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ORIGINAL ARTICLE

CMAP decrement by low-frequency repetitive nerve stimulation in different hand muscles of ALS patients

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Abstract

Objective To study compound muscle action potential (CMAP) decrement by low-frequency repetitive nerve stimulation (RNS) in different hand muscles of amyotrophic lateral sclerosis (ALS) patients and the relationship with split hand phenomenon and clinical manifestation.

Methods Clinical and decrement data of 51 ALS patients who had done RNS in different hand muscles were retrospectively reviewed from November 2016 to July 2017. Decrement data of 24 myasthenia gravis (MG) and 20 Lambert Eaton myasthenia syndrome (LEMS) patients was also reviewed to compare decrement pattern with hand muscles of ALS patients.

Results There was statistical significance between the decrement ratio of abductor digiti minimi (ADM) and abductor pollicis brevis (APB) as well as ADM and first dorsal interosseous (FDI). The decrements of the APB, ADM, and FDI were negatively correlated with their amplitude of CMAPs respectively. The difference between the decrement ratio of the APB and ADM was negatively correlated with the division ratio ($CMAP_{APB}/CMAP_{ADM}$). The decrement ratio of APB and FDI was negatively correlated with their muscle strength. There was a mild correlation between decrement ratio of APB and disease course. There was no statistical significance in the decrement pattern of the three-hand muscles of ALS patients. There was statistical significance in decrement pattern between APB of ALS and LEMS patients.

Conclusion Dysfunction of neuromuscular transmission was found in hand muscles of ALS patients, APB was involved most significantly. The dysfunction of neuromuscular transmission might be involved in the formation of the split hand phenomenon.

Keywords Amyotrophic lateral sclerosis · Repetitive nerve stimulation · Decrement · Hand muscles

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive loss of motor neurons in the brain and spinal cord [1]. Hand muscle atrophy is an important clinical manifestation, which often appears in a unique pattern called "split hand". The split hand manifests that hand muscle wasting preferentially affects the "thenar hand", with relative sparing of the hypothenar muscles although they are innervated by the same spinal segments (C8 and T1) [2]. The phenomenon is seen in more than half of ALS patients, and the mechanism is not completely known. Current studies have shown that the cortex, anterior horn of spinal cord, and peripheral motor axons may be involved [3–7], and some studies revealed that neuromuscular transmission was also involved primarily in the early stage of ALS animal models which indicated that dysfunction of neuromuscular junction (NMJ) would lead to or aggravate motor neuron death in dying back manner [8–10]. Several studies have

shown a significant amplitude decrement in compound muscle action potentials (CMAPs) on low-frequency repetitive nerve stimulation (RNS) of muscles involved in ALS, of which few studies focused on different hand muscles [11–13]. Whether the dysfunction of NMJ is involved in the formation of the split hand is unclear. The purpose of this study is to investigate whether the dysfunction of NMJ in different hand muscles in ALS patients is related to the split hand, whether the involvement of NMJ of hand muscles is related to hand function, and whether the involvement mechanism of NMJ of different hand muscles is consistent.

Methods

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University, China. All of the electrodiagnostic and clinical data of patients with ALS who were diagnosed at the Department of Neurology, Qilu Hospital of Shandong University were retrospectively reviewed from November 2016 to July 2017. The inclusion criteria were as follows: (1) definite, probable, and clinically probable laboratory-supported ALS according to the revised El-Escorial diagnostic criteria [14]; (2) low-frequency RNS was performed on at least two of the three hand muscles (abductor pollicis brevis, APB; abductor digiti minimi, ADM; dorsal first interosseous, FDI) in one side; (3) excluded patients with electrophysiological clues that was associated with peripheral neuropathies such as chronic inflammatory demyelinating neuropathy, and hereditary neuropathy [15]. Enrolled subjects consisted of 51 ALS patients. For assessment of muscle strength in intrinsic hand muscles, we used the motion angle of fingers instead of the Medical Research Council grading scale which is proved to be a crude way to monitor muscle strength [12], especially for the hand muscles. The method was as follows: the patients lay on his back, and their hands were placed on bed with full rotation. The motion distances (a) of ADM, APB, and FDI were measured with a ruler. For ADM, we measure the perpendicular distance from the fingertip of the little finger to the ring finger. For FDI, we measure the perpendicular distance from the fingertip of the index finger to the middle finger. For APB, we measure the perpendicular distance from the fingertip of the thumb to palmar. Then we measured the length of the fingers (c) respectively. The motion angle can be calculated by the following Excel function. Motion angle (°) = DEGREES(ASIN(a/c)).

Twenty-four myasthenia gravis (MG) patients with decrement in RNS diagnosed from November 2016 to July 2017 and twenty Lambert Eaton myasthenia syndrome (LEMS) patients diagnosed from January 2014 to July 2017 were also retrospectively enrolled to analyze the decrement pattern in RNS compared with ALS patients. The diagnosis of MG was confirmed by serological antibody and positive neostigmine test with fluctuant diplopia. LEMS patients were confirmed by increment more than 100% in high-frequency RNS or facilitation test.

Neurophysiological examinations

The electrodiagnostic studies were performed on a Keypoint4 electromyography system. Negative amplitude of CMAP in APB, ADM, and FDI of ALS patients were recorded. The split hand was defined as a split ratio < 0.6. Split ratio = Amplitude of $CMAP_{APB}$/Amplitude of $CMAP_{ADM}$.

RNS with 7 stimuli of low frequency 3 HZ was performed on the APB, ADM, and FDI muscles. The positions of stimulation were at the wrist, and recordings were made by placing the active electrode (G1) over the belly of the APB, ADM, and FDI muscles and the reference electrode (G2) on the tendons respectively. Supramaximal stimulus which was 20% above the maximal stimulation was applied. For each train of repetitive stimuli, decrement of the amplitudes from the first to fifth CMAPs was recorded and was expressed as a percentage. In order to analyze decrement patterns, ΔD was introduced. $\Delta D = (\text{decrement of } CMAP_{7th} - \text{decrement of } CMAP_{5th}) \times 100\%$. In 51 ALS patients, decrement data was collected from 56 APB muscles, 56 ADM muscles, and 38 FDI muscles (RNS was performed in bilateral APB and ADM muscles in 5 patients). Decrement data of MG patients was collected from 12 ADM muscles, 5 APB muscles, and 7 trapezius muscles. Decrement data of LEMS patients was collected from 4 ADM muscles and 16 APB muscles.

Statistical analysis

Results were reported as group means ± standard deviation (M ± SD). The Kolmogorov-Smirnov test was performed to assess the normal distribution. Fisher's exact test was used to compare the split hand frequency of ALS with different onset parts. The nonparametric Kruskal-Wallis test was performed to compare means of amplitude of CMAPs, decrement ratio, and ▵D in different hand muscles of ALS, and also used to compare ▵D in APB of ALS with that of MG and LEMS. The Spearman's correlation test was performed to examine for correlation between CMAPs and decrement and correlation between decrement and clinical data in ALS. A $P < 0.05$ was considered statistically significant. Calculations were done with GraphPad prism 7.00 software. All data generated or analyzed during this study are included in Online Resource 1.

Results

Patients

The onset age of 51 ALS patients ranged from 34 to 77 years old (58.3 ± 9.7), including 23 females and 28 males. The course of the disease ranged from 5 to 24 months (12.0 ± 5.8). Among them, 36 patients were upper limb onset, 10 patients were lower limb onset, and 5 patients were bulbar onset. The MG patients consisted of 9 men and 15 women, and the average age was 44.6 ± 11.6 years (range, 24–63). LEMS patients consisted of 16 men and 4 women, and the average age was 59.7 ± 9.0 years (range, 40–73).

Frequency of split hand syndrome

Among the fifty-one patients, thirty-one patients had split hand, consisting 24 patients with upper limb onset and 6 patients with lower limb onset. There was no statistical difference in the split hand frequency between upper limb onset group and lower limb onset group ($P = 0.7203$). There was no split hand in the 5 patients with bulbar onset.

CMAPs and decrement

The amplitudes of CMAP in APB, ADM, and FDI decreased in varying degrees. The amplitudes of APB decreased most obviously and had statistical significance with ADM ($P < 0.0001$). There was no statistical significance between ADM and FDI ($P > 0.9999$) (Fig. 1a). The decrement ratio of APB, ADM, and FDI was 12.9 ± 8.2%, 6.7 ± 5.4%, and 9.6 ± 7.7%, respectively. There was statistical significance between decrement of ADM and APB ($P < 0.0001$) as well as ADM and FDI ($P = 0.0156$) (Fig. 1b). The decrement in APB exceeded 10% in 53.6% patients including over 30% in two patients. The decrement in ADM was less than 5% in more than half of the patients, which exceeded 10% in 12.5% patients. The decrement in FDI was between 5 and 20% in most patients and exceeded 10% in 31.6% patients with over 30% in one patient (Fig. 1c). The decrement of APB, ADM, and FDI were negatively correlated with their CMAPs respectively. The difference between decrement of APB and ADM was negatively correlated with the split ratio. Additional data are given in Online Resource 2.

Decrement and clinical data

The decrement of APB and FDI was negatively correlated with their motion angles. The decrement of ADM was not correlated with its motion angle ($r = -0.07338$, $P = 0.7274$). There was mild correlation between decrement of APB and disease course. Disease course was neither related with the decrement of ADM ($r = 0.2799$, $P = 0.0567$) nor the decrement of FDI ($r = 0.2864$, $P = 0.1006$). Additional data are given in Online Resource 3. The decrements of all three muscles were not correlated with onset age.

Decrement pattern

The △D (see method) were − 0.693 ± 1.809, − 0.1221 ± 1.281, and − 0.2475 ± 1.868 in APB, ADM, and FDI of ALS patients respectively. △D was less than or equal to zero in 60.7% of APB, 62.5% of ADM, and 67.5% of FDI respectively. There was no statistical significance in △D of the three hand muscles of ALS ($P = 0.4384$, Fig. 2a). The △D were − 1.288 ± 1.583 in MG patients and 4.175 ± 3.23 in LEMS patients. There was statistical significance in △D between APB of ALS and LEMS patients($P < 0.0001$), and there was no statistical significance between ALS and MG patients ($P = 0.5477$, Fig. 2b). The typical decrement pattern of three muscles of ALS patients, ADM of LEMS and MG patients were show in Fig. 3.

Discussion

The overall frequency of split hand in ALS patients in our study is consistent with other studies [2]. Previous study had shown that the presence of split hand was not associated with the onset sites of ALS but rarely seen in patients with primary muscular atrophy and flail arm syndrome [16–19]. Although none of the ALS patients with bulbar onset included in this study showed split hand phenomenon, the number of cases was relatively small and the proportion needed further study.

There have been several RNS studies of hand muscles in ALS patients. Killian et al. reported that 67% of thenar muscles showed decrement in 12 ALS patients with decrement in trapezius muscles [12]. Wang et al. revealed that 54% of ALS patients showed an obvious decrement in APB, and the maximum decrement approached 35% [20]. Henderson et al. indicated that there was decrement in APB in 34% of ALS patients, while 10% patients showed decrement in ADM [13]. Yamashita et al. got the same proportion of positive decrement in APB, but none of patients showed decrement in ADM [21]. Decrement in RNS was not only found in ALS patients but also in other hereditary motor neuron diseases. Abnormal decrement to RNS was observed in 27.2% and 20% of ADM in patients with X-linked spinobulbar muscular atrophy and spinal muscular atrophy respectively [22, 23]. Unlike ALS, split hand syndrome was rare in these diseases, so there was no study focused on decrement in RNS of different hand muscles. In ALS patients, the decrement of proximal muscle was common, and when referred to the limb distal muscles, decrement in APB was more common, which was consistent with this study. However, there were few studies of RNS in FDI of ALS patients, which is also preferentially involved. Our study shows that there was decrement in FDI of

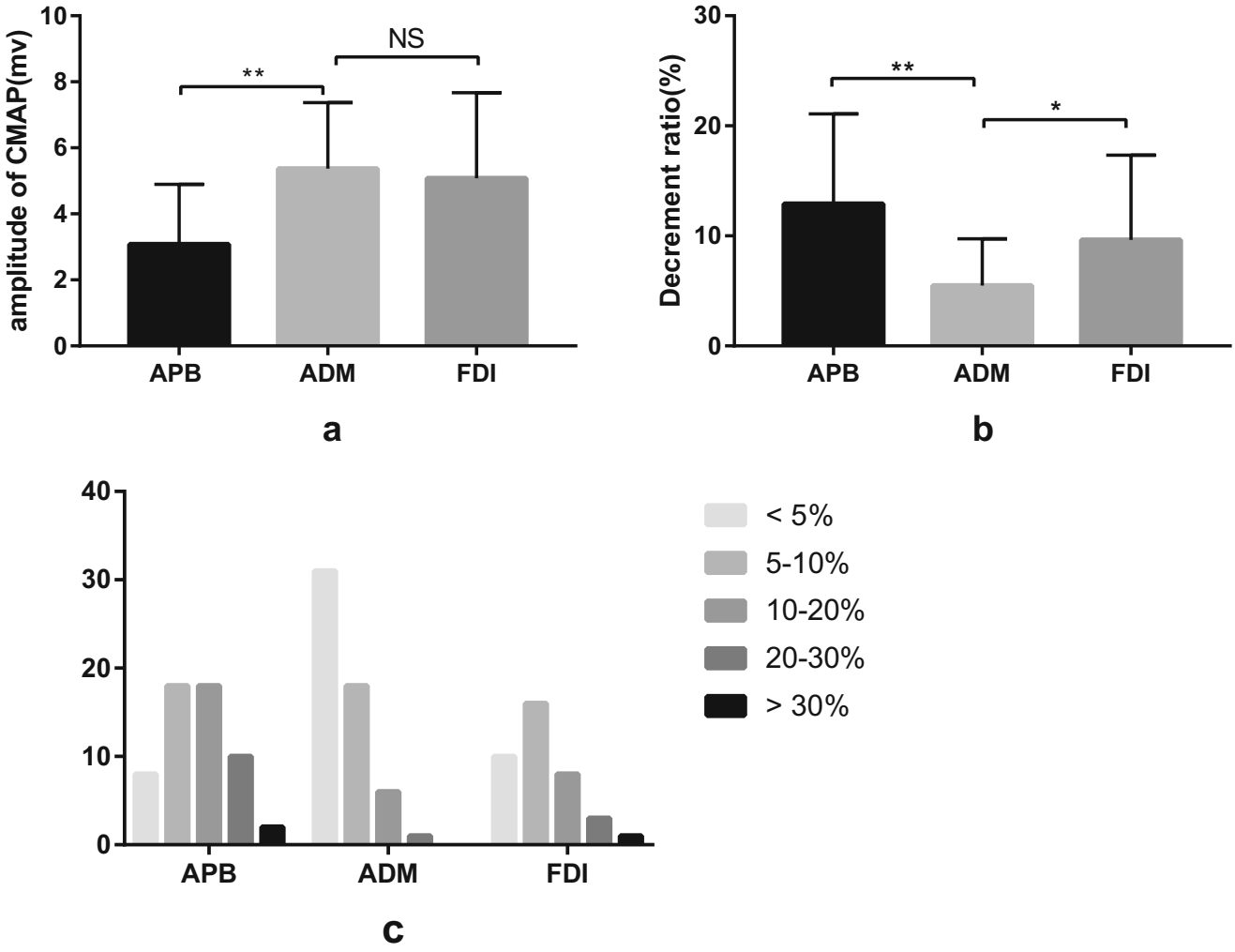

Fig. 1 Amplitude of CMAPs (**a**), decrement ratio of different hand muscles in ALS patients (**b**), and distribution of decrement ratio indifferent hand muscles of ALS patients (**c**)

ALS patients, and the frequency of decrement was between APB and ADM.

Previous studies about the relationship between decrement and muscle strength, course of disease, and prognosis in ALS patients were not consistent. Prospective study showed that APB decrement was associated with disease progression [18]. Retrospective study showed that decrement of APB was not related to the course of disease [24]. In patients with spinal muscular atrophy, the presence of an abnormal decrement was not associated with CMAP, clinical scores, or disease duration but was associated with test changes in 6-min walk test which implied fatigue [23, 25]. Our study revealed that the decrement of APB and FDI was negatively correlated with their motion angles, but the decrement of ADM was not

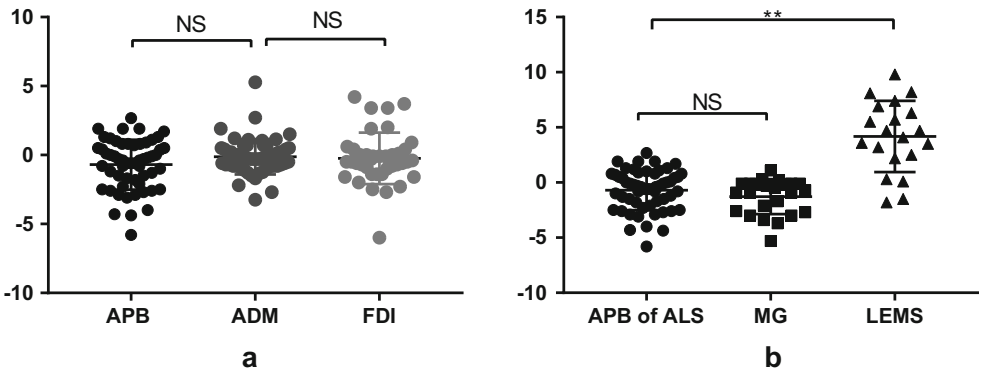

Fig. 2 △D in different hand muscles of ALS and compared with muscles from MG and LEMS patients

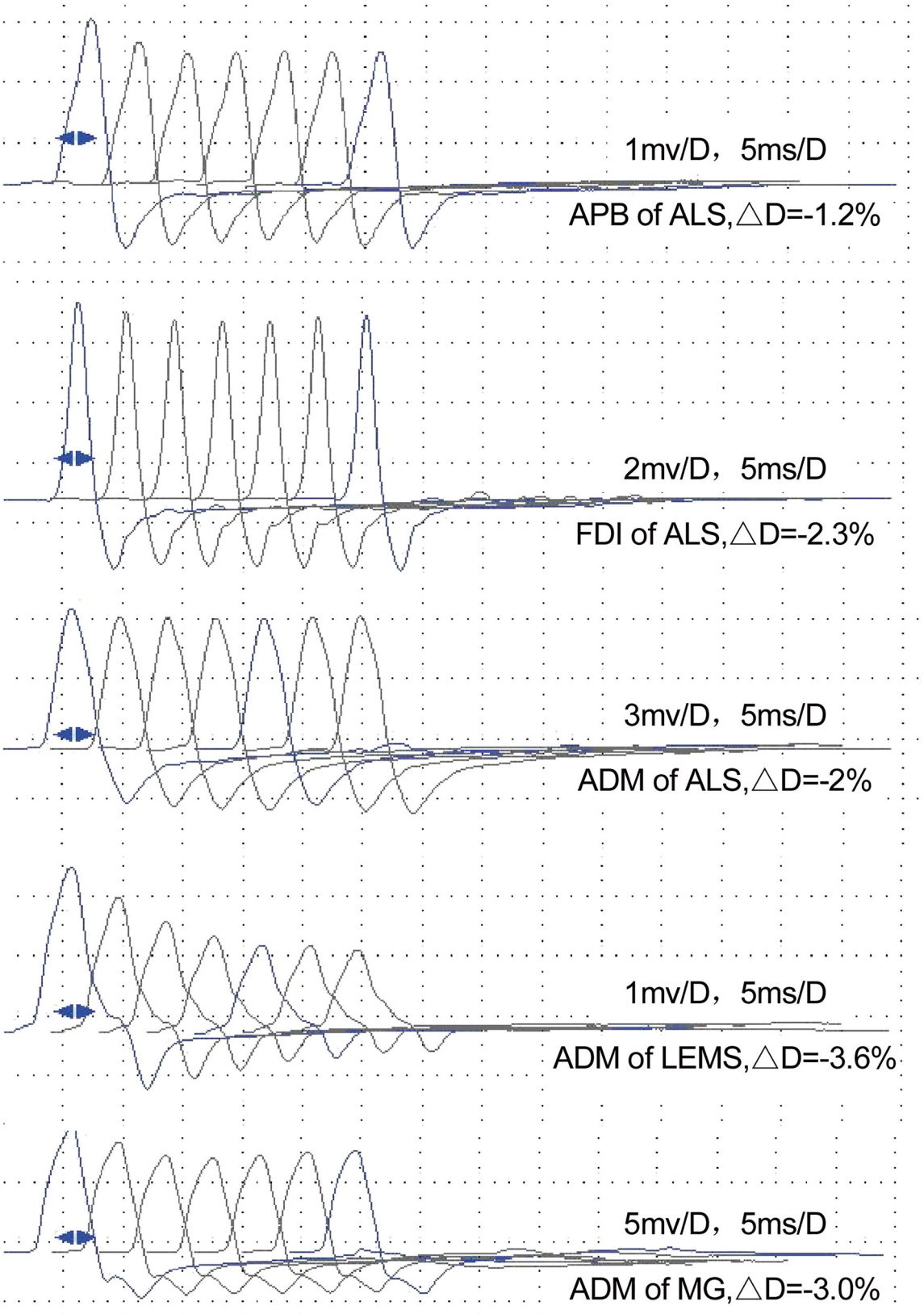

Fig. 3 Decrement pattern of different hand muscles of ALS patients, ADM of LEMS patient, and ADM of MG patient

correlated with its motion angle. The decrement in APB and FDI was more obvious than ADM. It suggests that disorders of NMJ might play a role in the decline of muscle strength at some stage of the disease course rather than at all times. The

decrement of APB had mild correlation with course of disease, whether this could be used as a prognostic indicator needs further prospective study. Fatigue was also a commonly reported symptom in people with ALS. Unfortunately, patients in this study did not undergo a 6-min walking test, whether fatigue is related to NMJ dysfunction needs further study.

The mechanism of decrement in skeletal muscles of ALS patients is not clear. It is speculated as follows: firstly, neuronal degeneration leads to axonal transport disorder resulting in choline acetyltransferase deficiency; secondly, the NMJ safety factor of new axonal is relatively low; thirdly, primary NMJ lesion does exist in ALS. Analysis of decrement pattern in low-frequency RNS indicates different blocking and the compensatory mechanisms under NMJ lesions. Previous studies have shown that positive decrement difference was the predominant pattern in LEMS patients, while on the other hand, predominant pattern in MG was negative decrement difference, indicating improvement of the CMAP size after the initial decrement, which is called U shape [26, 27]. Whether there is a "U" shape in RNS of muscles from ALS patients was not consistent in previous studies [12, 24, 28]. Our study showed that more than 60% of hand muscles of ALS patients had a negative △D which was similar to MG patients, but significantly different from LEMS patients, suggesting that postsynaptic abnormalities might play a major role. The decrement pattern of three-hand muscles was similar, and the split ratio was related to decrement difference between APB and ADM, suggesting that NMJ lesions may play a role in the phenomenon of split hand.

There are several limitations in this study. Firstly, the major ALS-associated genes were not screened in this study. Some differences considering genetic background might not be found. Besides, whether the difference between decrement of APB and ADM might be an early electrodiagnostic biomarker for ALS needs further prospective study.

Conclusion

Dysfunction of neuromuscular transmission was found in hand muscles of ALS patients, with the APB involved most significantly. The dysfunction of neuromuscular transmission especially the postsynaptic abnormalities might be involved in the formation of the split hand phenomenon.

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Contributions (I) Conception and design: Y Zhao, C Yan, D Zhang; (II) Administrative support: C Yan; (III) Provision of study materials or patients: Y Zhao, D Zhang, L Cao; (IV) Collection and assembly of data: D Zhang, W Li, L Cao; (V) Data analysis and interpretation: D Zhang, L Cao, W Li, Y Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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