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ORIGINAL ARTICLE

Split-hand phenomenon quantified by the motor unit number index for distinguishing cervical spondylotic amyotrophy from amyotrophic lateral sclerosis

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Summary
Objectives. — To investigate and compare split-hand phenomenon quantified by motor unit number index (MUNIX) between patients with cervical spondylotic amyotrophy (CSA) and those with amyotrophic lateral sclerosis (ALS).
Methods. — MUNIX was performed on abductor pollicis brevis (APB), abductor digiti minimi (ADM) and first dorsal interosseous (FDI) in 46 CSA patients, 39 ALS patients and 41 healthy subjects. Split-hand measurements including split-hand index (SHI = ABP × FDI/ADM), ratio of APB to ADM (AA), ratio of FDI to ADM (FA) were measured by compound muscle action potential (CMAP) and MUNIX.
Results. — There was a significant difference in both AA and SHI measured by two different methods between ALS and CSA patients ($P < 0.05$). Receiver operating characteristic (ROC) curve and logistic regression analysis demonstrated good differential diagnostic accuracy for AA, SHI and their combination between ALS and CSA. A larger area under the curve (AUC) was observed in these measurements calculated by MUNIX than those measured by CMAP (AA: 0.885 vs. 0.700, SHI: 0.865 vs. 0.703, Combination: 0.925 vs. 0.750; $P < 0.05$). Sub-group analysis of ROC curves revealed an AUC of 0.893 for AA_{MUNIX}, 0.801 for SHI_{MUNIX} and 0.896 for their combination in differentiating ''clinically possible'' ALS (Awaji-Shima criteria) from CSA ($P < 0.05$).

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Conclusions. — Both AA and SHI measured by two different methods are useful in distinguishing ALS from CSA, and those quantified by MUNIX may be a better differential diagnostic marker to provide an accurate and noninvasive additional test for distinguishing CSA from ALS, even in their early stages.

Introduction

Cervical spondylotic amyotrophy (CSA) is usually characterized by unilateral or asymmetric/symmetric bilateral muscle weakness and amyotrophy in the upper limbs without significant sensory abnormalities [19,23]. According to the predominantly involved muscles, CSA is generally divided into proximal (impairment of scapular, deltoid, and biceps muscles) and distal (impairment of forearms and hand muscles) types [19,22,23].

CSA is thought to involve selective damage of anterior horn cells or/and ventral nerve roots by bony spur compression or an indirect insufficient blood supply resulting from cervical canal stenosis, or by compression or stretching of the intra- and extramedullary vessels upon movement of the cervical spine [19,22,23]. Because of similar major lesion site, the clinical features of CSA, especially distal-type CSA, are similar to Hirayama disease (HD). Predominantly affecting male adolescents, HD features are obviously regional [12,14]. Most HD patients have characteristic ''loss of attachment'' in neck-flexion magnetic resonance imaging (MRI) without standard neck MRI abnormalities [14]. Unlike the compressive injury in CSA, ischemic injury of the cervical anterior horn and/or nerve root caused by the excessive forward displacement of the posterior dura during neck flexion is the main pathogenic mechanism of HD [14,32], and restricting neck flexion (e.g., neck collar support and cervical fusion) has become the main method of treating HD [11,18,34].

Although many previous studies have reported good surgical prognosis in CSA [8,15,17,35], relatively few CSA patients undergo surgical intervention since it is difficult to distinguish amyotrophic lateral sclerosis (ALS) from CSA, especially in their early stages [20,33]. Unlike CSA, ALS is a progressive, fatal neurodegenerative disease that may be exacerbated by surgery [29]. Therefore, accurate and early differential diagnosis of these two diseases is critical for the treatment of CSA.

Dissociated wasting of the lateral hand muscles with relative preservation of the medial hand muscles, the split-hand syndrome, is an early and specific clinical feature of ALS [5]. Many researchers have tried to quantify this clinical feature by various electrophysiological methods to facilitate the differential diagnosis of ALS [20,21,25,27,30]. Kuwabara et al. compared both the ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM) (AA) and the ratio of the first dorsal interosseous (FDI) to the ADM (FA) measured by compound muscle action potential (CMAP) between ALS and other conditions that mimic ALS, to identify specific pattern of hand amyotrophy in ALS and its possible mechanisms [25]. In our previous study, we confirmed different patterns of hand amyotrophy among ALS, CSA and Hirayama disease by the ADM/APB CMAP ratio [20]. A recently published study suggested that the split-hand index (SHI) measured by CMAP may be used to roughly differentiate ALS from disorders that mimic it [21,27]. Unfortunately, there is no definitive report regarding the differential diagnostic value of these split-hand measurements for CSA and ALS, although it may be important to the treatment of CSA.

The motor unit number index (MUNIX) is a novel quantitative method that provides an estimated index of the functional motor unit number in the tested muscle [7,28]. Compared with CMAP amplitude, MUNIX has been demonstrated as a more sensitive index in detecting motor unit loss [9]. Therefore, this quantitative method has been widely used in the assessment of many different neuromuscular diseases, such as adult spinal muscular atrophy, anti-myelin-associated glycoprotein (anti-MAG) neuropathy, Charcot-Marie-Tooth disease and ALS [2,6,10,28]. A recently published study further demonstrated that the SHI measured by MUNIX may be a better electrophysiological marker than that measured by CMAP amplitude for the split-hand phenomenon of ALS [24].

The aim of this study was to investigate the split-hand phenomenon quantified by CMAP or MUNIX in CSA compared with ALS and to identify the utility of these split-hand measurements for distinguishing between these two disorders.

Methods

Subjects

Forty-six patients with CSA (distal-type vs. proximal-type: 27 vs. 19), 39 patients with ALS and 41 healthy subjects were included in this study (Table 1; Fig. 1). All patients were recruited in Huashan Hospital from October 2016 to May 2018. The study was approved by Human Ethics Committees (Huashan hospital, Fudan University, China). All subjects gave informed consent.

The subjects in the control and patient groups were selected according to the inclusion and exclusion criteria that have been described previously [33,35]. The criteria for CSA diagnosis were [20,33]:

- the presence of cervical spondylosis supported by radiological evidence;
- unilateral or bilateral severe muscle atrophy of the upper extremities;
- mild or no sensory deficit in the upper extremities;
- normal sensation and motor function of the lower extremities, without gait disturbance;
- minimal or no radiative pain of the upper limbs.

Table 1 Demographic characteristics of the patients with CSA or ALS.

	Patients with CSA	Patients with ALS
Number of patients	46	39
Age range (years)	55.4 ± 8.5	59.1 ± 12.8
Height range (cm)	170.6 ± 5.7	168.6 ± 7.3
Duration (months)	24.2 ± 18.5	16.0 ± 5.8
Male:female	41:5	25:14
Symptomatic upper side (Right: Left)	25:21	15:24
Symptoms and signs (*n*/total patient (%))		
Muscle Wasting and/or weakness	46/46 (100.0%)	39/39 (100.0%)
Fasciculation	5/46 (10.9%)	28/39 (71.8%)
Cold paralysis	/	3/39 (7.7%)
Sensory abnormality	11/46 (23.9%)	4/39 (10.3%)
Hyperreflexia of deep tendon reflex	16/46 (34.8%)	39/39 (100.0%)
Positive Hoffmann sign	12/46 (26.1%)	31/39 (79.5%)
Positive Babinski sign	8/46 (19.6%)	17/39 (43.6%)
Positive Chaddock sign	7/46 (15.2%)	13/39 (33.3%)
The presentation of MRI (*n*/total patient (%))		
Cervical canal stenosis	43/46 (93.5%)	6/19 (31.6%)
Ossification of posterior longitudinal ligament	12/46 (26.1%)	2/19 (10.5%)
Intramedullary high-signal lesion	10/46 (21.7%)	2/19 (10.5%)

''/'': no subject; CSA: Cervical spondylotic amyotrophy; ALS: Atrophic lateral sclerosis; MRI: Magnetic resonance imaging; a/b: where a is the number of patients who had abnormal clinical and MRI findings, and b is the number of patients who underwent clinical and imaging evaluation.

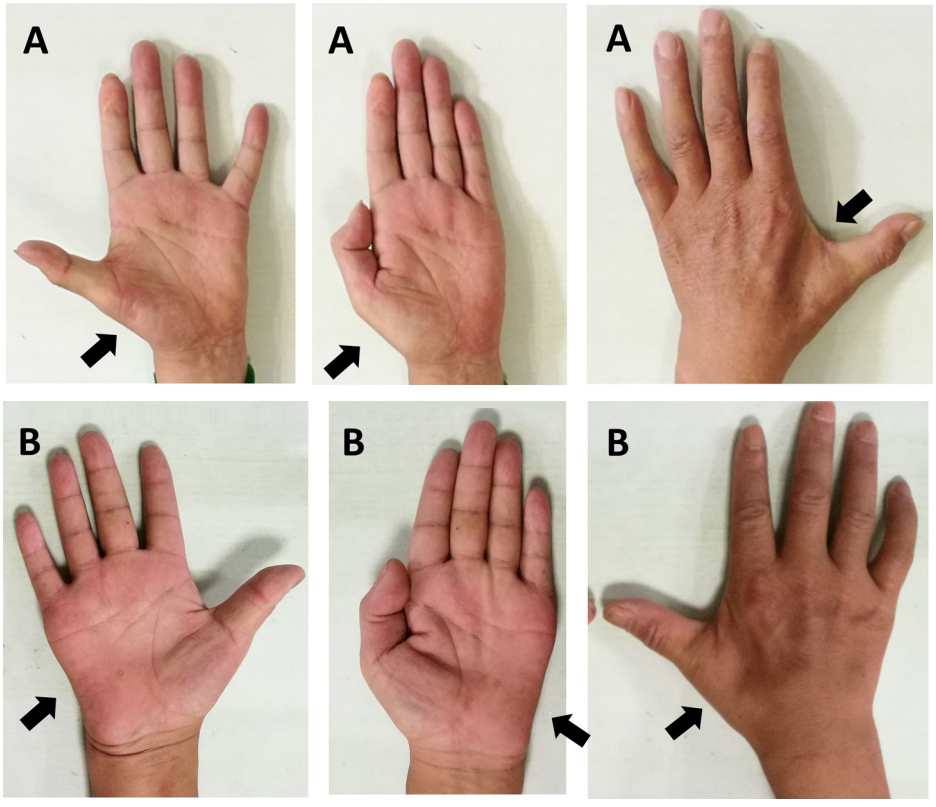

Figure 1 Clinical features of a patient with ALS and a patient with CSA. A. Significant wasting of the FDI and APB (black arrows) with relative preservation of the ADM in the patient with ALS. B. Clear wasting of the ADM and FDI (black arrows) but sparing of the APB in the patient with CSA. CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis; APB: abductor pollicis brevis; ADM: abductor digiti minimi; FDI: first dorsal interosseous.

Table 2 Nerve conduction studies and needle EMG detection in healthy subjects and the patient subjects.

	The patients with CSA	The patients with ALS	Healthy subjects
Number of cases	46	39	41
Age range (years)	55.4 ± 8.5	59.1 ± 12.8	49.3 ± 9.3
Height range (cm)	170.6 ± 5.7	168.6 ± 7.3	169.9 ± 5.9
Duration (months)	24.1 ± 18.5	16.0 ± 5.8	/
Motor nerve conduction studies			
Median nerve			
Latency (ms)	3.7 ± 0.7	4.0 ± 0.7[a]	3.4 ± 0.6
CMAP Amplitude (mV)	7.3 ± 2.7[a]	4.9 ± 2.2[a]	9.8 ± 2.2
CV (m/s)	55.7 ± 3.9	54.1 ± 5.9[a]	57.5 ± 3.7
Ulnar nerve			
Latency (ms)	2.8 ± 0.5[a]	2.9 ± 0.6[a]	2.3 ± 0.4
CMAP Amplitude (mV)	7.2 ± 2.7[a]	5.6 ± 2.5[a]	9.7 ± 2.0
CV-below elbow (m/s)	56.7 ± 6.6	56.6 ± 5.2	58.2 ± 6.5
CV-above elbow (m/s)	58.4 ± 9.5	57.5 ± 9.8	61.5 ± 7.6
Sensory nerve conduction studies			
Median nerve			
Latency (ms)	3.0 ± 0.6	3.0 ± 0.6	2.9 ± 0.5
SNAP Amplitude (μV)	36.5 ± 14.5	37.5 ± 16.0	37.8 ± 17.0
CV (m/s)	58.6 ± 8.2	58.1 ± 8.8	60.7 ± 5.9
Ulnar nerve			
Latency (ms)	2.5 ± 0.4	2.4 ± 0.5	2.3 ± 0.4
SNAP Amplitude (μV)	37.9 ± 15.7	36.7 ± 14.5	36.2 ± 14.9
CV (m/s)	57.0 ± 7.2	57.5 ± 7.0	58.6 ± 6.3
Needle EMG			
Spontaneous activities	44/46	39/39	
Changes in MUAPs	46/46	39/39	
Involved myotomes			
C4	3/46	18/46	
C5	27/46	28/46	
C6	28/46	28/46	
C7	29/46	35/46	
C8	31/46	36/46	
T1	31/46	36/46	

CSA: Cervical spondylotic amyotrophy; ALS: Amyotrophic lateral sclerosis; CMAP: Compound muscle action potential; SNAP: Sensory nerve action potential; CV: Conduction velocities; EMG: electromyogram; MUAP: Motor unit action potential; a/b: Where a is the number of HD patients who had abnormal needle EMG and b is the number of patients who underwent needle EMG tests.

[a] Significant statistical differences between the patients and normal controls.

ALS patients in this study were diagnosed clinically and by sequential electrophysiological studies according to the Awaji-Shima criteria [4]. The diagnostic categories of the patients with ALS in this study were as follows: 11 clinically definite, 19 clinically probable and 9 clinically possible patients.

The exclusion criteria for both patient groups were:

- history of syringomyelia or spinal cord tumour;
- other focal or multifocal neuropathy;
- brachial plexus injury;
- congenital muscular dystrophy;
- Hirayama disease;
- primary or concomitant neuromuscular junction diseases;
- concomitant trauma, inflammation or infection.

Both CSA patients and ALS patients in the lowest category (i.e., clinically possible) were followed up for at least six months after the MUNIX tests to identify the diagnosis, and patients in whom an alternative diagnosis was suspected at follow-up were excluded from this study.

Motor unit number index

MUNIX as described by Nandedkar et al. and Zhou et al. were applied in all normal controls (bilaterally) and patient subjects (more symptomatic side) [28,36]. The maximal CMAP was recorded from the ADM, APB and FDI in a belly-tendon montage (filters: 3 Hz—10 kHz). Subsequently, two series of surface electromyography (EMG) interference patterns (SIP) were recorded with isometric contraction at five different force levels (10% or slight, 25%, 50%, submaximal, and maximal contraction) (filters: 10 Hz—1 kHz).

According to the SIP and CMAP, both MUNIX and motor unit size index (MUSIX) values were measured by Excel table

Table 3 Measurements of both neurophysiological and clinical evaluation in normal controls and patient subjects.

	Patients with CSA	Patients with ALS	Controls
Number of cases	46	39	41
Age range (years)	55.4 ± 8.5	59.1 ± 12.8	49.3 ± 9.3
Height range (cm)	170.6 ± 5.7	168.6 ± 7.3	169.9 ± 5.9
Duration (months)	24.2 ± 18.5	16.0 ± 5.8	/
CMAP amplitudes			
APB	7.3 ± 2.7 (9)	4.9 ± 2.2 (24)	9.8 ± 2.2
ADM	7.2 ± 2.7 (16)	5.6 ± 2.5 (19)	9.7 ± 2.0
FDI	6.3 ± 3.7 (20)	5.1 ± 2.5 (21)	11.2 ± 3.2
Motor unit number index			
APB	124.0 ± 58.3 (13)	55.9 ± 28.7 (31)	175.0 ± 45.7
ADM	93.8 ± 56.9 (26)	78.9 ± 46.2 (22)	166.3 ± 40.2
FDI	99.9 ± 73.5 (26)	67.9 ± 52.3 (23)	206.2 ± 72.6
Motor unit size index			
APB	65.0 ± 20.3	92.7 ± 12.5	57.5 ± 9.6
ADM	88.1 ± 23.5	81.1 ± 22.2	59.2 ± 8.7
FDI	75.1 ± 19.7	91.8 ± 25.3	57.3 ± 12.2
The measurements of split-hand syndrome			
FA_{CMAP}	0.86 ± 0.32	0.86 ± 0.27	1.20 ± 0.37
FA_{MUNIX}	1.07 ± 0.47	0.83 ± 0.39	1.31 ± 0.58
AA_{CMAP}	1.12 ± 0.47	0.84 ± 0.32	1.04 ± 0.25
AA_{MUNIX}	1.62 ± 0.88	0.72 ± 0.34	1.10 ± 0.38
SHI_{CMAP}	6.58 ± 3.62	4.19 ± 2.21	11.40 ± 3.18
SHI_{MUNIX}	141.64 ± 101.81	44.98 ± 31.81	221.91 ± 98.29
Clinical functional evaluation			
HGS	34.1 ± 7.0	30.1 ± 11.4	42.5 ± 5.4
DASH	16.2 ± 10.5	/	/
ALSFRS-R	/	38.6 ± 4.0	/

CSA: Cervical spondylotic amyotrophy; ALS: Amyotrophic lateral sclerosis; CMAP: Compound muscle action potential; MUNIX: Motor unit number index; MUSIX: Motor unit size index APB: abductor pollicis brevis; ADM: abductor digiti minimi; FDI: first dorsal interosseus; FA: FDI/ADM ratio; AA: APB/ADM ratio; SHI: split-hand index; HGS: Handgrip strength; DASH: Disabilities of the arm, shoulder and hand; ALSFRS-R: ALS Functional Rating Scale-Revised scores; (a): a is the number of the patients who had abnormal CMAP amplitude or MUNIX values.

analysis. To avoid the influence of volume conduction from other muscles, MUNIX was not be calculated when one of the following conditions occurred: SIP area < 20 mV ms, ideal case motor unit count (ICMUC) > 100, SIP area/CMAP area < 1, or CMAP amplitude < 0.5 mV.

Split-hand measurements were calculated by CMAP amplitudes or MUNIX values using the following formulas:

- AA_{CMAP} = maximal $CMAP_{APB}$ / maximal $CMAP_{ADM}$;
- AA_{MUNIX} = $MUNIX_{APB}$ / $MUNIX_{ADM}$;
- FA_{CMAP} = maximal $CMAP_{FDI}$ / maximal $CMAP_{ADM}$;
- FA_{MUNIX} = $MUNIX_{FDI}$ / $MUNIX_{ADM}$;
- SHI_{CMAP} = (maximal $CMAP_{APB}$ × maximal $CMAP_{FDI}$) / maximal $CMAP_{ADM}$;
- SHI_{MUNIX} = ($MUNIX_{APB}$ × $MUNIX_{FDI}$) / $MUNIX_{ADM}$.

Clinical, imaging and electrophysiological examinations

All subjects underwent handgrip strength (HGS) tests and baseline electrophysiological examinations including needle EMG and nerve conduction studies (NCS), and cervical MRI was performed in all patients with CSA and 19 patients with ALS. The disabilities of the arm, shoulder and hand (DASH) scores were performed in all patients with CSA, along with the ALS Functional Rating Scale-Revised (ALSFRS-R) scores used in all ALS patients.

Measurements of each patient were considered abnormal if these measurements were absent or if the CMAP amplitude, MUNIX values or HGS were 2 standard deviations below the average values of the normal controls. All electrophysiological procedures were performed using the Keypoint EMG unit (version 2.32; Medtronic Dantec, Skovlunde, Denmark) with a skin temperature over 32 °C.

Statistical methods

Measurements were analysed using SPSS version 20.0 (IBM, Armonk, NY). The Kolmogorov-Smirnov test was used for testing normally distributed data. Measurements among the patients with CSA, patients with ALS and normal controls were compared by one-way ANOVA (Bonferroni correction), and the same test was utilized for multiple comparisons of the measurements among different sub-groups of the

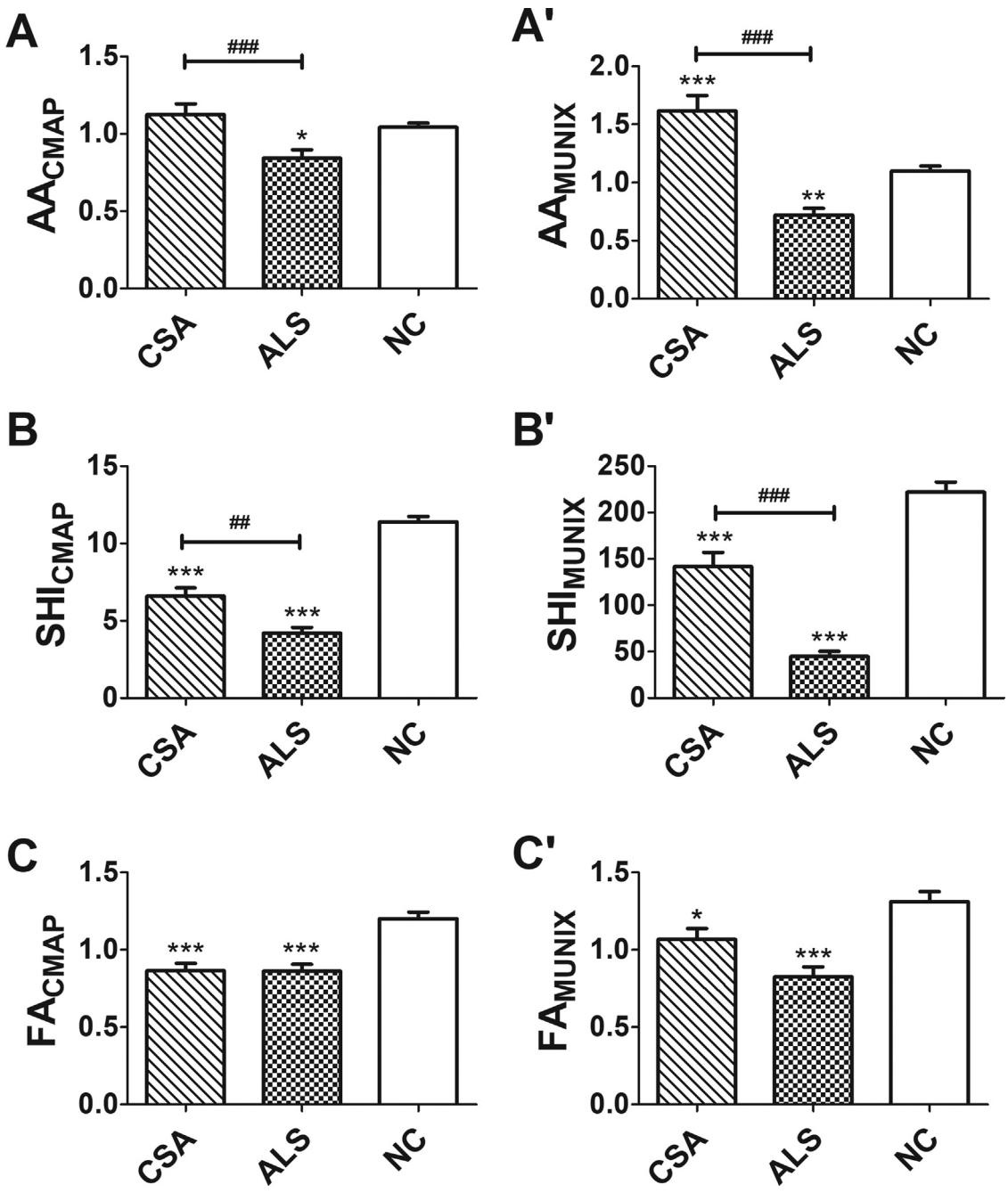

Figure 2 Split-hand measurements among the normal and ALS/CSA patient groups. A and A'. Both AA_{CMAP} and AA_{MUNIX} in patients with ALS were lower than those in normal controls, whereas patients with CSA showed increased AA_{MUNIX}. There were significant differences in both the AA_{CMAP} and AA_{MUNIX} between the patients with CSA and those with ALS. B and B'. SHI_{CMAP} and SHI_{MUNIX} in both patient groups were lower than those in normal controls, and there were significant differences in both the SHI_{CMAP} and SHI_{MUNIX} between the patients with CSA and those with ALS. C and C'. FA_{CMAP} and FA_{MUNIX} in both patient groups were lower than those in normal controls, and FA_{CMAP} and FA_{MUNIX} failed to show any difference between these two patient groups. FA: ratio of the first dorsal interosseous (FDI) to the abductor digiti minimi (ADM); AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis; NC: normal control; MUNIX: motor unit number index; CMAP: compound muscle action potential; *: Statistical differences between the patients and normal controls, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$; $^{\#}$: Statistical differences between the ALS and CSA patients, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$.

patients with ALS or CSA. Both logistic regression analysis and receiver operating characteristic (ROC) curves were used to determine the differential diagnostic utility of both individual split-hand measurements and their combination measured by MUNIX or CMAP between the CSA and ALS patients. The correlations between split-hand measurements and both clinical functional measures and disease duration in both patient groups were analysed by Pearson or

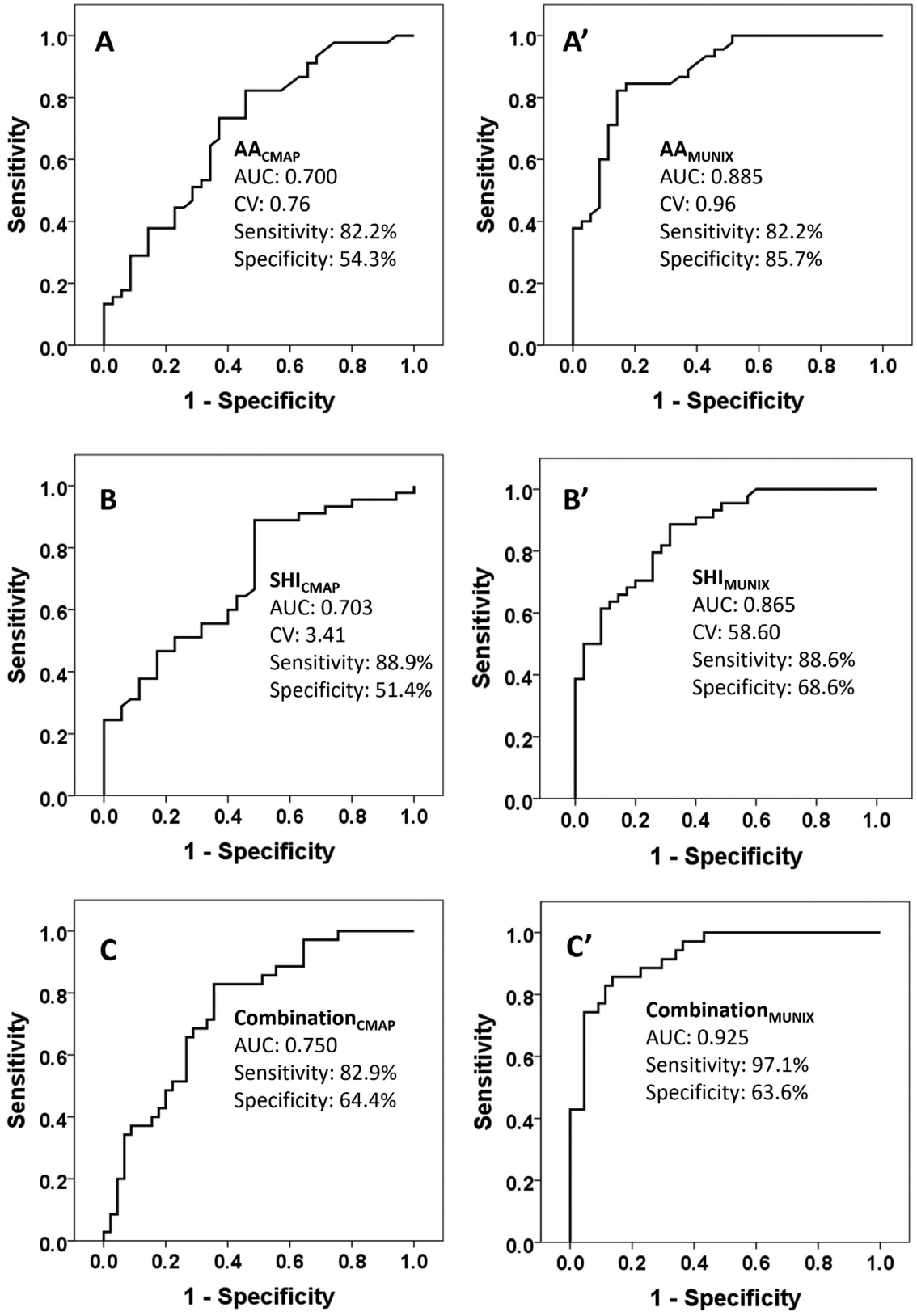

Figure 3 Receiver operating characteristic curve analysis revealed that both AA (A and A') and SHI (B and B') respectively measured by CMAP and MUNIX, as well as their combination (C and C'), can reliably differentiate ALS from CSA. Compared with the measurements calculated by CMAP (A, B and C), those measured by MUNIX (A', B' and C') showed obviously larger AUC ($P < 0.05$). ALS: amyotrophic lateral sclerosis; AUC: area under the curve; CSA: cervical spondylotic amyotrophy; CV: cut-off value; MUNIX: motor unit number index; CMAP: compound muscle action potential; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index.

Table 4 Split-hand measurements between patients with ''definite/probable'' ALS and patients with ''possible'' ALS.

	''Definite/probable'' ALS	''Possible'' ALS
Number of cases	30	9
Age range (years)	59.9 ± 13.3	56.6 ± 11.4
Height range (cm)	168.6 ± 7.7	168.6 ± 6.0
Duration (months)	16.6 ± 5.7	13.8 ± 6.0
FA_{CMAP}	0.86 ± 0.27	0.88 ± 0.28
FA_{MUNIX}	0.82 ± 0.41	0.85 ± 0.37
AA_{CMAP}	0.80 ± 0.33	0.96 ± 0.28
AA_{MUNIX}	0.72 ± 0.35	0.73 ± 0.33
SHI_{CMAP}	3.81 ± 1.97	5.29 ± 2.62
SHI_{MUNIX}	40.58 ± 26.15	57.72 ± 43.79

ALS: Amyotrophic lateral sclerosis; APB: abductor pollicis brevis; ADM: abductor digiti minimi; FDI: first dorsal interosseus; MUNIX: motor unit number index; CMAP: compound muscle action potential; FA: FDI/ADM ratio; AA: APB/ADM ratio; SHI: split-hand index; ''Possible'' ALS: ALS patients classified as ''clinically possible'' by Awaji-Shima criteria; ''Definite/probable'' ALS: ALS patients classified as ''clinically definite/probable'' by Awaji-Shima criteria.

Spearman correlation coefficient analysis. In all instances, a P-value < 0.05 was considered significant.

Results

There was no statistical difference in either age or height between patients with CSA and those with ALS ($P > 0.05$). The disease duration in patients with CSA was relatively longer than that in patients with ALS ($P < 0.05$). MRI findings and neurologic examination are presented in Table 1, along with the comparison of NCS and needle EMG among ALS cases, CSA cases and normal controls in Table 2.

Measurements between the normal and patient groups

Significantly reduced CMAP amplitudes and decreased MUNIX values, as well as increased MUSIX values, were observed in all tested muscles in both patient groups compared to normal controls ($P < 0.05$, Table 3). Both AA_{CMAP} and AA_{MUNIX} in patients with ALS were lower than those in normal controls, whereas patients with CSA showed increased AA_{MUNIX}

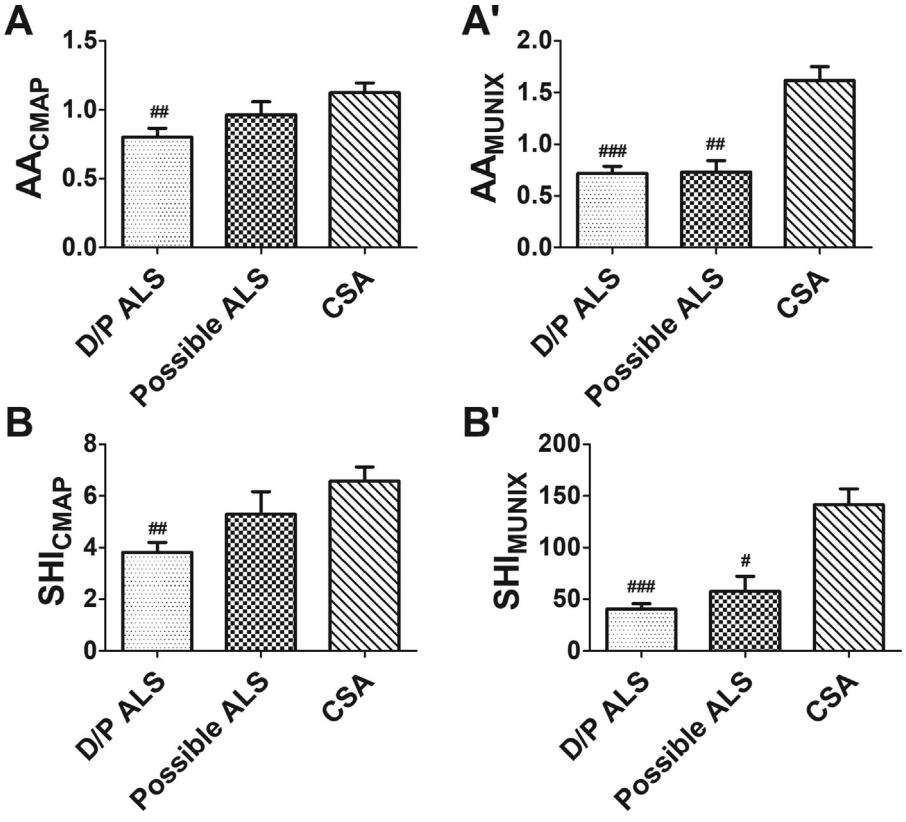

Figure 4 Split-hand measurements among the CSA/ALS patients classified as ''clinically definite/probable'' and ALS patients classified as ''clinically possible''. A. A significantly lower AA_{CMAP} was observed in patients with ''clinically definite/probable'' ALS compared with those with CSA. A'. Both the patients with ''clinically definite/probable'' ALS and those with ''clinically possible'' ALS showed a lower AA_{MUNIX} than those of the CSA patients. B. A significantly lower SHI_{CMAP} was observed in patients with ''clinically definite/probable'' ALS compared to those with CSA. B'. Both the patients with ''clinically definite/probable'' ALS and those with ''clinically possible'' ALS showed a lower SHI_{MUNIX} than those of the CSA patients. CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis; Possible ALS: ALS patients classified as ''clinically possible'' by the Awaji-Shima criteria; P/D ALS: ALS patients classified as ''clinically definite/probable'' by the Awaji-Shima criteria; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; MUNIX: motor unit number index; CMAP: compound muscle action potential. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$.

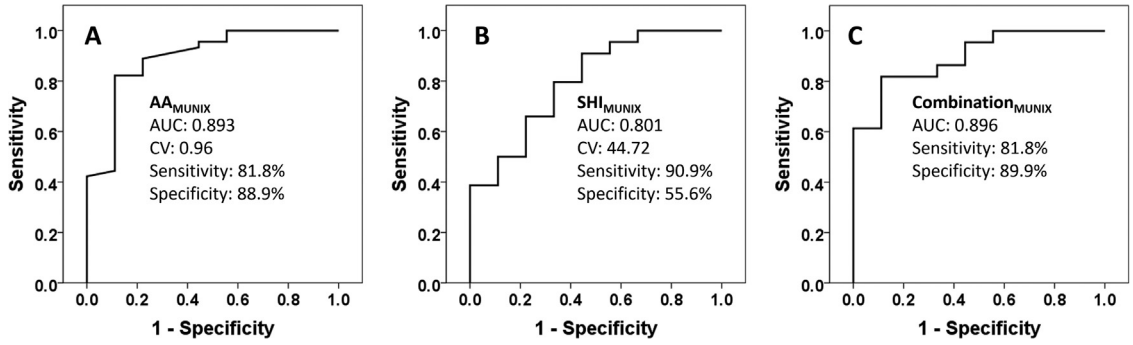

Figure 5 Receiver operating characteristic curve analysis revealed that both AA_{MUNIX} (A) and SHI_{MUINX} (B), as well as their combination (C) can reliably differentiate ''clinically possible'' ALS from CSA. AUC: area under the curve; CV: cut-off value; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; MUNIX: motor unit number index; CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis.

Table 5 The split-hand measurements between sub-groups of the patients with CSA.

	Distal-type CSA	Proximal-type CSA	ALS
Number of cases	27	19	39
Age range (years)	53.9 ± 9.3	57.6 ± 6.9	59.1 ± 12.8
Height range (cm)	169.4 ± 6.0	172.2 ± 5.2	168.6 ± 7.3
Duration (months)	24.3 ± 16.8	24.0 ± 21.1	16.0 ± 5.8
FA_{CMAP}	0.73 ± 0.22	1.05 ± 0.35	0.86 ± 0.27
FA_{MUNIX}	0.92 ± 0.38	1.27 ± 0.51	0.83 ± 0.39
AA_{CMAP}	1.22 ± 0.54	1.00 ± 0.31	0.84 ± 0.32
AA_{MUNIX}	1.87 ± 1.03	1.27 ± 0.47	0.72 ± 0.34
SHI_{CMAP}	4.35 ± 1.58	9.63 ± 3.39	4.19 ± 2.21
SHI_{MUNIX}	84.95 ± 47.75	216.23 ± 106.70	44.98 ± 31.81

CSA: Cervical spondylotic amyotrophy; ALS: Amyotrophic lateral sclerosis; APB: abductor pollicis brevis; ADM: abductor digiti minimi; FDI: first dorsal interosseus; MUNIX: motor unit number index; CMAP: compound muscle action potential; FA: FDI/ADM ratio; AA: APB/ADM ratio; SHI: Split-hand index.

($P < 0.05$, Table 3, Fig. 2). Both SHI and FA measured by two different methods in both patient groups were lower than those in normal controls ($P < 0.05$, Table 3, Fig. 2).

Split-hand measurements between the CSA and ALS

There were significant differences in both AA and SHI measured by two different methods between the CSA and ALS patients ($P < 0.05$, Table 3, Fig. 2), and FA_{CMAP} and FA_{MUNIX} failed to show any difference between these two patient groups ($P > 0.05$, Table 3, Fig. 2).

ROC curve analysis was performed to identify both the area under the curve (AUC) and the cut-off values (CVs) of individual split-hand measurements for distinguishing CSA from ALS: AA_{CMAP} (AUC: 0.700, sensitivity: 82.2%, specificity: 54.3%, CV: 0.76), AA_{MUNIX} (AUC: 0.885, sensitivity: 82.2%, specificity: 85.7%, CV: 0.96), SHI_{CMAP} (AUC: 0.703, sensitivity: 88.9%, specificity: 51.4%, CV: 3.41), and SHI_{MUNIX} (AUC: 0.865, sensitivity: 88.6%, specificity: 68.6%, CV: 58.60) (Fig. 3). Both AA and SHI measured by MUNIX showed larger AUC than those measured by CMAP ($P < 0.05$), and the combination of both AA_{MUNIX} and SHI_{MUNIX} (AUC: 0.925, sensitivity: 97.1%, specificity: 63.6%) showed a larger AUC than that measured by CMAP (AUC: 0.750, sensitivity: 82.9%, specificity: 64.4%) ($P < 0.05$, Fig. 3). The AUC of the combination of split-hand measurements was slightly larger than that of individual ones but without statistical difference ($P > 0.05$).

Split-hand measurements between the CSA and ''clinically possible'' ALS

All split-hand measurements tended to be higher in patients with ''clinically possible'' ALS compared with patients with ''clinically definite/probable'' ALS but without a statistical difference (Table 4, Fig. 4). Compared with patients with CSA, significant reductions in both AA and SHI measured by two different methods were found in patients with ''clinically definite/probable'' ALS ($P < 0.05$, Fig. 4), and patients classified with ''clinically possible'' ALS only showed reductions in both AA_{MUNIX} and SHI_{MUNIX} compared to those with CSA ($P < 0.05$, Fig. 4).

Sub-group analysis of the ROC curves in patients with ''clinically possible'' ALS revealed an AUC of 0.893 for AA_{MUNIX} (sensitivity: 81.8%, specificity: 88.9%, CV: 0.96), 0.801 for SHI_{MUNIX} (sensitivity: 90.9%, specificity: 55.6%, CV: 44.72) and 0.896 for their combination (sensitivity: 81.8%, specificity: 89.9%) in distinguishing ''clinically possible'' ALS from CSA ($P < 0.05$, Fig. 5).

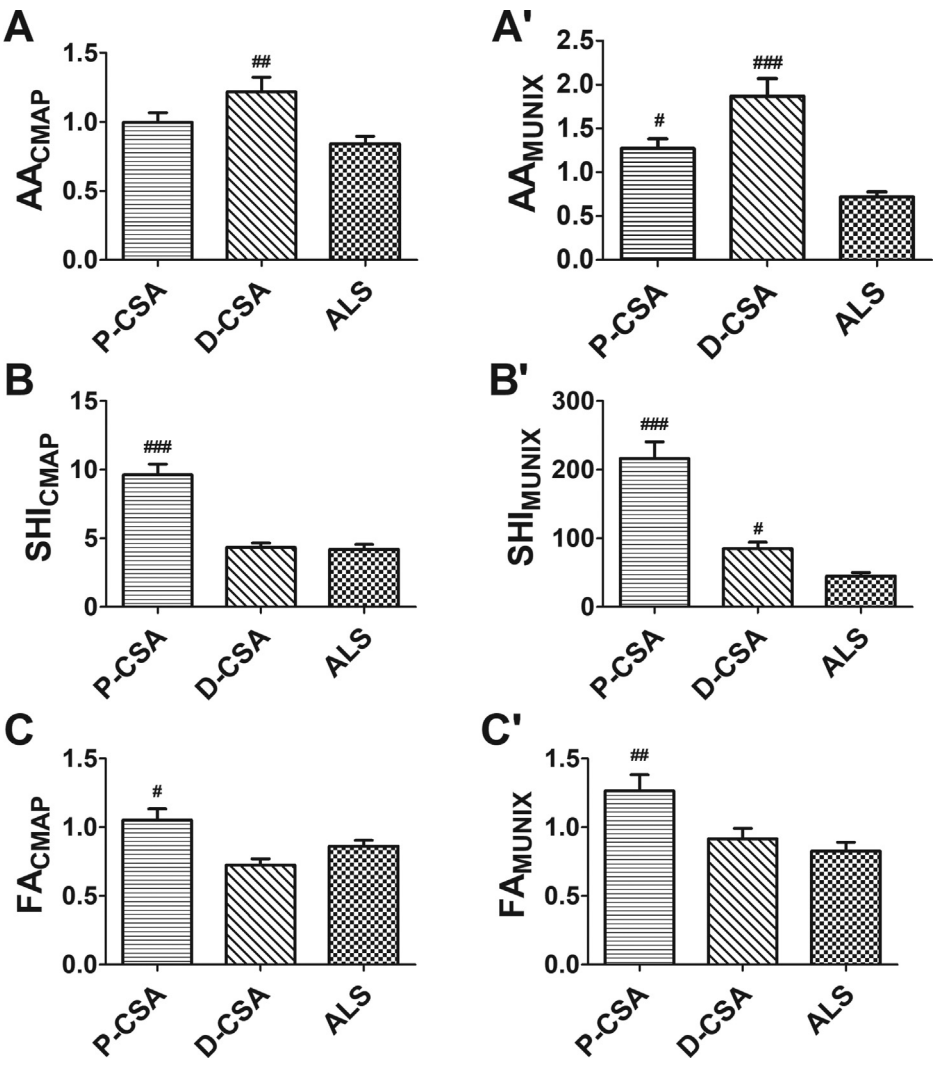

Figure 6 Split-hand measurements among the patients with distal-type CSA, patients with proximal-type CSA and those with ALS. A. A significantly higher AA_{CMAP} was observed in patients with distal-type ALS. A'. Both the patients with proximal-type CSA and those with distal-type CSA showed higher AA_{MUNIX} than those of the ALS patients. B. A significantly higher SHI_{CMAP} was observed in patients with proximal-type CSA. B'. Both the patients with proximal-type CSA and those with distal-type CSA showed higher SHI_{MUNIX} than those of the ALS patients. C. A significantly higher FA_{CMAP} was observed in patients with proximal-type CSA. C'. A significantly higher FA_{MUNIX} was observed in patients with proximal-type CSA. D-CSA: distal-type cervical spondylotic amyotrophy; P-CSA: proximal-type cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; FA: ratio of the first dorsal interosseous (FDI) to the abductor digiti minimi (ADM); MUNIX: motor unit number index; CMAP: compound muscle action potential. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$.

Split-hand measurements between the distal/proximal-type CSA and ALS

There were significant differences in all split-hand measurements except AA_{CMAP} between the patients with proximal-type CSA and those with ALS ($P < 0.05$, Table 5, Fig. 6), and patients with distal-type CSA showed higher SHI_{MUNIX}, AA_{MUNIX} and AA_{CMAP} compared to those with ALS ($P < 0.05$, Table 5, Fig. 6).

SHI (AUC: $SHI_{CMAP} = 0.918$, $SHI_{MUNIX} = 0.970$), FA_{MUNIX} (AUC: 0.754), AA_{MUNIX} (AUC: 0.841), and their combination measured by MUNIX (AUC: 0.985) were demonstrated to be useful in distinguishing ALS from proximal-type CSA ($P < 0.05$, Fig. 7). Furthermore, AA measured by CMAP (AUC: 0.729) or MUNIX (AUC: 0.916), SHI_{MUNIX} (AUC: 0.785) and their combination measured by MUNIX (AUC: 0.910) showed diagnostic value in differentiating ALS from distal-type CSA ($P < 0.05$, Fig. 8).

Split-hand measurements and clinical function

In this study, SHI was correlated with HGS in both patient groups (CSA-SHICMAP, $r = 0.51$, CSA-SHIMUNIX, $r = 0.50$; ALS-SHICMAP, $r = 0.42$, ALS-SHIMUNIX, $r = 0.43$; $P < 0.05$; Fig. 9), and there was a correlation between DASH scores and both SHI and FA in patients with CSA (SHI_{CMAP}, $r = -0.36$, SHI_{MUNIX}, $r = -0.44$; FA_{MUNIX}, $r = -0.44$; $P < 0.05$; Fig. 9). There was no

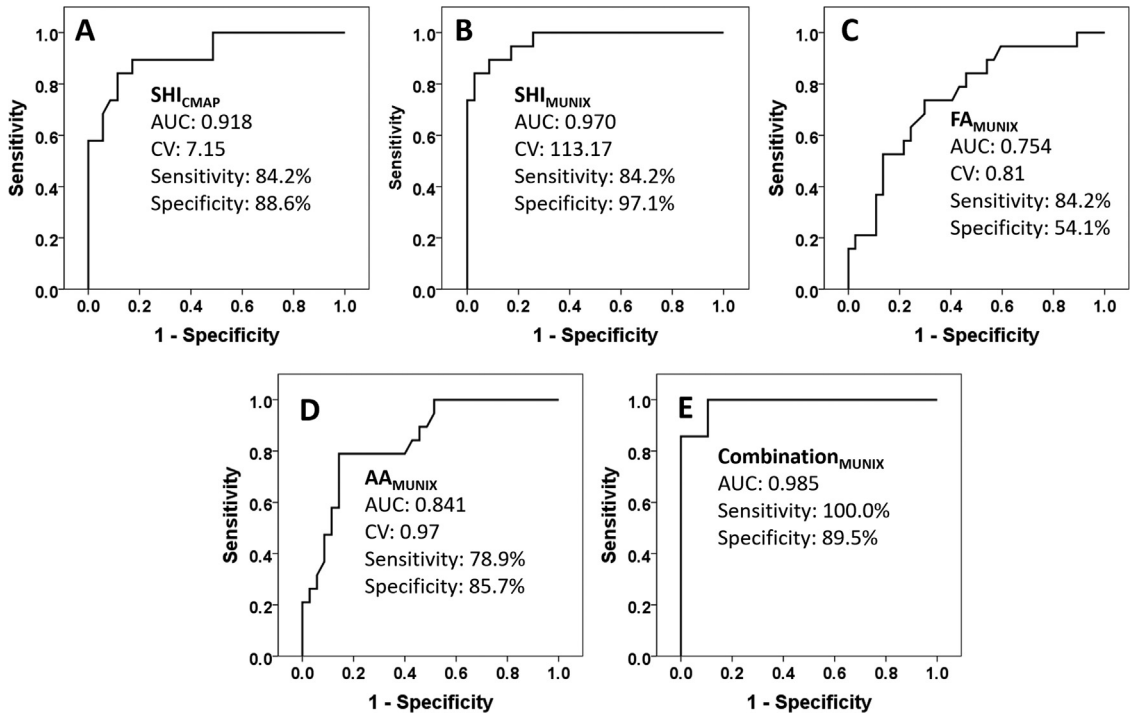

Figure 7 Receiver operating characteristic curve analysis revealed that the SHI (respectively measured by CMAP [A] and MUNIX [B]), FA_{MUNIX} (C), AA_{MUNIX} (D), and the combination of these measurements calculated by MUNIX (E) can reliably differentiate ALS from proximal-type CSA. AUC: area under the curve; CV: cut-off value; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; FA: ratio of the first dorsal interosseous (FDI) to the abductor digiti minimi (ADM); MUNIX: motor unit number index; CMAP: compound muscle action potential; CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis.

correlation between all split-hand measurements and disease duration in both patient groups ($P > 0.05$).

Discussion

The results of this study demonstrated a significant difference in split-hand measurements between ALS and CSA, and these measurements calculated by MUNIX showed obviously higher differential diagnostic values for distinguishing ALS from CSA than those calculated by CMAP.

Contrary to patients with ALS, significant wasting of the ADM with relative preservation of the APB was observed in patients with CSA, which may be ascribed to the different innervation of these muscles. In a previous study, Imajo et al. demonstrated significant abnormal central motor conduction time (CMCT) recorded from APB in patients with C6-7 myelopathy without abnormal CMCT recorded from ADM [16], and Lo et al. also demonstrated abnormal F-wave from APB in patients with C6-7 radiculopathy or myelopathy [26]. These findings suggest that the APB may be innervated by both C6-C7 and C8-T1 roots, while the ADM is only innervated by the C8-T1 roots. Equally important, this 'proximal' (upper cervical) innervation of the APB can be also used to explain why the AA ratios are higher in patients with distal-type CSA compared to patients with proximal-type CSA, and the opposite performance in FA between these two patient groups may be ascribed to the fully 'distal' (lower cervical) innervation of both FDI and ADM.

In the present study, patients with distal-type CSA showed a relatively greater reduction in both MUNIX values and CMAP amplitudes in the FDI than those in the ADM, although both muscles are innervated by both C8 and T1 roots/segments [3]. Different axonal excitability properties between these two muscles may be a possible explanation, and a previous study demonstrated that greater nodal persistent Na^+ currents in FDI axons may cause more instability in membrane potentials in the FDI axons compared to the ADM axons [1]. Thus, FDI motor axons may be more vulnerable than ADM axons. More importantly, this pattern of involvement of hand muscles gave similar performance of the FA between ALS and distal-type CSA. Therefore, it may not be appropriate to use either FA_{CMAP} or FA_{MUNIX} to distinguish ALS from distal-type CSA.

Both AA and SHI, as well as their combination, measured by MUNIX demonstrated significantly better performance than those measured by CMAP for distinguishing ALS from CSA. The likeliest reason is that CMAP amplitudes are less sensitive for detecting early motor unit loss than MUNIX values, which was further supported by normal CMAP amplitudes in approximately a quarter of the tested muscles with reduced MUNIX values in the patient groups. CMAP amplitudes in neurodegenerative disorders are reduced by the loss of motor neurons, while this reduction can be compensated by collateral reinnervation. The markedly increased MUSIX values in all tested muscles further identified the existence of this collateral reinnervation in both patient groups. Therefore, the split-hand phenomenon quantified by CMAP

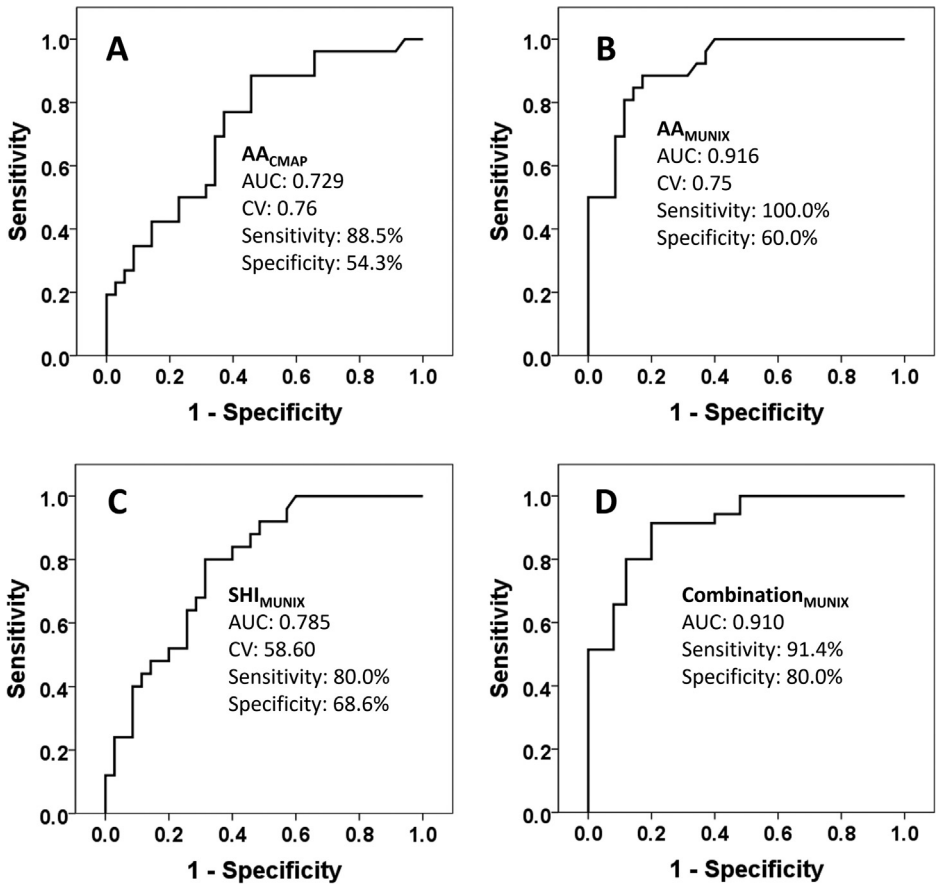

Figure 8 Receiver operating characteristic curve analysis revealed that the AA (respectively measured by CMAP [A] and MUNIX [B]), SHI_{MUNIX} (C), and the combination of these measurements calculated by MUNIX (D) can reliably differentiate ALS from distal-type CSA. AUC: area under the curve; CV: cut-off value; AA: ratio of the abductor pollicis brevis (APB) to the abductor digiti minimi (ADM); SHI: split-hand index; MUNIX: motor unit number index; CMAP: compound muscle action potential; CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis.

may not be obviously altered until serious motor unit loss occurs.

Compared with the measurements calculated by CMAP, the split-hand phenomenon quantified by MUNIX was demonstrated to be useful in distinguishing ''clinically possible'' ALS from CSA, suggesting the potential value of the measurements calculated by MUNIX in establishing an earlier differential diagnosis of ALS and CSA. The lack of correlation between disease duration and split-hand measurements in the patient groups further supported that split-hand phenomenon quantified by MUNIX could be used in distinguishing ALS from CSA during their early stages. This finding is of clinical significance, since unlike other ALS-like diseases (e.g., Hirayama disease), CSA and ALS share clinical features, MRI findings, and electrophysiological signs, especially in their early stages [20,33]. Furthermore, the previous studies demonstrated a significant correlation between early surgical treatment and CSA prognosis [31]. Therefore, additional diagnostic information involving early differentiation of CSA and ALS provided by the split-hand phenomenon quantified by MUNIX may be helpful for early surgical treatment, which can effectively improve surgical outcomes in patients with CSA.

In our previous study, we demonstrated that repetitive nerve stimulation (RNS) could be used to distinguish ALS from CSA [33], and a similar result was also confirmed by Hatanaka et al. [13]. Unlike RNS (which requires multiple supramaximal stimulations), MUNIX requires relatively few nerve stimulations, and the split-hand phenomenon quantified by MUNIX does not require the examination of proximal muscles. Therefore, the MUNIX method used in this study is less time-consuming and is well-tolerated by patients. Furthermore, split-hand phenomenon measured by MUNIX correlated with clinical function in both patient groups in this study, suggesting the potential value of the split-hand phenomenon quantified by MUNIX in the supplementary assessment of disease severity and its progression.

The results of the current study should be explained with caution. It is not possible to differentiate ALS from CSA by split-hand measurements alone because the mechanism leading to different patterns of hand muscle involvement between ALS and CSA is still unclear, and some patients with ALS subtypes may present with absent split-hand syndrome [30]. Another clinical limitation of this study is that the MUNIX measurements are easily influenced by both the

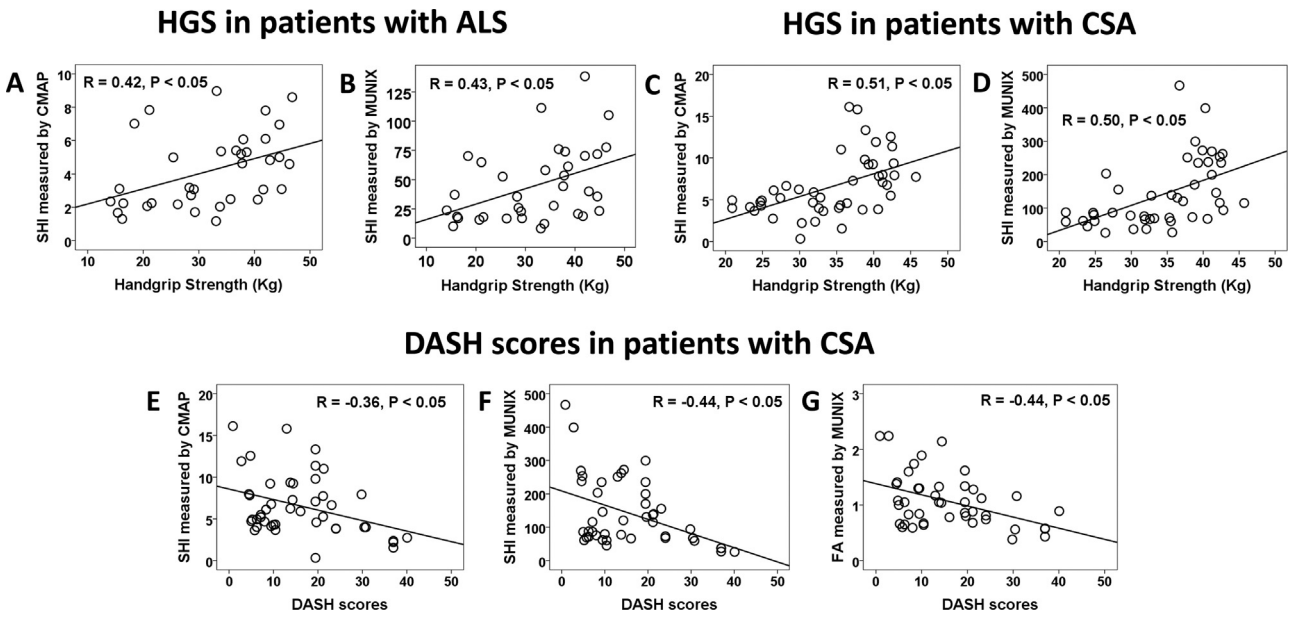

Figure 9 Correlation between clinical functional measures and split-hand measurements calculated by CMAP or MUNIX in patients with ALS or CSA. In the ALS patient group, there was a positive relationship between HGS and SHI measured by CMAP (A) or MUNIX (B). In the CSA patient group, there was a positive relationship between HGS and SHI measured by CMAP (C) or MUNIX (D). The patients with CSA presented with negative correlation between DASH scores and both SHI measured by CMAP (E) or MUNIX (F) and FA measured by MUNIX (G). SHI: split-hand index; FA: ratio of the first dorsal interosseous to the abductor digiti minimi; MUNIX: motor unit number index; CMAP: compound muscle action potential; CSA: cervical spondylotic amyotrophy; ALS: amyotrophic lateral sclerosis; HGS: handgrip strength.

examiner and methods. Therefore, a standard protocol for positioning the electrodes and a fixed examiner were used in this study. Compared with individual split-hand measurement, the combination of these different measurements failed to show obvious advantages in distinguishing ALS from CSA, and more significant results might be achieved in future studies with an increased number of patients.

In conclusion, both AA and SHI measured by two different methods are useful in distinguishing ALS from CSA. Significantly better performance of the split-hand measurements calculated by MUNIX suggests that this may provide a simple, accurate and noninvasive supplementary test in facilitating identification of CSA and ALS, even in the early stage of these diseases.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

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