



Research paper

The split-elbow index: A biomarker of the split elbow sign in ALS

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ABSTRACT

Objective: The split elbow sign is a clinical feature of amyotrophic lateral sclerosis (ALS), characterised by preferential weakness of biceps brachii muscle compared to triceps. A novel neurophysiological index, termed the *split elbow index (SEI)*, was developed to quantify the split-elbow sign, and assess its utility in ALS.

Methods: Clinical and neurophysiological assessment was prospectively undertaken on 34 ALS patients and 32 ALS mimics. Compound muscle action potential (CMAP) amplitude was recorded from biceps brachii and triceps muscles from which the SEI was calculated using the following formula:

$$SEI = \frac{CMAP_{amplitude}^{BICEPSBRACHII}}{CMAP_{amplitude}^{TRICEPSBRACHII}}$$

Results: The split elbow sign was significantly more common in ALS patients when compared to ALS mimic patients ($P < 0.05$). The SEI was significantly reduced in ALS patients when compared to ALS mimics ($P < 0.01$). This reduction was evident in spinal and bulbar onset ALS. A SEI cut-off value of ≤ 0.62 exhibited a sensitivity of 71% and specificity of 61%.

Conclusions: The split elbow sign is significantly more common in ALS patients, and was supported by a reduction in the SEI.

Significance: The SEI may be utilised as a surrogate biomarker of the split elbow sign in future ALS studies.

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1. Introduction

Dissociated muscle atrophy is an established clinical feature of amyotrophic lateral sclerosis (ALS), best characterised by the split hand phenomenon, which clinically manifests as preferential dysfunction of the thenar group of intrinsic hand muscles (abductor pollicis brevis and first dorsal interosseous) compared to hypothenar muscles (Kuwabara et al., 2008, Menon et al., 2013, Menon et al., 2014a). Additionally, the split hand plus sign and split leg phenomenon have been recognised in ALS, being clinically heralded by greater dysfunction of thenar muscles compared to the flexor pollicis longus (Menon et al., 2013) and greater weakness of ankle plantar flexors compared to dorsiflexor muscles respectively (Simon et al., 2015). A preponderance for weakness of thenar muscles, hand extensors and knee flexor muscle groups were also reported in ALS (Ludolph et al., 2020). The dissociated pattern of muscle dysfunction has been attributed to stronger corticomotoneuronal projections onto motor neurons innervating affected muscles, thereby resulting in more prominent neurodegeneration via an antegrade excitotoxic mechanism (Eisen et al., 2017). Such a notion is supported by transcranial magnetic stimulation (TMS) studies establishing a greater degree of cortical hyperexcitability in the prominently affected muscle groups (Menon et al., 2014b).

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Recently, a split elbow sign was reported to be a clinical feature of ALS, characterised by preferential weakness of biceps brachii compared to triceps muscle (Khalaf et al., 2019, Ludolph et al., 2020). Specifically, the biceps brachii muscle was shown to exhibit a greater degree and frequency of weakness, as reflected Medical Research Council (MRC) score, when compared to the triceps muscle. Interestingly, there was no concordance between hand dominance and the split elbow sign. Given that the biceps brachii muscle has a greater density of corticomotoneuronal inputs when compared to the triceps (Neige et al., 2017), it has been suggested that cortical hyperexcitability may mediate the development of the split elbow sign in ALS (Vucic, 2019).

The notion of whether the split elbow sign was a sensitive and specific feature of ALS was not addressed in the previous study as a control group was not utilised. In addition, the MRC score is a subjective measure of muscle strength, susceptible to examiner and

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subject variability (Brandsma et al., 1995). The development of a simple neurophysiological biomarker, akin to the split hand index (Menon et al., 2014a), may provide an objective measure of the split elbow sign in ALS. The split elbow index (SEI) was derived by dividing the compound muscle action potential (CMAP) negative peak amplitude recorded over the biceps brachii muscle by the CMAP negative peak amplitude recorded over the triceps brachii muscle. Consequently, the aim of the present study was to determine whether the split elbow phenomenon was a feature of ALS by utilising clinical and neurophysiological biomarkers.

2. Methods

2.1. Patients

Patients with suspected diagnosis of ALS were prospectively recruited from the multidisciplinary ALS clinic (Westmead Hospital, Sydney) between April 2019 and July 2020. Patients presenting with a pure motor disorder with clinical features of upper and lower motor dysfunction in at least one body region and progressing over a 6-months period were recruited. Following extensive assessment clinical, neurophysiological, radiological and laboratory studies, patients were diagnosed as either ALS as defined by the Awaji criteria (de Carvalho et al., 2008) or ALS mimicking disorders.

The neurological disorders included in the ALS mimics cohort were as follows; chronic inflammatory demyelinating polyneuropathy (50%), Charcot-Marie-Tooth disease (3%), facioscapulo-humeral muscular dystrophy (3%), spinal-bulbar muscular atrophy/Kennedy's disease (6%), myasthenia gravis (6%), multifocal motor neuropathy (6%), stiff person syndrome (3%), head-drop syndrome (3%), cervical myelopathy (3%), myotonic dystrophy (3%), inclusion body myositis (3%), limb girdle muscular dystrophy (3%), oculopharyngeal muscular dystrophy (3%), and muscular dystrophy (3%).

All ALS patients were clinically staged using the amyotrophic lateral sclerosis functional rating score (ALSFRS-R) (Cedarbaum et al., 1999) and ALSFRS-R progression rate, a marker of survival, was measured according to the previously reported formula; $(48 - \text{ALSFRS-R}) / \text{duration of symptoms}$ (Labra et al., 2016). Disease duration (months) from time of symptom onset and the site of disease onset were recorded. Muscle strength was assessed by the Medical Research Council (MRC) score (O'Brien, 2004). Muscle strength was considered preserved with MRC score of 5 and weakness is defined as MRC 0 to 4. The split elbow pattern of weakness is defined by a lower MRC score with elbow flexion when compared to elbow extension in the same limb. In addition to determining the MRC score for the biceps brachii and triceps muscle, a total MRC score was recorded from the following group of muscles; shoulder abduction, elbow flexion and extension, wrist extension, finger abduction and thumb abduction, hip flexion, knee extension, and ankle dorsiflexion bilaterally, yielding a maximal score of 90. Handedness was determined by using the Edinburgh Inventory. All participants gave informed consent to the procedures, that were approved by the Sydney West Area Health Service Human Research Ethics Committee.

2.2. Split elbow index

Prior to assessing the split-elbow index, patients underwent routine nerve conduction studies and electromyography (EMG) using the Nicolet EDX machine (Synergy Reader software, Version 22.1.0.151). Needle EMG testing was performed in at least 3 regions on the ALS patients. Needle EMG testing was not routinely undertaken in patients with other neuromuscular disorders unless

the diagnosis was not apparent. For calculations of the SEI, the musculocutaneous and radial nerves were supramaximally stimulated at Erb's point (100 mA, 1 ms duration), with filter settings set between 3 Hz and 10 kHz and upper limb temperature maintained at 32 °C. A supramaximal stimulus was confirmed on each occasion, and the neurophysiologist performing the measurement was not aware of the diagnosis at the time of recording. The resultant baseline to negative peak CMAP amplitude (mV) was recorded over the biceps brachii and triceps brachii muscles using Ag/AgCl electrodes (3 M RedDot) arranged in a belly-tendon arrangement. For biceps brachii the G1 (active) electrode was positioned over the mid-point of the muscle belly on the anterior surface of the arm, while the G2 (reference) electrode was placed over the biceps brachii tendon in the cubital fossa for all patients. For recording of CMAP responses over the triceps brachii muscle, the G1 (active) electrode placed over the long head of the muscle, while The G2 (reference) electrode was placed over the olecranon point. The surface ground electrode was placed over the tendon insertion point of the ipsilateral deltoid muscle.

The split-elbow index was derived by dividing the CMAP amplitude recorded over the biceps brachii by the CMAP amplitude of the triceps brachii muscle, as follows:

$$\text{SEI} = \text{CMAP amplitude}_{\text{BICEPS BRACHII}} / \text{CMAP amplitude}_{\text{TRICEPS BRACHII}}$$

2.3. Statistical analysis

The Shapiro-Wilk test was used to assess for data normality. For normally distributed data a Student's *t*-test was used to assess for statistical difference; for data that was not normally distributed the Mann-Whitney *U* test was used for analysis. Pearson's correlation coefficient or Spearman's rho (non-parametric data) were used to examine association between parameters. Receiver operator characteristic (ROC) curves were used to determine the diagnostic utility of the SEI. A probability (*P*) value of <0.05 was considered statistically significant. The results are expressed as mean ± standard error of the mean, or median (interquartile range; IQR).

3. Results

3.1. Clinical features

In total, 34 ALS (18 males, 16 females; mean 65 years, range 39 to 83) and 32 ALS mimics (22 males, 10 females; mean age 60 years, range 22 to 90) patients were recruited. Spinal (or limb) onset disease was evident in 74% and bulbar onset in 26% of ALS patients. Fifty percent of ALS patients were diagnosed as Awaji definite/probable and 50% as Awaji possible ALS. In ALS patients, median disease duration from symptoms onset was 10.6 months (7–18), with a mild-to-moderate degree of functional disability evident as indicated by a median ALSFRS-R score of 41 (38–44) and median total MRC score of 79 (71–87). Additionally, the median rate of disease progression was 0.38 (0.21–1.21), in keeping with a moderate rate of functional decline (Labra et al., 2016). The median disease duration in ALS mimics was 70 months (56–77). In addition, the median total MRC score of ALS mimics was 85 (82–87).

In 68 ALS patient limbs and 64 ALS mimic patient limbs, comparisons were undertaken between the MRC score for elbow flexion and elbow extension. In ALS patients, weakness of elbow flexion was significantly more common (29% of limbs) when compared to ALS mimic patients (8% of limbs, $\chi^2 = 10.02$, $P < 0.01$, Fig. 1). Elbow flexion MRC scores were significantly lower when compared to elbow extension in ALS patients ($P = 0.017$). In con-

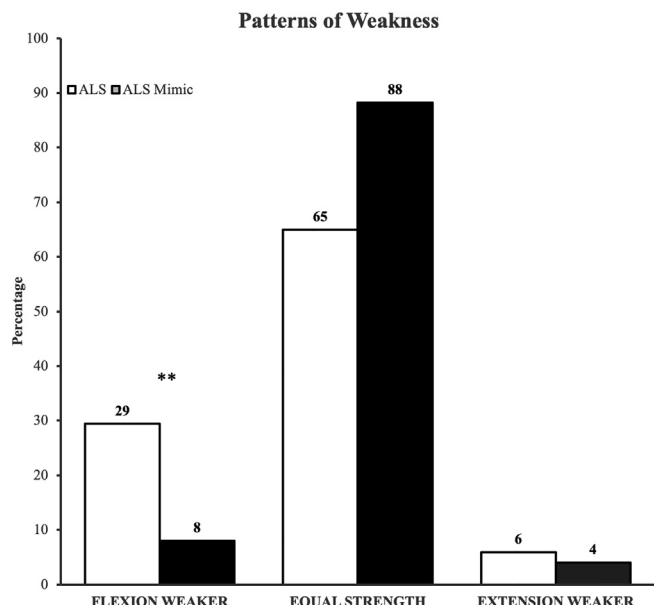


Fig. 1. The split elbow pattern (weakness of elbow flexion) was significantly more common in ALS patient limbs (29%) compared to ALS mimics (7%). Predominant weakness of elbow extension was not significantly different between ALS (6%) and ALS mimic (4%) patient limbs. **P < 0.01.

trast, elbow flexion and extension MRC scores were comparable in ALS mimics (P = 0.24). The frequency of equal elbow flexion and extension MRC scores was significantly less in ALS patients (65%) when compared to ALS mimics limbs (88%, $\chi^2 = 9.33$, P < 0.01). Furthermore, elbow flexion strength was preserved (MRC grade 5) in 63% of ALS patient limbs and 78% of ALS mimic limbs. Preservation of elbow extension strength was evident in 78% of ALS patient limbs and 81% of ALS mimic limbs. There was no significant difference in the frequency of predominant elbow extension weakness ($\chi^2 = 0.09$, P = 0.76).

3.2. Neurophysiological features

Having established that the split elbow sign was more frequent in ALS patients, the degree of preferential dysfunction was quantified by neurophysiological studies. The CMAP amplitude recorded over the biceps brachii muscles were comparable between in ALS patients and ALS mimics. In addition, the triceps brachii CMAP amplitudes were comparable between ALS patients and ALS when recorded over the triceps muscle (Table 1). There were no significant differences in distal motor onset latencies between the ALS and ALS mimics.

A novel split elbow index was subsequently calculated to quantify the degree of preferential muscle atrophy. There was a significant reduction of SEI in ALS when compared to ALS mimics (Table 1, Fig. 2). Sub-group analysis revealed that in spinal-onset patients, there was a significant reduction in SEI when compared to ALS mimics. Additionally, SEI was significantly reduced in bulbar onset ALS when compared to ALS mimics. In contrast, the reduction in SEI was comparable between spinal and bulbar onset ALS patients (P = 0.44).

The SEI was also significantly reduced in the onset and contralateral limbs when compared to ALS mimics. Of further relevance, the SEI was not influenced by hand dominance, being reduced in both the dominant and non-dominant limbs in ALS patients when compared to ALS mimics (Table 1).

Table 1

	CMAP Amplitude (mV)		SEI
	Biceps	Triceps	
ALS	5.7 ± 0.3	10.7 ± 0.6	0.51 (0.43–0.66)
ALS mimics	6.3 ± 0.4 (P = 0.17)*	9.4 ± 0.7 (P = 0.12)*	0.73 (0.44–1.05) (P < 0.01)*
<i>ALS Subgroups</i>			
Spinal	5.57 ± 0.4 (P = 0.20)**	11.28 ± 1.13 (P = 0.94)**	0.52, (0.44–0.66) (P < 0.01)**
Bulbar	5.62 ± 0.42 (P = 0.30)**	10.51 ± 0.65 (P = 0.96)**	0.49 (0.42–0.59) (P < 0.05)**
Onset Side	5.33 ± 0.54 (P = 0.11)**	9.97 ± 0.92 (P = 0.81)**	0.53 (0.44–0.63) (P < 0.05)**
Contralateral Side	6.23 ± 0.6 (P = 0.65)**	11.28 ± 1.03 (P = 0.95)**	0.55 (0.43–0.70) (P < 0.05)**
Dominant Hand	5.51 ± 0.43 (P = 0.22)**	11.03 ± 0.79 (P = 0.98)**	0.51 (0.43–0.59) (P < 0.01)**
Non-dominant Hand	5.66 ± 0.46 (P = 0.23)**	10.41 ± 0.8 (P = 0.89)**	0.50 (0.44–0.70) (P < 0.05)**
ALS FRS < 38	5.76 ± 0.83 (P = 0.52)**	8.43 ± 1.4 (P = 0.68)**	0.79 (0.56–0.84) (P < 0.01)**
ALS FRS ≥ 38	5.5 ± 0.35 (P = 0.33)**	10.95 ± 0.61 (P = 0.03)**	0.49 (0.42–0.6) (P < 0.01)**

Biceps Brachii and Triceps Brachii Compound Muscle Action Potential (CMAP) and the resultant Split Elbow Index (SEI) for all ALS patients and ALS subgroups, compared to ALS mimics. *All ALS patients compared to ALS mimicking disorders. **ALS subgroups compared to ALS mimicking disorders.

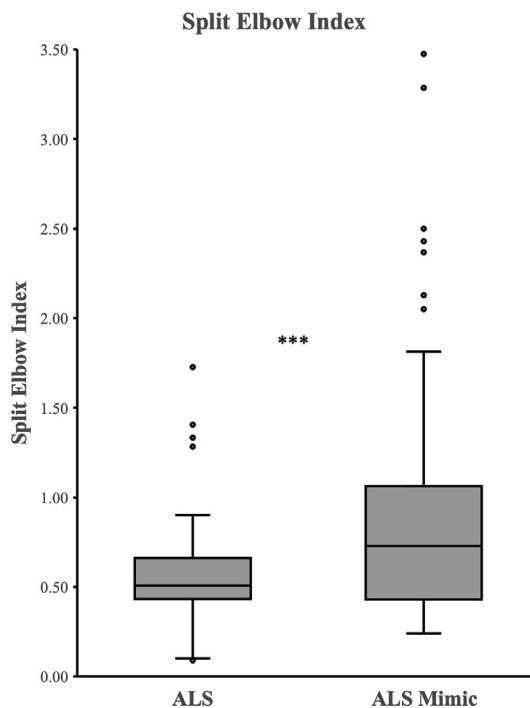


Fig. 2. The split-elbow index (SEI) was significantly reduced in patients with amyotrophic lateral sclerosis (ALS) when compared to ALS mimic patients. ***P < 0.001.

Sub-group analysis disclosed a significant reduction of SEI in ALS patients exhibiting a milder function deficit (ALSFRS-R_{score} ≥ 38) compared to ALS mimics (Table 1), suggesting that the split elbow phenomenon may be an early feature in ALS. In contrast, there was no significant difference in between ALS patients with greater functional deficits (ALSFRS-R_{score} < 38) and ALS mimics (Table 1). Additionally, SEI was significantly reduced in ALS patients with shorter and longer disease durations when compared to ALS mimics (Table 1).

In order to determine the diagnostic utility of the split-elbow index, analysis of ROC curve analysis was undertaken. The area under the curve (AUC) was 0.65 (95%CI, 0.55 to 0.75, $P = 0.004$), suggesting an acceptable level diagnostic utility for SEI in differentiating ALS from mimicking disorders. A cut-off value of ≤ 0.62 exhibited a sensitivity of 71% and specificity of 61%.

4. Discussion

In this prospective study, incorporating 66 patients (34 ALS and 32 ALS mimics), the split elbow sign was established as a clinical feature of ALS and quantified with a novel split elbow index. The split elbow index was significantly reduced in ALS patients when compared to ALS mimics, being evident in both spinal and bulbar onset patients. Additionally, the reduction of SEI appeared to be an early feature in ALS, and was more prominent in patient with less functional disability as defined by the ALSFRS-R. At a diagnostic level, the SEI was of moderate utility in differentiating ALS from mimicking disorders. Taken together, these findings support the presence of dissociated muscle atrophy in ALS, and the pathophysiological implications of these findings are discussed.

4.1. Split elbow sign and ALS

Prior to undertaking a detailed discussion on the utility of the SEI in ALS, it was imperative to establish that the split elbow sign was a clinical feature in the current ALS cohort. Previous studies have reported conflicting results regarding the presence of the split elbow sign in ALS. Khalaf and colleagues (Khalaf et al., 2019) reported that the split elbow sign was feature of ALS, clinically characterised by preferential weakness of biceps brachii muscle when compared to the triceps. Specifically, Medical Research Council (MRC) scores determined from the biceps brachii were significantly smaller when compared to triceps MRC scores, and the frequency of preferential biceps brachii weakness was significantly greater when compared to triceps muscle weakness. These findings were corroborated by a subsequent study demonstrating a greater propensity for elbow flexion weakness in ALS patients when compared to the elbow extensors (Ludolph et al., 2020). In contrast, the split elbow sign was not reported to be a clinical feature in a cohort of ALS patients from Asia (Liu et al., 2021).

The present study re-affirmed that the split elbow sign was a clinical feature of ALS and extended previous observations by demonstrating that the sign was significantly less common in ALS mimicking disorders. Clinically, the split elbow sign was characterised by significantly lower MRC scores for the biceps brachii when compared to triceps muscle in ALS patients, but not ALS mimics. Given that most of the ALS patients in the present study were Caucasian, it could be argued that the split elbow sign is a specific feature for this racial group although future studies are required to confirm this notion.

4.2. Split elbow index in ALS

Having established that the split elbow sign as a specific clinical feature in the current ALS cohort, neurophysiological studies were undertaken to quantify the split elbow phenomenon. A novel split elbow index was developed, whereby the CMAP amplitude recorded from the biceps brachii muscle was expressed as a fraction of the CMAP amplitude recorded from the triceps. The SEI was significantly reduced in ALS patients when compared to pathological controls. A comparable reduction in SEI was evident in spinal and bulbar onset patients, suggesting that the split elbow phenomenon may be evident in different ALS phenotypes. In con-

trast, abnormalities of SEI were comparable between the dominant and non-dominant limbs, arguing against a significant effect of hand dominance.

A potential limitation of this study relates to submaximal stimulation at Erb's point and volume conduction from neighbouring muscles. Specifically, Erb's point stimulation is subject to submaximal stimulation which could potentially impact the CMAP amplitudes recorded over biceps brachii and triceps brachii. Additionally, volume conduction from inadvertently stimulated neighbouring muscles could potentially impact the CMAP amplitude. Taken together these limitations could account for the modest diagnostic utility of SEI in ALS. Although no significant difference in triceps brachii CMAP amplitude was evident between ALS and ALS mimicking patients, the discussed limitations may account for the larger mean triceps brachii CMAP amplitude observed in ALS patients.

The area under the curve 0.65 (considered a fair test), with optimal diagnostic cut off value of ≤ 0.62 exhibited a sensitivity of 72% and specificity of 62%. Importantly, the findings suggest that SEI is of limited diagnostic value when compared to other biomarkers of lower motor neurone loss in ALS (Corcia et al., 2021, Kalita et al., 2017, Kim et al., 2016, Kuwabara et al., 2008, Menon et al., 2014a, Wang et al., 2020). Separately, the use of neurophysiological measures such as the motor unit number index (MUNIX), rather than CMAP amplitudes to calculate the split hand index, were shown to exhibit greater diagnostic utility in ALS (Kim et al., 2016). Future studies should address whether MUNIX based SEIs, exhibit greater diagnostic utility.

At a pathophysiological level, the mechanisms underlying the development of the split elbow phenomenon remain to be fully elucidated, although a cortical mechanism has been previously proposed (Khalaf et al., 2019, Ludolph et al., 2020, Vucic, 2019). The *dying forward hypothesis* has been proposed as a potential pathogenic mechanism in ALS, whereby corticomotoneuronal hyperexcitability was postulated to mediated neurodegeneration via an anterograde glutaminergic mechanism (Eisen et al., 1992). Cortical hyperexcitability has been identified as an early and intrinsic feature of ALS (Stefan et al., 2001, Vucic and Kiernan, 2006, Vucic and Kiernan, 2008, Vucic et al., 2008, Zanette et al., 2002), correlating with motor neurodegeneration (Vucic and Kiernan, 2006) and patterns of disease spread (Dharmadasa et al., 2020, Menon et al., 2017), as well as underlying the development of the split hand phenomenon (Menon et al., 2014b). Of relevance to the split elbow phenomenon, electrophysiological studies in non-human primates have established strong corticomotoneuronal (CM) projection to the biceps brachii muscle (Clough et al., 1968, Lemon, 2008, Maier et al., 1998, McKiernan et al., 1998). In human subjects, transcranial magnetic stimulation (TMS) studies have established a greater density of CM inputs to the biceps brachii muscle when compared to the triceps muscle (Neige et al., 2017). Given the greater cortical representation of the biceps brachii muscle, the possibility of cortical hyperexcitability underlying the development of the split elbow sign in ALS is attractive.

Alternatively, peripheral mechanisms for development of the split elbow sign are not discounted. Upregulation persistent Na^+ conductance, leading to axonal hyperexcitability, has been proposed as a potential pathogenic mechanism for the split hand sign in ALS (Shibuya et al., 2013). Additionally, greater physiological dysfunction at the neuromuscular junction, as well as specific metabolic abnormalities at the spinal motor neuron level, have also been invoked as potential mechanisms for development of the split hand sign in ALS (de Carvalho and Swash, 2019, Kuwabara et al., 2008). In order to dissect out the relative contribution of central and peripheral mechanisms in development of the split elbow phe-

nomenon, future studies should assess the entire neuroaxis utilising cortical and peripheral nerve studies. Resolution of this issue may have broader implications for the understanding of ALS pathogenesis.

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