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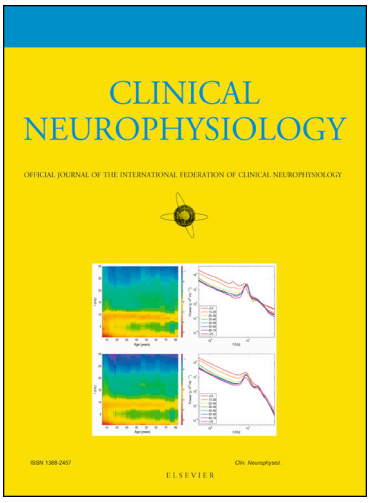

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Differential involvement of forearm muscles in ALS does not relate to sonographic structural nerve alterations

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Highlights

- In ALS, strength of finger extensors is weaker than finger flexors.
- Nerve ultrasound is of adjunctive diagnostic value in ALS.
- Relative preservation of finger-flexion in ALS is not related to nerve ultrasound pattern.

Abstract

Objective: We aimed to assess whether differential peripheral nerve involvement parallels dissociated forearm muscle weakness in amyotrophic lateral sclerosis (ALS).

Methods: The analysis comprised 41 ALS patients and 18 age-, sex-, height- and weight-matched healthy controls. Strength of finger-extension and -flexion was measured using the Medical Research Council (MRC) scale. Radial, median and ulnar nerve sonographic cross-sectional area (CSA) and echogenicity, expressed by the hypoechoic fraction (HF), were determined.

Results: In ALS, finger extensors were significantly weaker than finger flexors. Sonographic evaluation revealed peripheral nerve atrophy, affecting various nerve segments in ALS. HF was unaltered.

Conclusions: This systematic study confirmed a long-observed physical examination finding in ALS – weakness in finger-extension out of proportion to finger-flexion. This phenomenon was not related to any particular sonographic pattern of upper limb peripheral nerve alteration.

Significance: In ALS, dissociated forearm muscle weakness could aid in the disease's diagnosis. Nerve ultrasound did not provide additional information on the differential involvement of finger-extension and finger-flexion strength.

Introduction

Some neuromuscular disorders are characterized by particular patterns of muscle involvement. For instance, ocular muscle weakness in myasthenia gravis or progressive external ophthalmoplegia (CPEO); limb-girdle weakness in early muscular dystrophy syndromes; as well as predominant finger-flexion and quadriceps muscle involvement in inclusion body myositis (IBM).

Likewise, in amyotrophic lateral sclerosis (ALS) dissociated atrophy of the intrinsic hand muscles occurs in which the lateral thenar (abductor pollicis brevis [APB], first dorsal interosseous [FDI]) is more severely affected than the medial hypothenar (abductor digiti minimi [ADM]) muscles. This phenomenon is commonly termed split hand syndrome (Eisen and Kuwabara, 2012; Kiernan and Turner, 2015). Additionally, in the forearm, severe finger-extension weakness with relatively preserved finger-flexion is well known among experienced clinicians. This phenomenon was recently described more systematically in a large ALS cohort (Shemesh et al., 2016). Although incompletely understood, the underlying mechanism seems to involve both cortical and spinal/peripheral alterations (Eisen and Kuwabara, 2012; Menon et al., 2014; Shibuya et al., 2013).

High-resolution ultrasound has the potential to reveal changes in the peripheral nervous system (PNS). In ALS, ultrasound has identified atrophy in the form of reduction of peripheral nerve cross-sectional area (CSA) (Cartwright et al., 2011; Mori et al., 2014; Schreiber et al., 2015; Schreiber et al., 2016). Nerve atrophy may relate to alterations of the intranerval fascicular portion which, in turn, can be assessed sonographically by nerve echogenicity, i.e. the hypoechoic fraction (HF) (Boom and Visser, 2012). Several studies have disclosed HF increase in various neuropathies including multifocal motor neuropathy (MMN) (Goedee et al., 2014; Goedee et al., 2015; Goedee et al., 2017b; Lee et al., 2016; Simon et al., 2015). It has thus been suggested that echogenicity is sensitive against alterations of the peripheral nerve structure (Boom and Visser, 2012).

This prospective and cross-sectional study, therefore, sought to systematically assess dissociated forearm muscular involvement in ALS and examine whether it can be related to sonographic measures of CSA and HF.

Methods

Sample

Our study comprised 41 ALS patients recruited from the Departments of Neurology at Otto-von-Guericke University, Magdeburg, and, Hannover Medical School, Hannover, Germany. Diagnosis was based on the El Escorial criteria and included patients with definite, probable, or possible ALS (Brooks et al., 2000). Standardized testing of finger extensor and flexor strength was performed using the Medical Research Council (MRC) scale that ranges from grade 0 (no contraction / complete palsy) to grade 5 (normal muscle strength). To control for the effect of upper motor neuron (UMN) involvement, we chose the upper extremity sub-score (ranging from 0 – 7 points) from the Penn UMN Score (for details see (Woo et al., 2014)). All measures, i.e. upper limb muscle strength, UMN involvement and peripheral nerve ultrasound (see below) were performed on both right and left sides.

Overall disease severity was assessed using the revised ALS functional rating scale (ALSFRS-R). Statistical analysis took account of the ALSFRS-R fine motor sub-score and its individual items (item 4: handwriting, item 5: cutting food, item 6: dressing and hygiene) (Cedarbaum et al., 1999). Disease duration was defined as time in months between symptom onset and the sonographic measure.

Sonographic examination was additionally conducted in a cohort of 18 controls. None of the control subjects suffered from any neuromuscular disorders, i.e. peripheral neuropathies, muscle or motor neuron disease nor did they display any specific abnormalities on the neurological exam.

The study was approved by the local ethics committee (No. 150/09; No. 16/17), and all subjects gave written informed consent.

Ultrasound

All sonographic examinations were performed at the Department of Neurology, Otto-von-Guericke University, Magdeburg. Each subject was in a seated position with the investigator

facing the participant. Radial, median and ulnar nerve ultrasound was performed by the same ultrasonographer (CG) not blinded to the diagnosis using a 12 MHz linear array probe (GE High-End LOGIQ®7 System). During all examinations the initial settings, comprising contrast (gain), frequency, focus (number and position), time gain compensation and depth were kept constant. Compression of the tissue and oblique scanning were avoided. Transverse images were obtained (i) of the ulnar nerve at the wrist and at the lower to middle third of the forearm approximately half to three-quarters distance from the medial epicondyle of the humerus to the ulnar styloid process, (ii) of the median nerve at the mid-forearm around 10 cm above the retinaculum flexorum and at the mid-humerus, and (iii) of the radial nerve at the forearm radial nerve bifurcation scanning the deep radial nerve (posterior interosseous nerve [PIN]) only and between the medial and lateral head of the triceps muscle in the spiral groove at the posterior aspect of the humerus (Brown et al., 2016). These sites were chosen as they are commonly assessed during nerve ultrasound because nerve segments can be readily visualized (Grimm et al., 2017a; Kerasnoudis et al., 2015; Loewenbruck et al., 2016).

Peripheral nerve ultrasound is well established locally with very good to excellent intra- and interrater agreements (Schreiber et al., 2015; Schreiber et al., 2016).

Images were stored and offline ultrasound analysis was performed by the same physician (SS) blinded to the diagnosis. In each image the respective nerve was delineated as a region of interest (ROI) by continuous manual tracing of the nerve circumference (excluding the hyperechoic epineural rim). The pixels of each nerve ROI were extracted and the nerve CSA was computed. HF was derived using the max entropy algorithm to automatically determine an intensity threshold to assess hypoechogenicity in the ROIs' pixels; this has been reported to indicate the intranerval fascicular portion (Goedee et al., 2014; Goedee et al., 2017a).

All analyses were conducted using MATLAB R2016a and its Image Processing Toolbox v9.4.

Statistics

Within-patient comparisons of (i) finger-extension and finger-flexion, (ii) finger-extension of the (a) dominant vs. the non-dominant hand or (b) disease onset vs. non-onset upper limb side and (iii) finger-flexion of the (a) dominant vs. the non-dominant hand or (b) disease onset vs. non-onset upper limb side were conducted using a Wilcoxon signed-rank test. Bonferroni-corrected p-values ≤ 0.05/5 = 0.01 were deemed to be statistically significant.

To assess whether muscle strength was affected by UMN involvement, finger-extension and finger-flexion function was (i) compared between patients without (upper limb UMN score = 0) and with UMN involvement (upper limb UMN score > 0) applying a Mann-Whitney U test and (ii) related to the upper limb UMN score (bivariate correlations). Bonferroni-corrected p-values ≤ 0.05/2 = 0.03 were deemed to be statistically significant.

Pairwise comparisons were conducted to contrast the median nerve CSA against the radial nerve CSA or the ulnar nerve CSA against the radial nerve CSA using a Wilcoxon signed-rank test or a paired-sample t test. Bonferroni-corrected p-values ≤ 0.05/5 = 0.01 were deemed to be statistically significant.

For group comparisons general linear models were conducted with each sonographic measure as respective dependent variable and group (patients vs. controls) as independent variable. As two ultrasound outcome measures and six nerve segments were considered, Bonferroni-corrected p-values ≤ 0.05/12 = 0.004 were deemed to be statistically significant.

Relationship between sonographic measures, demographics (age, sex, height, weight), disease duration, MRC scale and the ALSFRS-R fine motor sub-score (and its individual component items) was assessed using bivariate correlations and independent-samples t tests. Bonferroni-adjusted p-values ≤ 0.05/12 = 0.004 were deemed to be statistically significant.

Analyses were performed using the IBM SPSS Statistics 23.0 software.

Results

Clinical data

The demographics and clinical data of the sample are given in **Table 1**. There were no differences between ALS patients and controls with respect to age, sex, height and weight (**Table 1**).

In ALS, finger extensor strength was highly related to finger flexor strength. There was, moreover, a medium- to large-effect size relationship between the MRC scale and the ALSFRS-R fine motor sub-score and its individual items, indicating good consistency of the evaluation of the patients' clinical function **(Table 2)**.

N = 35 (85%) on finger-extension and n = 22 (54%) on finger-flexion showed MRC scale measures < 5 in ALS. For finger-extension n = 14 (34%) and for finger-flexion n = 7 (17%) subjects demonstrated asymmetry on the clinical examination. Finger-extension weakness was more severe than finger-flexion weakness (right: $z = 4.5$, $p < 0.001$; left: $z = 4.4$, $p < 0.001$) (**Figure 1**).

Finger-extension weakness was more pronounced in the dominant hand compared to the non-dominant hand ($z = 2.1$, $p = 0.04$ [trend-level]). Likewise, finger-flexion weakness of the dominant hand was more pronounced than of the non-dominant hand ($z = 1.9$, $p = 0.06$ [trend-level]).

In ALS, finger-extension weakness of the onset upper limb side was more distinct than the non-onset upper limb side ($z = 2.2$, $p = 0.03$ [trend-level]). The same was true of finger-flexion ($z = 2.5$, $p = 0.01$ [trend-level]).

Handedness was related to upper limb onset side ($\chi(1) = 5.8$, $p = 0.06$ [trend-level]), e.g. right-handed ALS patients were more likely to have right-sided upper limb onset.

There was neither a difference in MRC scale measures between patients with and without upper limb UMN involvement nor was there a significant relationship between MRC scale values and the upper extremity UMN score **(Table 2)**.

Sonographic data

A larger right forearm radial nerve CSA was related to younger age ($r = -0.5$, $p = 0.003$); larger left forearm median nerve CSA was related to heavier weight ($r = 0.5$, $p = 0.001$); and larger left upper arm median nerve CSA was related to greater height ($r = 0.5$, $p = 0.002$). There was no significant association between CSA and HF. None of the sonographic measures was related to disease duration in ALS.

There were differences when contrasting the median or ulnar nerve CSA against the radial nerve CSA (right/left; controls: upper arm median nerve vs. upper arm radial nerve $Z = 2.5$, $p = 0.01$, $t(6) = 4.8$, $p = 0.003$, forearm median nerve vs. forearm radial nerve $t(8) = 3$, $p = 0.02$ [trend-level], $Z = 2.2$, $p = 0.03$ [trend-level], forearm ulnar nerve vs. forearm radial nerve $Z = 1.8$, $p = 0.08$ [trend-level], $Z = 2.5$, $p = 0.01$; ALS: $Z = 3.5$, $p < 0.001$, $t(14) = 8.4$, $p < 0.001$; $t(21) = 9$, $p < 0.001$, $Z = 4.2$, $p < 0.001$; $Z = 1.7$, $p = 0.08$ [trend-level], $Z = 2.6$, $p = 0.009$). Findings have to be interpreted this way that in controls and ALS the median and ulnar nerve had a larger caliber than the radial nerve **(Table 3)**.

Compared to controls, ALS patients displayed upper limb nerve atrophy, sparing the right upper arm radial nerve and the left forearm median nerve (**Figure 2A; Table 3**). There were, however, no group differences when considering the nerves' HF **(Figure 2B).**

There was no significant association in ALS between any sonographic measure and the MRC scale score or the ALSFRS-R fine motor sub-score and its individual items.

Discussion

This study shows in an independent ALS cohort that finger-extension weakness is more pronounced than finger-flexion weakness. This result was independent of clinical upper limb UMN involvement. Both side of upper limb dominance and side of onset were associated with more pronounced forearm muscle weakness. Sonographic evaluation revealed peripheral nerve atrophy in ALS (radial, median and ulnar nerves) that similarly affected distal and proximal nerve segments. Nerve atrophy was not accompanied by significant changes in nerve echogenicity. Relatively preserved finger-flexion in the face of more pronounced finger-extension weakness was not explained by better structural integrity of median or ulnar (innervating finger-flexors) compared to radial nerve (innervating finger-extensors).

Split hand has been deemed a useful physical diagnostic sign in ALS as it is rarely seen in other neuromuscular disorders (Menon et al., 2013; Menon and Vucic, 2014). Our data, however, reveal another characteristic pattern of differential muscular involvement, i.e. finger-extension weakness with relatively preserved finger-flexion. This pattern might also aid diagnosis in ALS, especially in comparison with IBM in which finger-flexors are typically more impaired.

Only one third of our patients displayed side-to-side differences of upper limb muscle strength. This is different from the high rate of unilateral motor manifestations which is found in the majority of all cases of limb-onset ALS (Devine et al., 2014; Ravits et al., 2007). This apparent discrepancy may be related to the sample's relatively long disease duration (mean 3 years) as there is a high degree of left and right clinical muscle decline over the course of time (Rushton et al., 2017). In this instance, we refrained from the calculation of MRC scale inter-side differences, which seems to be not promising in long-standing disease (Rushton et al., 2017).

Our results showing that the dominant hand was weaker and more likely to be the side of onset additionally replicates previous findings conducted in large ALS cohort studies (Devine et al., 2014; Ravits et al., 2007; Turner et al., 2011). These data support the theory of an association between greater use and earlier weakness of the upper limb.

Our results additionally offer further evidence that peripheral nerve atrophy in ALS can be measured using high-resolution ultrasound. CSA was significantly reduced at all sites sampled with the exception of the right upper arm radial nerve and the left forearm median nerve whose CSAs were decreased but did not reach statistical significance. Our finding that despite atrophy in ALS physiological nerve caliber differences remain the same as in controls (in terms of that the median and ulnar nerve CSA is larger than the radial nerve CSA), suggests that CSA decline should take place linearly, similarly affecting all upper limb nerve sites. Several studies conducted by ourselves and in other groups have demonstrated CSA decrease of the cervical nerve roots and upper limb nerve segments (Cartwright et al., 2011; Mori et al., 2016; Nodera et al., 2014; Nodera et al., 2016; Schreiber et al., 2015; Schreiber et al., 2016). These findings appear especially relevant for discriminating between ALS and multifocal motor neuropathy (MMN) in which peripheral nerve enlargement can occur (Hobson-Webb and Grimm, 2017).

Focusing only on atrophy without taking account of other parameters of PNS involvement potentially risks an oversimplification when assessing nerve alterations (Hobson-Webb and Grimm, 2017). Indeed, in ALS virtually nothing is known about quantitative sonographic parameters beyond CSA. In the present study we thus additionally quantified nerve echogenicity. HF did not differ between ALS and controls suggesting that, for differential diagnosis, increased HF may be a pointer to an ALS mimic (e.g. MMN) (Goedee et al., 2017b). One may suppose that manual delineation of the fascicle area might be more sensitive against nerve fiber alterations, especially as HF not only indicates the nerve's fascicular portion but also its water content (Boom and Visser, 2012). That manual measure of the fascicle area is working quite well when applied in demyelinating neuropathies

displaying CSA and fascicular enlargement (Goedee et al., 2015; Goedee et al., 2017b; Grimm et al., 2017b). In ALS, however, visualization and manual separation of fascicles is much more challenging. We speculate that this difficulty may be related to reduction of nerve size making fascicular pattern harder to visualize. In this context, high-resolution magnetic resonance neurography (MRN) may shed more light on the reasons underlying PNS atrophy in ALS.

We speculate further that mechanisms underlying differential involvement of finger-extension and finger-flexion might be similar to those suggested to explain the split hand. For instance, finger extensor function may be faced with greater axonal excitability, may display higher susceptibility to cumulative oxidative stress or lower functional reserve, and, may exhibit an altered corticomotoneuronal representation (Bae et al., 2014; Eisen and Kuwabara, 2012; Menon et al., 2014; Shemesh et al., 2016; Shibuya et al., 2013).

There were some limitations with the present study. The MRC scale is a robust and simple measure with easy applicability in clinical practice. It has been used widely in several imaging studies, frequently demonstrating a good correlation between muscle strength and various ultrasound and MRI metrics (Cartwright et al., 2011; Di Pasquale et al., 2015; Goedee et al., 2014; Loewenbruck et al., 2016; Rasoanandrianina et al., 2017). The categorical nature of the MRC scale, however, lacks sensitivity to make fine-grained discrimination of strength - for instance, a broad range of strengths can potentially yield a score of 4/5. Further studies should thus also take account of more precise methods of muscle strength assessment, e.g. dynamometry, to capture more subtle effects and greater variance of the forearm's function. Furthermore, in this study we did not account for the potential effects of the finger posture on the tendon force transmission within the finger extensor and flexor apparatus (Lee et al., 2008). The impact of finger posture should be carefully considered when studying finger motor control in future ALS studies.

In conclusion, our results revealed dissociated muscle weakness beyond split hand in ALS and demonstrated the applicability of CSA and HF for the assessment of structural PNS alterations. These measures, therefore, might help to distinguish ALS from its mimics.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

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Figure 1. MRC scale measures of finger-extension and finger-flexion in ALS.

Plot demonstrates the mean finger extensor and finger flexor strength of 41 ALS patients as assessed by applying the Medical Research Council (MRC) scale (y-axis). Of note is the significant pronounced finger-extension weakness in face of better preserved finger-flexion. ** $p \leq 0.001$.

Figure 2. Upper limb nerve sonographic measures in ALS compared to controls.

Plots demonstrate the cross-sectional area (CSA) **(A)** and the hypoechoic fraction (HF) **(B)** of various upper limb nerve segments in ALS patients (n = 41) compared to controls (n = 18). ALS subjects displayed peripheral nerve atrophy **(A)**, but unaltered HF **(B)**. CON, controls; FA, forearm; UA, upper arm; WR, wrist; ** $p \leq 0.004$, * $p < 0.05$ [trend-level].

Figure 1

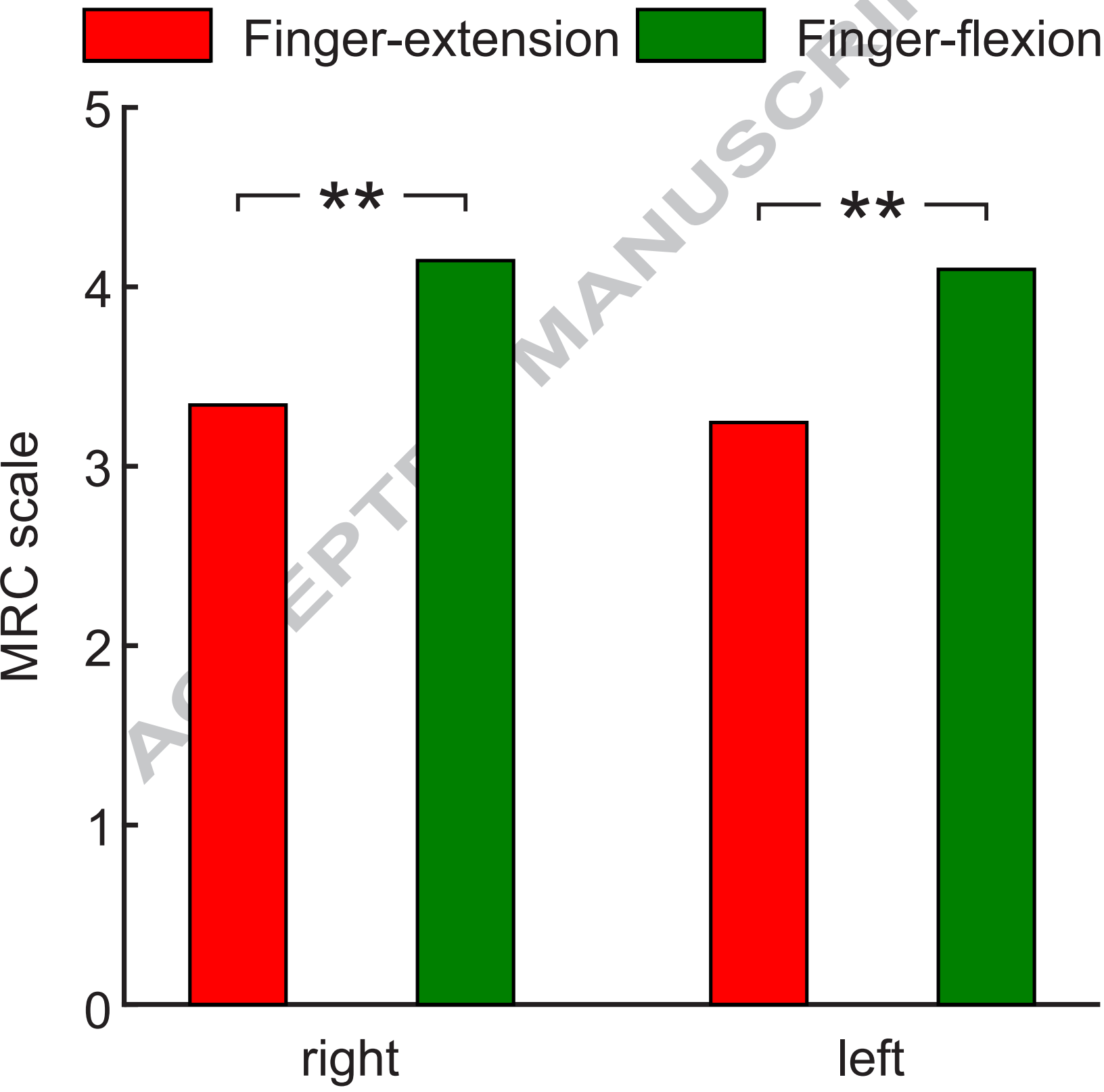

Figure 2

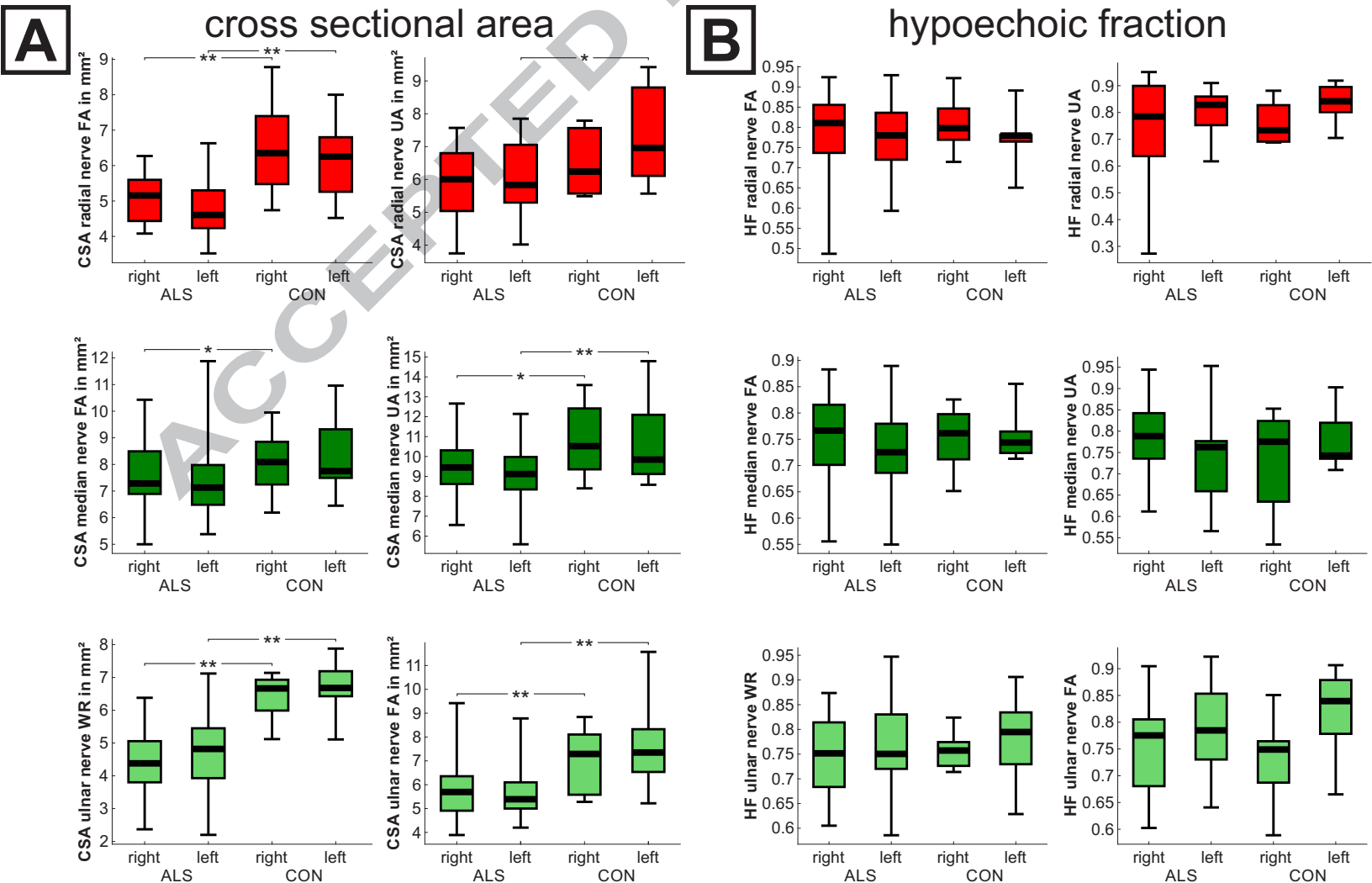

Table 1. Demographics and clinical data of the sample under investigation

	ALS (n = 41)	Controls (n = 18)	p-value
Age, in years	64 [10] (42-81)	59 [8] (51-77)	0.1
Male sex, n (%)	26 (63)	12 (67)	1.0
Height, in m	1.73 [0.1] (1.52-1.88)	1.75 [0.1] (1.59-1.93)	0.4
Weight, in kg	76 [15] (54-126)	81 [15] (54-104)	0.2
Disease onset bulbar / limb, n (%)	6 (15) / 35 (85)		
Disease onset upper limb / lower limb, n (%)	20 (57) / 15 (43)		
Disease onset right / left / bilateral upper limb, n (%)	12 (60) / 7 (35) / 1 (5)		
Disease duration, in months	34 [38] (0.1-190[#])		
ALSFRS-R total score	31 [11] (7-48)		
ALSFRS-R fine motor sub-score	6 [4] (0-12)		

Unless otherwise reported mean [SD] (range) is given. Group comparisons were conducted using an independent-samples t test, Mann-Whitney U test or χ^2-test; p-values ≤ 0.05 were deemed to be statistically significant. [#] Maximum disease duration of 190 months stems from one ALS patients suffering from flail leg phenotype.

Table 2. Upper limb motor function of the ALS sample under consideration

	Right upper limb	Left upper limb
Finger-extension ~ finger-flexion, r (p)	**0.7 (< 0.001)**	**0.8 (< 0.001)**
Finger-extension ~ ALSFRS-R, fine motor sub-score, r (p)	**0.6 (< 0.001)**	**0.6 (< 0.001)**
Finger-flexion ~ ALSFRS-R, fine motor sub-score, r (p)	**0.6 (< 0.001)**	**0.6 (< 0.001)**
Finger-extension ~ ALSFRS-R, item 4, r (p)	**0.7 (< 0.001)**	**0.7 (< 0.001)**
Finger-flexion ~ ALSFRS-R, item 4, r (p)	**0.6 (< 0.001)**	**0.6 (< 0.001)**
Finger-extension ~ ALSFRS-R, item 5, r (p)	**0.6 (< 0.001)**	**0.7 (< 0.001)**
Finger-flexion ~ ALSFRS-R, item 5, r (p)	**0.7 (< 0.001)**	**0.7 (< 0.001)**
Finger-extension ~ ALSFRS-R, item 6, r (p)	**0.5 (0.002)**	**0.5 (0.001)**
Finger-flexion ~ ALSFRS-R, item 6, r (p)	0.4 (0.005)	**0.5 (0.002)**
Dominant hand, n (%)	34 (84)	7 (16)
UMN involvement, n (%)	15 (37)	14 (34)
Finger-extension ~ UMN involvement, r (p)	0.1 (0.6)	0.1 (0.7)
Finger-flexion ~ UMN involvement, r (p)	< 0.1 (1.0)	-0.1 (0.7)

Correlations (~) between forearm muscle strength as assessed using the MRC scale, ALSFRS-R fine motor sub-score/its items and upper motor neuron (UMN) involvement are given; n, number of patients; r, correlation coefficient; p, p-value; significant correlations are marked bold.

Table 3. Sonographic cross-sectional area (CSA) in mm² of the upper limb nerves of the cohort under investigation

		ALS (n = 41)	Controls (n = 18)	p-value
Radial nerve				
Forearm	Right	5.0 [0.9] (3.8-7.5)	6.1 [1.3] (4.6-8.7)	**0.004**
	Left	4.7 [0.8] (3.3-6.5)	6.1 [1.2] (4.3-8.5)	**< 0.001**
Upper arm	Right	5.7 [1.3] (3.5-7.6)	6.6 [1.1] (5.1-7.8)	0.08
	Left	5.7 [1.1] (3.8-7.8)	7.1 [1.5] (5.0-9.9)	0.01
Median nerve				
Forearm	Right	7.4 [1.2] (4.8-10.3)	8.6 [1.5] (6.1-11.3)	0.02
	Left	7.4 [1.7] (5.4-11.9)	8.6 [1.5] (6.5-10.9)	0.05
Upper arm	Right	9.3 [1.5] (6.4-13.2)	10.8 [2.1] (8.2-16.0)	0.009
	Left	9.2 [1.5] (5.4-12.1)	11.2 [2.3] (8.6-14.9)	**0.001**
Ulnar nerve				
Wrist	Right	4.4 [0.9] (2.4-6.2)	6.8 [1.0] (4.9-8.5)	**< 0.001**
	Left	4.5 [1.0] (2.5-7.0)	6.2 [1.0] (4.9-7.8)	**0.001**
Forearm	Right	5.6 [1.2] (3.9-9.6)	7.6 [1.5] (5.0-9.8)	**< 0.001**
	Left	5.5 [1.2] (4.0-8.7)	7.0 [1.4] (5.0-9.0)	**0.001**

Mean [SD] (range) is given. P-values ≤ 0.004 were deemed to be statistically significant (marked bold); p-values < 0.05 were considered to be on trend-level.