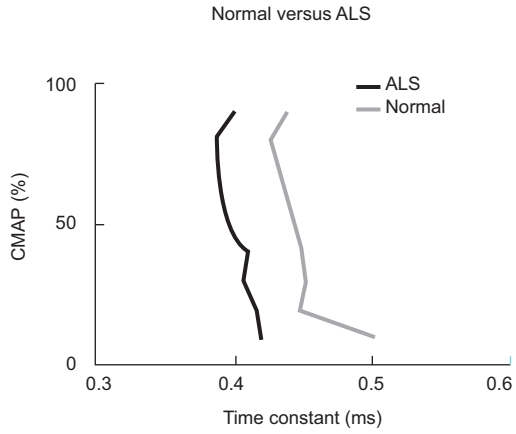

Fig.-3: *Peripheral mechanism in split hand*
APB motor axons of amyotrophic lateral sclerosis patients and normal controls.
Amyotrophic lateral sclerosis axons have a longer SDTC than normal axons, suggesting more prominent persistent sodium currents[16]

Increased metabolic demand

Thenar muscles are more frequently used than hypothenar muscles for execution of complex fine fractionated hand movements. As a result, increased metabolic demands of AHCs innervating APB and FDI lead to greater oxidative stress resulting early involvement in neurodegeneration[8].

Split-hand index (SI)

Split hand index (SI) is a neurophysiological technique for quantifying the degree of split handedness. Here supramaximal (120%) stimulation is given to median and ulnar nerves at wrist and the resultant baseline-to-peak CMAP amplitudes (mV) are recorded over APB, ADM and FDI muscles by positioning electrodes in a belly tendon arrangement. Then SI is calculated by following formula[14].

$$SI = (CMAP_{APB} \times CMAP_{FDI}) / CMAP_{ADM}$$

Methods of SI measurement

SI was originally proposed using CMAP amplitude[15] but till now three methods have been applied to measure SI – compound muscle action potential (CMAP) based[8, 13, 15, 17], motor unit number index (MUNIX) based[18] and F- wave persistance based (Fp)[19, 20] by using same formula.

CMAP based SI: In CMAP based study CMAP amplitudes (baseline to peak) in mV were measured over APB by giving supra maximal (120%) stimulus to median nerve at wrist and over FDI & ADM by giving supra maximal (120%) stimulus to ulnar nerve at wrist. Here G1 (active) and G2 (reference) electrodes were placed in belly-tendon arrangement respectively maintaining skin temperature about 32^0C. Then SI_{CMAP} was measured applying above mentioned formula. In several study CMAP based SI was used with high diagnostic and prognostic accuracy in ALS and differentiating ALS from other potential mimic disorders[8, 13, 15, 17].

MUNIX based SI: In MUNIX based study at first CMAP amplitudes in mV were measured in APB, FDI and ADM in above mentioned way. Then muscles were activated in a manner of their prime action (APB-abduction of thumb, FDI-abduction of index finger, ADM-abduction of fifth finger) at 5 different levels of isometric force ranging from minimal to maximal. This procedure were repeated to obtain 10 surface EMG interference pattern (session irritation protocol-SIP) signals. The CMAP and SIP values were used to measure ideal case motor unit count (ICMUC). Then MUNIX was analyzed by DOS program for each muscle. Then SI_{MUNIX} was measured. In this study SI_{MUNIX} was compared to SI_{CMAP} to see difference in diagnostic accuracy in ALS. SI_{MUNIX} showed higher diagnostic accuracy than SI_{CMAP}. But this procedure is time consuming and complicated[18].

F-wave persistence (Fp) based SI: In this method F-waves were recorded from APB, FDI and ADM by giving 100 consecutives supramaximal (120%) stimulation to median and ulnar nerve at wrist at 1 Hz placing cathode proximal to anode. F-wave persistence was defined as number of F responses obtained with 100 stimuli. Then SI_{Fp} was measured. Wang et al. (2019) showed greater accuracy of SI_{Fp} than SI_{CMAP} regarding earlier diagnosis of ALS[19, 20].

Utility of SI

Split hand is found in about 40% ALS patients in early stage of disease. But it also has been reported in some other cases like spinal muscular atrophy (SMA), cervical spondylotic amyotrophy, spinocerebellar ataxia type 3 (SCA 3) and even in normal elderly individual[12]. But split- hand Index (SI) may be used to differentiate ALS from other potential mimic disorders along with diagnosis of it. It may also be used as a simple, easy diagnostic as well as prognostic tool for ALS which can be performed in standard electrophysiological setting.

Related previous studies

Menon et al. (2011) reported SI was significantly reduced in ALS than non ALS (SI_{ALS} - 3.1±0.4, $SI_{Non\ ALS}$ – 9.4±0.4; p<0.001) with a cut-off value d”5.2 had 81% sensitivity of 81% and 82% specificity. SI also significantly correlated with NI (r = +0.4, p<0.05), MRC score (r = +0.76, p<0.001) and ALSFRS-R (r = +0.41, p<0.05). This study was CMAP based[8].

In 2013 Menon et al. again showed SI to be significantly reduced in ALS than patients with other neuromuscular disorders mimicking ALS (ALS - 3.5±0.6, NMS – 9.1±0.3; p<0.0001) with a cut-off value d”5.2 had sensitivity of 74% and specificity of 80% in differentiating ALS from other mimic disorders. SI also significantly correlated with NI (r = 0.8, p<0.001), MRC score (r + 0.7, p<0.001) and ALSFRS-R. SI was significantly reduced in limb-onset ALS than bulbar-onset ALS (Limb onset – 2.3±0.5, bulbar onset – 5.3±1.2; p<0.0001). This study was also CMAP based[15].

In another study Menon et al. (2014) stated SI as an objective biomarker of preferential atrophy of APB and FDI muscles was significantly reduced in ALS than controls (SI_{ALS} – 7.8±1.7, SI_{HC} – 13.1±1.1; p<0.0001) as well as axonal excitability studies identified significant prolongation of strength-duration time constant in ALS patients when recording over the APB and ADM axons but not FDI axons. The study reinforced the significance of the split-hand phenomenon in ALS and argued against a significant peripheral contribution in the underlying development[11].

Kim et al. (2016) performed a MUNIX based study to determine SI and compared it with CMAP based SI regarding diagnostic accuracy in ALS. The study showed both SI_{CMAP} and SI_{MUNIX} were significantly lower in ALS than healthy controls but SI_{MUNIX}

Table

CMAP based electrophysiological profile of split hand in different studies

Study	SI (MeaniSD)			Correlation of SI			ROC curve analysis		
	ALS	CG	P S-R	ALSFR score	MRC	NI Of SI	Cut off	Sensitivity	Specificity
Menon et al. 2011	3.1±0.4	9.4±0.4	<0.001	r -0.41 p<0.05	r+0.76, p<0.001	r -0.4 p<0.05	≤5.2	81%	82%
Menon et al. 2013	3.5±0.6	9.1±0.3	p<0.001		r - 0.7, p<0.001	r +0.8, p<0.001	≤5.2	74%	80%
Menon et al. 2014	7.8±1.7	13.1+1.1	0.0001						
Kim et al. 2016							9.4	85%	79%
Kallta et al. 2017	2.12±1.9	11.99±2.44	0.001						
Wang et al. 2019							11.8	76.5%	86%
Mohammed et al. 2020	10.28±6.82	15.35±5.36	0.004						

CMAP-Componnd muscle action potential, SI-Split-hand Index. ROC-Receiver operating characteristic, ALS-Amyotrophic lateral sclerosis, CG-Comparison group, ALSFRS-R-ALS functional rating scale-revised, MRC-Medical research council, NI-Neurophysiological index, r-Correlation coefficient

seemed to have more diagnostic accuracy than SI_{CMAP}. Receiver operating characteristic (ROC) curve analysis showed SI_{CMAP} value 9.4 had sensitivity 85% and specificity 79.5%. But SI_{MUNIX} value 144.5 had high sensitivity (95%) and specificity (84.6%). ROC noted significant difference between them [18].

Kalita et al. (2017) compared CMAP based SI and ulnar-median (UM) ratio ($CMAP_{ADM}/CMAP_{APB}$) between ALS (n = 31) and Hirayama disease (HD) (n = 26). The study showed high diagnostic accuracy of SI in ALS with a cut-off value d"5.2 had sensitivity of 82% and specificity of 88.8% than UM ratio. But in case of HD UM ratio had more diagnostic accuracy than SI[17].

Wang et al. (2019) performed F-wave persistence (Fp) based study to determine SI and compared it with CMAP based SI regarding diagnostic accuracy in ALS. The study showed both SI_{CMAP} and SI_{Fp} were significantly lower in ALS than healthy controls but SI_{Fp} seemed to have more diagnostic accuracy than SI_{CMAP} regarding earlier diagnosis. Receiver operating characteristic (ROC) curve analysis showed SI_{CMAP} value 11.8 had sensitivity 76.5% and specificity 86%. But SI_{Fp} value 80.7 had high sensitivity (81.2%) and specificity (97%). ROC noted significant difference between them[19].

Mohammed et al. (2020) evaluated CMAP based SI and pattern of F wave in ALS. The study showed significant reduction of SI in ALS than controls (SI_{ALS} – 10.28±6.82, SI_{HC} – 15.35±5.36; p0.004). SI was significantly reduced in limb-onset ALS than bulbar-onset ALS (Limb onset – 7.38±3.71, bulbar onset – 11.42±4.5; p0.048)[20].

Conclusion:

Motor neuron disease (MND) is the third most common neurodegenerative disorder and amyotrophic lateral sclerosis (ALS) is most common type of it. Split hand is considered to be a specific and early clinical sign in ALS and Split-hand Index (SI) is a neurophysiological measure of split handedness which can be utilized in a standard electrophysiology setting. A reduction of SI may be of diagnostic utility in ALS and can differentiate ALS from other mimic disorders. It may also potentially facilitate an earlier diagnosis and patient can undergo an early therapeutic trial. SI can also be effectively correlated with functional decline in ALS. So, it may be used as diagnostic as well as prognostic electrophysiological marker in ALS patients

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