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SHORT COMMUNICATION

Exploring the split hand phenomenon with the neurophysiological index

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Abstract In 164 subjects of different age groups, we studied the neurophysiological index (NI) ([CMAP amplitude/Distal motor latency] *[F-wave frequency]; CMAP=compound muscle action potential) for three hand muscles (APB= abductor pollicis brevis; FDI= first dorsal interosseous; ADM= abductor digiti minimi). A split hand index based on CMAP amplitude (SHI_CMAP) and NI (SHI_NI) were calculated ([APB CMAP amplitude or NI * FDI CMAP amplitude or NI]/[ADM CMAP amplitude or NI]). All these neurophysiological measurements differed between age groups ($p<0.001$). Hand muscle NIs, as well as SHI_NI and SHI_CMAP were age dependent. This may be relevant for diagnostic purposes in motor neuron diseases.

Introduction

A dissociated pattern of muscle atrophy is described in small hand muscles in amyotrophic lateral sclerosis (ALS), consisting of pronounced atrophy of thenar eminence muscles with relative preservation of hypothenar muscles; known as the split hand phenomenon, first described by Wilbourn [1,2]. Although its full pathophysiology it is still not fully elucidated, it is present in up to 40% of ALS patients, including in the early stages [3], which is useful in ALS diagnosis. The split hand index (SHI), first described by Menon and co-workers, quantifies this phenomenon [4]. It is derived from amplitudes of the compound muscle action potentials (CMAP) of the abductor pollicis brevis (APB), abductor digiti minimi (ADM) and first dorsal interosseous (FDI) muscles following median and ulnar nerve stimulation at the wrist (SHI= ([APB CMAP amplitude * FDI CMAP amplitude]/[ADM CMAP amplitude]) [4]. SHI can be useful for distinguishing ALS from mimic disorders, such as neuropathies and cervical spondylotic amyotrophy, with a reported sensitivity of 81% and a specificity of 82% [5,4]. In a recent paper we studied the influence of age on the SHI in a large population of control subjects and demonstrated that SHI is strongly age dependent [6], an aspect that has been neglected in

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considerations of its possible pathophysiological significance in ALS. The neurophysiological index (NI) was first proposed in 2000 by de Carvalho and Swash [7], who observed that motor amplitude of the ADM muscle and its F-waves frequency decreased in parallel with progressive muscle weakness, while its distal latency increased. It is derived from CMAP amplitude but includes also distal motor latency (DML) and F-wave frequency (NI= [CMAP amplitude/DML] * [F-wave frequency]). It seems to be more sensitive in detecting disease progression in ALS than CMAP amplitude changes alone [8]. However, the influence of age on NI is unknown. Therefore, is our aim with this study to elucidate it. The split-hand index could be calculated using the neurophysiological index of each studied hand muscle (SHI_NI = [APB NI * FDI NI]/ [ADM NI]), as well as from the CMAPs (SHI_CMAP = [APB CMAP amplitude * FDI CMAP amplitude]/ [ADM CMAP amplitude]). Given this, we report the effect of age on the NI and on the SHI calculated from NI data (SHI_NI), compared to SHI calculated from CMAPs (SHI_CMAP).

Methods

We retrospectively analyzed data consecutively collected between 2018 and 2022 from adult subjects ($\geq$ 18 years old) who had been referred to our neurophysiology lab by neuro-ophthalmologists or neurologists for neurophysiological investigation to exclude the remote possibility of an ocular myasthenia gravis. All had normal nerve conduction studies, repetitive nerve stimulation and single-fiber electromyography. The final diagnosis was of various unrelated medical or ophthalmologic conditions rather neuromuscular disease.

For nerve conduction studies, supramaximal stimulation was applied to the right median and ulnar nerves using bipolar surface electrodes with the cathode 7 cm proximal to the active recording electrode (20 $\times$ 15 mm) that was placed over the motor endplate. The position of the stimulator on the ulnar nerve was kept constant for FDI and ADM studies. Reference electrodes were placed over the proximal interphalangeal joint of the fifth finger for the ADM, or the thumb interphalangeal joint for APB and FDI (Supplemental Figure 1). The site of the active electrode was adjusted at least three times on each muscle to ensure maximal motor amplitude. Muscle relaxation was controlled by the device loudspeaker. We measured the baseline-to-peak CMAP amplitude of the largest motor response (filter setting, 20 Hz−10 kHz), DML and F-wave frequency (20 stimuli) for ABP, FDI and ADM. Skin temperature was maintained >32 °C at the target muscle. The Natus-EMG Keypoint-NET equipment (Natus Medical Inc., Pleasanton, CA) was used for recording and analysis. The same neurophysiologist performed all tests (MdC).

The NI was calculated for each of the 3 muscles, according to the following formula:

$$\left(\frac{\text{CMAP amplitude}}{\text{DML}}\right) * F - \text{wave Frequency (20 stimuli)}$$

SHI was calculated, according to the standard formula:

$$\frac{\text{APB CMAP amplitude} * \text{FDI CMAP amplitude}}{\text{ADM CMAP amplitude}}$$

SHI based on NI (SHI_NI) for each muscle/nerve system was also calculated by substitution into the SHI formula.

Three age groups were defined in the subjects analyzed, using median and interquartile ranges (IQRs): first IQR (Q1), second and third IQR (Q2-Q3), fourth IQR (Q4). The 5th percentile of the data distribution was used to define the lower limit of normal for each age group. The CMAP amplitude and NI for APB and FDI did not follow a normal distribution (Shapiro- Wilk test). We applied the Mann−Whitney U test for comparing genders, Kruskal−Wallis one-way analysis of variance for comparing the three age groups and a post-hoc Dunn's test with Bonferroni correction for testing pair differences. Given the large size of the sample, Pearson correlation coefficient and linear regression were used for testing age-dependence of measurements. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software (version 26.0). A p-value < 0.005 was considered statistically significant.

The protocol was approved by the Institutional Ethics Committee and all participants provided informed consent.

Results

Complete data was available from 164 subjects (median age 56.0 years; IQR 41.0−72.8); 85 (52%) were women; 52 of

Table 1 Comparison of neurophysiological data between women and men.

	Total (n = 164)	Women (n = 85)	Men (n = 79)	p-value
Age	56.0 (41.0−72.8)	55.0 (40.0−72.0)	58.0 (41.0−73.0)	0.711
APB_CMAP amplitude	8.5 (7.0−10.0)	8.5 (6.9−10.0)	8.4 (7.2−9.8)	0.813
FDI_CMAP amplitude	11.9 (10.0−13.7)	11.1 (9.8−12.5)	12.6 (10.3−14.9)	**<0.001**
ADM_CMAP amplitude	8.2 (7.0−9.4)	8.2 (7.0−9.4)	8.2 (7.1−9.5)	0.954
APB_NI	2.3 (1.9−2.9)	2.3 (1.7−3.0)	2.2 (1.9−2.8)	0.421
FDI_NI	2.9 (2.4−3.5)	2.8 (2.4−3.4)	3.1 (2.6−3.7)	**0.041**
ADM_NI	3.0 (2.4−3.5)	3.1(2.4−3.5)	3.0 (2.4−3.4)	0.533
SHI_CMAP amplitude	12.0 (9.1−15.2)	11.4 (8.6−14.6)	12.2 (9.7−15.3)	0.156
SHI_NI	2.2 (1.6−3.1)	2.2 (1.6−3.1)	2.2 (1.7−3.1)	0.538

Data expressed as median (IQR). APB, abductor pollicis brevis; FDI, first dorsal interosseous; ADM, abductor digiti minimi; CMAP, compound muscle action potential; NI, neurophysiological index; SHI_amplitude, split-hand index (calculated using CMAP amplitude); SHI_NI, split-hand index (calculated using NI). Mann−Whitney U test. Significant values ($p < 0.005$) are shown in bold.

these were included in a previous study concerning age effect on SHI [6]. None was diagnosed with a neuromuscular condition during clinical follow-up. Overall, the median SHI_CMAP was 12.0 (IQR 9.1−15.2) and median SHI_NI was 2.2 (IQR 1.6−3.1).

Age and neurophysiological parameters were similar between genders, except FDI CMAP amplitude which was 12% higher in men (12.6 versus 11.1, $p<0.001$). FDI-NI was 10% higher in men (3.1 versus 2.8, $p = 0.041$), but this difference was not statistically significant (Table 1). Median values differed significantly between age groups for all the neurophysiological measurements ($p<0.001$) (Table 2). Only FDI and ADM CMAP amplitudes and NI were not significantly different between the youngest (Q1) and the intermediate (Q2-Q3) groups; regarding APB CMAP and NI, and for calculated SHI there was a statistically significant difference in all pair groups comparison (Supplemental Table 3). All parameters were strongly correlated with age (Supplemental Table 4). APB, FDI and ADM CMAP amplitudes decreased around 0.07, 0.05 and 0.03 mV/year, respectively. APB, FDI and ADM CMAP NI decreased by 0.03, 0.02 and 0.01, respectively. SHI_CMAP decreased 0.12/year (around 1.0%/year, considering median SHI=12.0); SHI_NI decreased 0.03/ year (around 1.4%/year, considering median SHI based on NI=2.2) (Supplemental Figures 2 and 3, respectively).

Discussion

Several methods have been proposed to quantify the progressive lower motor neuron loss in ALS, in particular CMAP amplitude, motor unit number estimation techniques and the NI. The latter has been confirmed as more sensitive than the CMAP amplitude and having a near-linear decay [9−11]. This index was proposed in 2000 by observing that CMAP amplitude and F-frequency decline in the weak hand of ALS patients, while distal motor latency increases in the same spinal segment used for F wave studies [7]. The main limitation of the method is that it cannot to be applied in proximal muscles and there is no data from distal lower limb muscles. The effect of age on CMAP amplitude is well known [12], resulting from a loss of functioning motor units [13], but age-related changes in NI have not been reported, although this is relevant for determining normative values. SHI_CMAP lower limit of normal has been defined [8] but without considering the subjects' ages, and we have previously demonstrated that SHI_CMAP is age-related [6].

The present study, with a uniform protocol, confirms that CMAP and SHI_CMAP are strongly age-dependent, and that this relationship holds true for NI and SHI_NI, as well. Moreover, this age influence is similar in CMAP studies and in NI studies. In addition, our results confirm that ADM is more resistant to this age-effect, as it is also in ALS, maybe due its greater reinnervation capacity, but the underlying cellular and neurophysiological mechanisms are unknown. There was no gender difference except for a small (about 10%) FDI CMAP amplitude and FDI difference, which we did not observe in our previous investigation, which was based on a different older population than our present work (total sample median age 61.5 vs 56.0 years old), [6]. Future studies should approach this issue.

The main limitation of our study is that our subjects were not healthy controls but patients with suspected myasthenia gravis, in whom this condition was excluded, and a non-neuromuscular disease was diagnosed. However, we cannot exclude the possibility that their clinical condition (in general ophthalmologic) could influence our results.

In summary, SHI, NI and SHI based on NI are all age dependent. These results support the importance of normative values in clinical neurophysiology that should always investigate the age effect, which seems universal.

Table 2 Comparison of neurophysiological data by age group, categorized as interquartile ranges (Q1-Q4).

	$Q1_{(\leq 40\ years)}$	$Q2\text{-}Q3_{(41-72\ years)}$	$Q4_{(\geq 73\ years)}$	p-value
APB CMAP amplitude	10.7 (9.5−12.0)	8.5 (7.0−9.5)	6.6 (5.8−7.7)	**<0.001**
LLN	7.70	5.78	3.95	
FDI CMAP amplitude	12.5 (11.0−15.0)	12.4 (10.5−14.3)	10.3 (8.8−12.0)	**<0.001**
LLN	9.00	8.10	7.22	
ADM CMAP amplitude	8.5 (7.2−10.0)	8.7 (7.1−10.7)	7.6 (6.5−8.0)	**<0.001**
LLN	6.30	5.85	5.21	
APB NI	3.1 (2.6−3.5)	2.3 (1.9−2.6)	1.6 (1.3−2.0)	**<0.001**
LLN	2.10	1.35	0.73	
FDI NI	3.2 (2.6−3.9)	2.9 (2.5−3.5)	2.5 (2.1−2.9)	**<0.001**
LLN	1.90	2.02	1.71	
ADM NI	3.2 (2.7−3.8)	3.1 (2.5−3.8)	2.5 (2.1−2.8)	**<0.001**
LLN	2.30	2.10	1.80	
SHI_amplitude	15.8 (11.4−20.4)	11.6 (9.2−14.1)	9.0 (7.2−11.4)	**<0.001**
LLN	8.00	6.95	5.20	
SHI_NI	3.1 (2.5−4.2)	2.1 (1.7−2.4)	1.5 (1.1−2.1)	**<0.001**
LLN	1.18	1.07	0.79	

Data expressed as median (IQR). LLN, lower limit of normal (≤ 5%). APB, abductor pollicis brevis; FDI, first dorsal interosseous; ADM, abductor digiti minimi; CMAP, compound muscle action potential; NI, neurophysiological index; SHI_amplitude, split-hand index (calculated using CMAP amplitude); SHI_NI, split-hand index (calculated using NI). Kruskal-Wallis test. Significant values ($p < 0.005$) are shown in bold.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neucli.2023.102864.

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