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Subclinical involvement of small hand muscles in early amyotrophic lateral sclerosis: Selective susceptibility leads to 'split hand' phenomenon

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ABSTRACT

Objectives: Split-hand phenomenon is common in patients with amyotrophic lateral sclerosis (ALS), but it is unknown if first dorsal interosseous (FDI) and abductor pollicis brevis (ABP) are affected earlier than abductor digiti minimi (ADM). We aimed to address this issue.
Methods: One clinically normal hand from ALS patients was investigated, including needle EMG of the FDI, motor amplitude, distal latency, F-waves, neurophysiological index (NI) and split-hand index (SHI). Hands were categorised as G1 (normal FDI) and G2 (FDI with neurogenic changes). In patients who agreed EMG of the 3 muscles was done. A subset of G1 patients underwent a second evaluation 4–5 months later.
Results: We studied 133 patients; EMG of the 3 muscles was done in 77 patients. There was no evidence for an earlier loss of motor units in FDI/ABP. In G2 patients, CMAP amplitude and NI were significantly lower ($p < 0.001$), but ADM changes were minor. Reassessment of G1 patients confirmed significant SHI, and amplitude and NI decrease in all muscles, but F-waves frequency remained stable in ADM.
Conclusions: Loss of motor units in the 3 hand muscles began in parallel, but ADM spinal motoneurons showed stronger resistance to degeneration.
Significance: Dysfunction of intrinsic spinal circuits can influence split-hand phenomenon.

1. Introduction

More marked atrophy of thenar muscles than of hypothenar muscles in ALS was first described by Wilbourn (Wilbourn and Sweeney, 1994; Wilbourn, 2000) and has been confirmed subsequently by many other clinicians (Corcia et al., 2021). The pathophysiological mechanism for this phenomenon is uncertain, but differences in the pattern of cortical representation of thenar and hypothenar muscles have achieved prominence in the literature as a possible causative factor (Weber et al.,2000; Bae et al., 2014), leading to a corticomotoneuronal hypothesis for generation of the ALS syndrome. Differing functions between these muscle groups in neuromuscular activities have also been considered, but comparison with susceptibility studies of other muscles in ALS does not support this (Corcia et al., 2021). Specific biological features of these small hand muscles could also be relevant, and we have previously reported that in ALS patients with clinically normal hands neuromuscular junction stability in abductor digiti minimi (ADM) was greater than in abductor pollicis brevis (APB) and first dorsal interosseus (FDI) (De Carvalho and Swash, 2019). In addition, the APB is more dependent on T1 innervation than the ADM and FDI (Levin et al., 1996), which may contribute to the varied susceptibility of hand muscles in ALS.

The split hand phenomenon has been defined using several different indices, or ratios. The most frequently applied uses surface recordings for the formula: APB amplitude x FDI amplitude/ADM amplitude (Menon et al., 2014). A cutoff value for this ratio of 5.2 was suggested, although this did not take account for the effect of increasing age. The specificity of the split hand phenomenon for ALS has remained puzzling but, in particular, the timing of onset of neurogenic changes in these two muscle groups, and the rate of change have not been determined. For example, it is not known whether the phenomenon develops due to earlier onset of denervation or differing rates of neurogenic change in these three muscles. Their peripheral nerve supply involves both ulnar (FDI and ADM) and median nerves (APB), a feature that led earlier investigators to consider cortical factors (Corcia et al., 2021). The differing properties of motor units in the muscles of the human body have not been studied in detail (Duchateau and Enoka, 2022); although, Stålberg

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and Trontelj (1979) provided some early data on differences in neuromuscular jitter in different muscles in normal subjects, they did not investigate small hand muscles. Nonetheless, it is probable that there are important biological differences in spinal motor neurons behaviour that could be relevant in differential susceptibility of muscles to the degenerative process of ALS. We have therefore addressed these questions in very early affected hands of patients diagnosed with ALS.

2. Material and Methods

Subjects.

Patients with ALS were recruited consecutively at their first diagnostic EMG in Lisbon or, in patients referred for a second opinion. The inclusion criteria were ALS diagnosed according to the Gold Coast recommendations (Shefner et al., 2020). The diagnosis that was ultimately confirmed by clinical follow-up. A second requirement was that in these patients the studied hand was at that time clinically normal, regarding absence of muscle atrophy and of small hand muscle weakness. The occurrence or absence of fasciculations in these muscles was not considered relevant for the investigation.

Patients were excluded from the investigation if they had an active history, past history or family history of polyneuropathy, cervical root lesions or cervical myelopathy, diabetes mellitus, or other neurological or muscular disorder. Those with neuromuscular abnormalities found at the diagnostic EMG, such as carpal tunnel syndrome or ulnar neuropathy, were also excluded. Since we had no normative values for subjects older than 80 years, only subjects younger than 80 years were included. In order to exclude subjects with slowly progressive disease, we restricted the study to subjects with a disease duration of $\leq$ 24 months. In each subject only one hand, the clinically normal hand, was studied. If both hands were clinically normal, for convenience we selected the right for study.

All the patients were clinically evaluated at diagnosis using the ALS Functional Rating Scale-Revised (Cedarbaum et al.,1999). A second assessment was made 4–9 months after the initial evaluation and the monthly progression rate was calculated as 1st evaluation-second evaluation/number of elapsed months.

Electrophysiological studies.

The investigation was centred on the APB, FDI and ADM muscles and their innervation. Median and ulnar nerves were stimulated at the wrist and active recording electrodes were placed 7cms distally overlying the APB and ADM muscles. When studying the FDI the stimulating electrode placement used was the same as that for ADM studies. The distance to the FDI muscle recording site cannot be accurately assessed for anatomical reasons.The recording electrode was moved over the studied muscle at least 3 times in order to ensure that a maximum amplitude response was recorded. In each of the three muscles we measured the CMAP amplitude peak-to-peak, and the distal motor latency. We recorded F-wave responses in each of the three muscles after 20 supramaximal nerve stimuli at 1 Hz, measuring F-wave frequency. We could then calculate the Neurophysiological Index (NI) from each nerve-muscle recording (Swash and De Carvalho, 2004; de Carvalho et al., 2005) and also the ALS split hand index (SHI) (Menon et al., 2013). Hand temperature was kept above 30 degrees Celsius.

In every studied hand, as part of the diagnostic work-up, a concentric needle EMG needle was introduced into the FDI muscle (a sensitive muscle selectively investigated in all ALS patients in our centre) and recordings made with the needle in different positions to search for early neurogenic changes in this muscle. Fasciculation potentials, fibrillation/positive sharp waves, unstable and reinnervated motor unit potentials were sought in these locations. In those patients who agreed to take part in the full investigation the same protocol was followed in the APB and ADM muscles. In small hand muscles it is not possible to acquire 20 or more MUPs for statistical study without undue discomfort, so MUP morphology, stability, and recruitment pattern and rate were studied qualitatively in mild contractions and also in full contraction.

Table 1
Comparison of clinical features in patients in G1 and G2.

	G1	G2	p value
Median age	63 (IQR 50-71y)	64 (IQR 57–71.75y)	0.24
Region of onset	B: 14 UL: 10 LL: 43 Resp/axial: 2	B: 21 UL: 8 LL: 32 Resp/axial: 3	0.75
El Escorial diagnostic category	Definite ALS: 1 Probable: 41 Possible: 10 PMA: 17	Definite: 5 Probable: 42 Possible: 7 PMA: 10	0.18
Disease duration	9 months IQR 6-18mo	10 months IQR 6-18mo	0.63
Functional decay/month	0.5units/month IQR 0.28–0.79	0.53units/month IQR 0.27–1.08	0.33

B-bulbar; UL-upper limb; LL-lower limb; Resp/axial-Respiratory or axial onset; IQR-interquartile range.

Table 2
EMG data in 77 patients with ALS in whom all three muscles of one hand were studied.

n = 77	FDI	APB	ADM	p value
Fibs/sw	15	10	4	0.03*
FPs	55	45	42	0.08
Neurogenic MUPs	45	49	54	0.32

FPs – fasciculation potentials; MUPs – motor unit potentials.
* p value refers to differences between all three muscles (Fisheŕs exact test). Comparing FDI and ADM p = 0.017.

The study protocol was approved by the Lisbon Academic Medical Centre Ethics Committee, and required written consent from each subject.

Statistics.

Categorical variables were compared with the Fisher's exact test. This information has been included in the table's footnote. For other comparisons we used non-parametric tests, the Mann-Whitney and Wilcoxon tests. A p value < 0.05 was considered significant. The data is presented here as median values and the first and third interquartile range (IQR).

3. Results

Clinical and Electrophysiological results.

We evaluated 133 patients with ALS, as defined above; 73 were men (55 %). The median age of these patients was 63 years (IQR 51.5–71 years). The median disease duration was 10 months ((IQR 6–18 months). In this whole group, bulbar- onset occurred in 35 patients (36.3 %), upper limb-onset in 18 patients (13.5 %), lower limb-onset in 75 patients (56.4 %) and respiratory/axial-onset in 5 patients (3.8 %). According to the revised El Escorial diagnostic criteria (Brooks et al., 2000) for diagnosis of ALS, 6 patients (4.5 %) had 'definite ALS', 83 (62.4 %) had 'probable ALS' and 'probable lab-supported ALŚ, and 17 (12.8 %) had 'possible ALS'. At diagnosis 27 (20.3 %) presented with the progressive muscle atrophy syndrome. The mean functional decay in the whole group in the ALSFRS data was 0.5 units (IQR 0.27–0.92).

Of these patients 69 (52 %) had a normal FDI in the studied hand and the remainder (48 %) had an abnormal FDI EMG study. These findings in FDI were used to categorise two groups, those with normal EMG findings in FDI (G1) and those with abnormal EMG features in FDI (G2). Comparison of clinical features in G1 and G2 (Table 1) revealed no significant differences. Of the 133 subjects with ALS, 77 (58 %) agreed to take part in the full research protocol. This required needle exploration of all three hand muscles in the studied hand (Table 2). In these 77 patients, fibs/sw were more frequent in the FDI, but not other difference was

Table 3
Motor nerve conduction results – expressed as medians.

FDI		Group 1	Group 2	p values
	CMAP amplitude	10.4 mV IQR 8.95–11.75	8.10 mV IQR 5.4–10.3	<0.001
	Distal motor latency	4.0 ms IQR 3.8–4.2	4.2 ms IQR 3.9–4.5	0.001
	F-wave frequency	95 % IQR 87.5–100	85 % IQR 70–95	<0.001
	Neurophysiological index	2.441 IQR 1.917–2.869	1.479 IQR 0.989–2.128	<0.001
APB				
	CMAP amplitude	7.0 mV IQR 5.7–8.55	5.25 mV IQR 4.13–6.38	<0.001
	Distal motor latency	3.7 ms IQR 3.55–4.0	3.95 ms IQR 3.7–4.2	0.07
	F-wave frequency	90 % IQR 70–95	60 % IQR 40–80	<0.001
	Neurophysiological index	1.575 IQR 1.05–1.97	0.818 IQR 0.481–1.211	<0.001
ADM				
	CMAP amplitude	7.8 mV IQR 6.8–8.75	7.2 mV IQR 5.75–7.88	0.003
	Distal motor latency	2.90 ms IQR 2.8–3.15	3.0 ms IQR 2.7–3.3	0.42
	F-wave frequency	100 % IQR 97.5–100	95 % IQR 85–100	<0.001
	Neurophysiological index	2.555 IQR 2.309–2.983	2.006 IQR 9.662–2.612	<0.001

The neurophysiological index (NI) is calculated using the formula:
CMAP peak to peak amplitude x F-wave frequency/distal motor latency.
For this calculation the F-wave frequency was expressed as a percentage of positive trials, in 20 trial recordings; this was assigned the numeral 1 for 100% responses and 0.9 for 18/20 responses etc.

found, in particular regarding MUPs analysis (Table 2). In 32 of these 77 patients, in whom the FDI was normal, classified as G1, we compared the clinical and EMG data from APB and ADM. None of the muscles studied in these patients showed fibs/sw, but FPs were present in 20 APB muscles and 15 ADM muscles ($p = 0.21$); and neurogenic changes were found in 10 APB and 10 ADM muscles. In the 45 patients with ALS in whom the FDI was abnormal, in G2, fibs/sw were found in 9 APB and 4 in ADM ($p = 0.023$) and FPs were recorded in 28 and 27 APB and ADM muscles. Abnormal MUPs were found in 38 APB and 40 ADM muscles ($p = 0.78$).

The data from the nerve conduction studies at the first examination are presented in Table 3. The CMAP amplitude, F-wave frequency and the NI were markedly different in the muscles studied between G1 and G2. The CMAP amplitudes was 25 % less in APB, 22 % less in FDI but only 7.7 % less in ADM. The NI was 48 % less in G2 than G1 for APB; 39.4 % for FDI and 21.5 % for ADM. The NI reflects changes in CMAP, DML and F-wave frequency, explaining its marked sensitivity (Fig. 1). The normative data for age in our lab of these hand muscles are published (Silva et al., 2023). Regarding APB 15.9 % of patients in G1 and 53.1 % in G2 had an abnormal CMAP amplitude. The NI was abnormal in 29 % of patients in G1, but in 73.4 % in the G2 group. In the APB muscle in G2 patients the NI was more sensitive as an abnormal test result than CMAP amplitude ($p = 0.028$). Concerning FDI, in G1 18.8 % showed an abnormal CMAP amplitude, but in G2 46.9 % were abnormal. The FDI NI was abnormal in 30 % of the patients in G1 patients, but 73 % in G2, consistent with the greater sensitivity to change ($p = 0.004$). In ADM the amplitude was abnormal in 5.8 % in G1, increasing to 23.4 % in G2. The NI was abnormal in 23.5 % in G1 and 42.2 % in G2, again showing the greater sensitivity of this technique in assessing change ($p = 0.04$).

Split hand phenomenon

We considered our data using first our normative data corrected for age (Claudia et al., 2023) and then the normative data of Menon et al. (2013), which defined a SHI < 5.2 as abnormal. We found a median split hand index of 8.92 (IQR 7.22–11.31) in G1 and 5.96 (IQR 3.91–7.58) in G2, a difference which was highly significant ($p < 0.001$). Using the 5.2 cutoff value, we found that 2 patients in G1 and 21 in G2 were abnormal but, using our age-related correction, we detected 7 patients with abnormal results in G1 and 38 in G2. We therefore found that by using age-related data more abnormal results were detected in G2 than using the conventional limit ($p = 0.005$).

Longitudinal changes.

It was possible to re-evaluate a subgroup of 25 patients from G1, 4–5 months later. The baseline values were very similar to those observed in the whole G1 group, and follow-up results very close to those observed

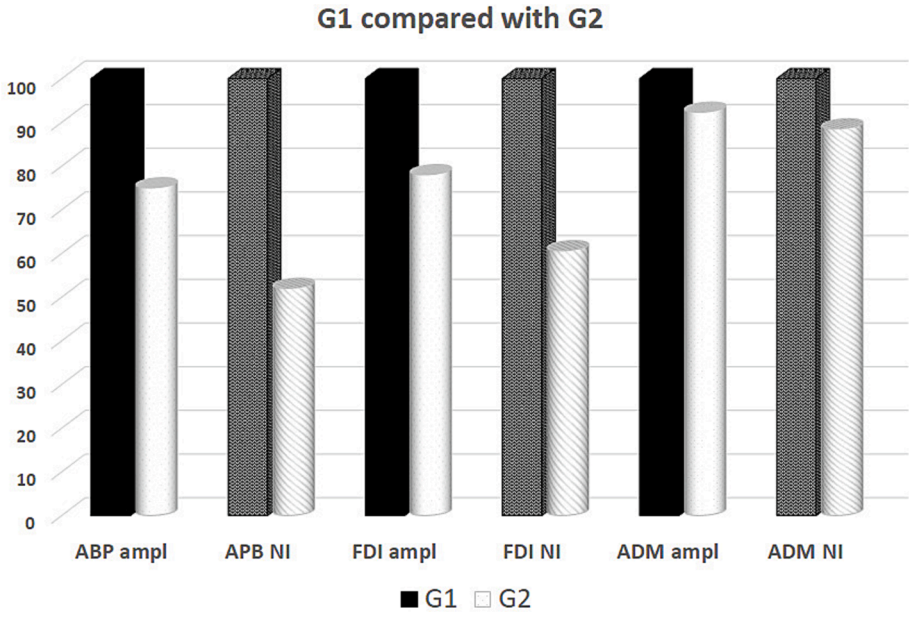

Fig. 1. Comparison between G1 (hands with normal EMG) and G2 (hands with minor EMG changes) Footnote: In G1, values for CMAP amplitude (black) and NI (dark grey) were significantly higher compared with G2 (light grey) ($p < 0.001$), but difference was greater for NI.

Table 4
Motor nerve conduction results (expressed as median values) in G1 baseline and at follow-up.

FDI		G1 baseline	G1 follow-up	p values
	CMAP amplitude	11.1 mV IQR 9.25–13.75	7.4 mV IQR 4.7–10.95	<0.001
	Distal motor latency	3.9 ms IQR 3.75–4.1	4.1 ms IQR 3.8–4.4	0.001
	F-wave frequency	95 % IQR 85–100	90 % IQR 60–100	0.03
	Neurophysiological index	2.484 IQR 2.14–3.117	1.510 IQR 0.625–2.545	<0.001
APB				
	CMAP amplitude	7.0 mV IQR 5.7–8.55	5.50 mV IQR 4.75–6.30	<0.001
	Distal motor latency	3.7 ms IQR 3.45–4.0	4.0 ms IQR 3.55–4.35	0.03
	F-wave frequency	85 % IQR 60–95	75 % IQR 30–95	0.03
	Neurophysiological index	1.428 IQR 1.086–1.788	0.950 IQR 0.265–1.640	0.001
ADM				
	CMAP amplitude	7.7 mV IQR 6.65–8.2	6.3 mV IQR 5.45–7.15	0.003
	Distal motor latency	2.8 ms IQR 2.7–2.9	2.9 ms IQR 2.7–3.3	0.045
	F-wave frequency	100 % IQR 95–100	100 % IQR 85–100	0.10
	Neurophysiological index	2.630 IQR 2.285–3.036	2.050 IQR 1.425–2.645	<0.001
SHI		10.17 IQR 7.595–13.65	5.90 IQR 3.965–8.28	<0.001

G1 – patients with normal FDI needle EMG; G1 – follow-up – patients revaluated 4–5 months later;
FDI – first dorsal interosseous; APB – abductor pollicis brevis; ADM – abductor digiti minimi;
IQR- 1st- 3rd interquartile range; Amplitude is expressed as peak-to-baseline;
SHI- split-hand index.
The neurophysiological index (NI) is calculated using the formula:
CMAP amplitude x F-wave frequency/distal motor latency.
For this calculation the F-wave frequency was expressed as a percentage of positive trials, in 20 trial recordings; this was assigned the numeral 1 for 100% responses and 0.9 for 18/20 responses etc.

in G2 (Table 4). All measurements changed significantly, in particular CMAP amplitude, NI and SHI ($p \leq 0.001$). However, F-wave frequency from ADM did not decline significantly.

4. Discussion

The two groups we have defined for study (G1 and G2) were clinically similar, being defined by electrophysiological criteria (see Table 1). In our observations, in both groups ADM was affected in parallel with the other small hand muscles; i.e., FDI and APB. However, fibs/sw were less frequent in ADM and APB than in FDI. It is possible that this reflects the longer course of the deep branch innervating FDI, associated with more axonal branching and tapering (Trojaborg, 1964). Cappellari et al. (1999) found that, in general, more distal muscles in ALS showed more prominent fib/sw than more proximal muscles, indicating an effect of axonal length and Wallerian degeneration in the disease. In addition, our results support that FPs antedate other muscle changes in early affected muscles of ALS patients, as described elsewhere (De Carvalho and Swash, 2013).

We found that the CMAP amplitude was reduced (Table 3) in all three muscles in mildly affected hands (G2) but unaffected in G1. The reduction in amplitude was greater in APB (25 %) and FDI (22 %) than in ADM (7.7 %). The F-wave frequency was significantly reduced in G2 patients compared to those in G1 (Table 3), although the F-wave frequency was always greater in ADM than in the other two muscles. The NI was much more reduced in G2 patients (APB 48 %; FDI 39 %; ADM 21.5 %) than in those in G1 (Table 3), and in G2 this was a more sensitive feature than amplitude measurements. This derived from a combination of reduced CMAP amplitudes and reduced F-wave frequency. Longitudinal data confirmed significant changes in all measurements, in particular for amplitude, NI and SHI, but ADM F-wave frequency did not decrease significantly.

The reduced F-wave frequency probably resulted from disruption of excitatory synaptic transmission in spinal microcircuits, interfering with backfiring induced by antidromic stimulation of anterior horn cells (Özyurt et al.,2024).It has been been shown that F-waves are derived especially from larger, fast motor units innervated by fast-conducting axons (Guiloff and Modarres-Sadeghi, 1991; Dengler et al., 1992). However, other researchers do not favor a selective activation of motor units in the F response (Kimura et al., 1984; Thomas et al., 2002). Recent studies suggest that F-waves from ADM are more excitable than the ones from other hand muscles in healthy subjects (Li, 2024; Lopes, 2024), these findings can implicate different spinal motor neurons properties in the ADM pool.

SHI proved to be a sensitive measuring to detect early changes in hand muscles, but in this study, it was proved the convenience of using age-corrected normal values for increasing sensitivity (Pechirra et al.,2022; Silva et al., 2023).

A major limitation of this study is the inability to perform quantitative MUP analysis in the 3 muscles due to patient intolerance. However, assessment of spontaneous activity, MUP morphology, stability, and recruitment patterns during contraction is a more sensitive and reliable method for detecting early changes than estimating the number of motor units using any other technique, as recently confirmed in a study (Vacchiano et al., 2024).

A cortical drive originating earlier ABP and FDI spinal motor neuron degeneration is not supported by our findings. It seems that the 3 muscles start losing motor neurons in parallel but ADM spinal motor neurons are more resistant to degeneration, as supported by slower CMAP and NI decay and higher number of F-responses. There is no evidence for a higher number of motor units in ADM than in other hand muscles (Sica et al., 1974; Higashihara et al., 2020). Moreover, the proportion of type II fibers is not higher in ADM; in fact, there is a trend toward a higher proportion in FDI and APB (Polgar et al., 1973).

We propose that a group of hyperexcitable type II spinal motor neurons innervating the ADM are more resilient in ALS, which can be related to a hypothetical lower loss of inhibitory V1 interneurons in this neuron pool (Allodi et al., 2021), further supporting ALS as an interneuropathy (Stephens et al.,2006; Castro et al., 2023).

We conclude that split-hand in ALS derives from different mechanisms, and that spinal motor neuron properties play a critical role.

Author Contribution Statement.

M. de C. is responsible for conception, design, acquisition, analysis, interpretation of data, and manuscript draft.

M.O. S. is responsible for acquisition of data and manuscript revision.

M.S is responsible for interpretation of data and manuscript revision.

All authors reviewed the manuscript and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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