Significant CMAP decrement by repetitive nerve stimulation is more frequent in median than ulnar nerves of patients with amyotrophic lateral sclerosis

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ABSTRACT

Introduction: Several studies have shown a significant amplitude decrement in compound muscle action potentials (CMAP) on repetitive nerve stimulation (RNS) of muscles involved in ALS. In ALS, muscle wasting preferentially affects the thenar muscles (APB) rather than the hypothenar muscles (ADM).

Methods: We performed RNS studies in the APB and ADM muscles of 32 ALS patients to determine whether the effect of RNS differs between the median and ulnar nerves.

Results: The decremental responses to RNS were greater in the APB than in the ADM. Reduced CMAP amplitude was negatively correlated with CMAP decrement in median but not in ulnar nerves.

Discussion: The greater CMAP decrement in median nerve was attributed to preferential involvement of the APB in the pathophysiology of ALS or some underlying difference in the biology of the two muscles/nerves. Further investigation may further our understanding of the pathophysiology of ALS.

Abbreviations: ADM, abductor digiti minimi; ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; APB, abductor pollicis brevis; CMAP, compound muscle action potential; RNS, repetitive nerve stimulation; SD, standard deviation

Key words: amyotrophic lateral sclerosis; repetitive nerve stimulation; decremental motor responses; median nerve; ulnar nerve

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disease of unknown etiology which can selectively affect both upper and lower motor neurons[1]. It is diagnosed on the basis of clinical and electromyographic findings and by excluding other diseases with similar symptoms, because there are no specific tests or biologic markers to confirm the diagnosis[2].

A decremental motor response to repetitive nerve stimulation (RNS) in ALS patients was originally reported by Mulder et al. in 1959[3]. In previous studies, the decremental response was attributed to failure of conduction of repeated stimuli by degenerating motor axon branches or by regenerating nerves undergoing collateral sprouting[4-6].

For a furtherer understanding of the pathophysiology of ALS, we sought to determine whether the effect of RNS differs between the median and ulnar nerves in ALS patients, because it is known that different nerves/muscles have different physiological properties.

MATERIALS AND METHODS

The procedures followed were in accordance with the standards of the Committee on Human Experimentation of Kumamoto University. Thirty-two consecutive patients diagnosed with ALS were examined between July 2010 and March 2011. The patients fulfilled the revised El Escorial criteria for definite, probable, or probable laboratory-supported ALS. The study group included 11 men and 21 women with ages ranging from 17 to 83 years (mean ± standard deviation (SD), 60.4 ± 18.3 years). Disease duration ranged from 4 to 66 months (mean ± SD, 17.4 ± 13.7 months). The scores for the revised ALS functional rating scale (ALSFRS-R)[7], which is a well-established and widely used scoring system for the functional status of patients with ALS, ranged from 28 to 47 (39.8 ± 5.6).

Surface electrodes were used to record the CMAP of the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles in response to 3-Hz stimulation of the median and ulnar nerves at the wrist. The median nerve was stimulated at the wrist and recordings were made by placing the active electrode (G1) over the belly of the APB muscle and the reference electrode (G2) on the tendon. The ulnar nerve was stimulated at the wrist with recording from the belly of the

ADM muscle (G1) and G2 on the tendon. The recordings were obtained using a Neuropack (Nihon-Kohden, Tokyo, Japan). For each train of repetitive stimuli, the amplitudes of the first and fifth CMAPs at supramaximal stimulus intensity were compared, and the resulting decrement of the latter was expressed in terms of percentage. A significant CMAP decrement was defined as a difference of more than 10%. All tests were performed in a warm room, and the skin temperatures over the APB and ADM muscles were maintained above 32^{o}C. CMAP amplitudes were divided by each cutoff value (median 4.6 mV; ulnar 3.8 mV), and compared. Data were analyzed using a two-tailed Student *t*-test. Regression analyses were performed by the Pearson correlation test.

RESULTS

We examined 32 median and ulnar nerves of the ALS patients. The CMAP amplitudes divided by each cutoff value were significantly larger in the ulnar nerves (1.52 ± 0.83 fold) than in the median nerves (0.98 ± 0.72 fold) (Fig. 1A). Significant CMAP decrements were observed in 34.4% and 0.0% of the median nerves and ulnar nerves, respectively. In contrast, the percentages of patients with the decrements of less than 10% were 28.1% and 18.8% in the median nerves and ulnar nerves, respectively. The decremental responses to RNS were significantly larger in the APB muscle (9.10% ± 8.71%) than in the ADM muscle (2.92% ± 2.50%) (Fig. 1B). In the case of the median nerves, the size of the CMAP decrement and the amplitude of the CMAP were negatively correlated ($R = -0.3824$, $P = 0.0002$) (Fig. 1C), whereas in the ulnar nerves, this negative correlation was not observed ($R = -0.0424$, $P = 0.2584$) (Fig. 1D). Neither the median nor the ulnar nerves showed any significant correlation between the size of the CMAP decrement and age, disease duration, or ALSFRS-R scores.

DISCUSSION

In ALS patients, muscle wasting preferentially affects the thenar muscle (APB) rather than the hypothenar muscles (ADM), and this type of dissociated small hand muscle atrophy has been termed the split hand[8]. Recent studies have clearly shown that ALS patients have a significantly reduced APB/ADM amplitude compared with normal individuals[9]. A decreased APB/ADM ratio is frequently (~40%) observed in ALS patients, although it can be found in other motor neuron diseases, including Hirayama disease[10], and even in normal elderly individuals[11]. Our finding that the CMAP amplitudes were significantly larger in the ulnar nerves than in the median nerves was consistent with the findings of these studies.

To date, several studies have shown a significant decrement in CMAP on RNS of the muscles involved in ALS[3,12-15]. One study showed a relationship between muscle atrophy and decremental responses[12]. Another study showed that disease activity and speed of disease progression might be more important factors for a decremental CMAP to RNS[13]. A more recent study suggested that CMAP decrement arises from regenerating neurons; this finding was based on the theory that the decrement persists despite reduced CMAP amplitudes[16].

Our study shows that the decremental motor response to RNS differs between the median and ulnar nerves. The greater CMAP decrement in the median nerve was attributed to preferential involvement of the APB muscle in pathophysiology of ALS[17,9]. Our finding that the CMAP decrement was inversely correlated with CMAP amplitude may support the theory that the CMAP decrement is not likely to arise from dying axons but is more likely to arise from insecure conduction in newly sprouted nerve terminals.

Alternatively, the CMAP decrement could be a reflection of some underlying difference in the biology of the two nerves. A recent study demonstrated that there were quite different effects of RNS on the CMAP amplitude in the different commonly tested nerves in normal subjects[18]. The authors proposed several possible factors responsible for the change in CMAP size with RNS in normal subjects: (1) properties of muscle; (2) changes in neuromuscular transmission; and (3) changes in the nerve membrane. We speculate that such differences in physiological properties between APB and ADM muscles, or median and ulnar nerves could arguably be a reason for the preferential involvement of median nerves in ALS.

This study should be interpreted with caution. It is not possible to conclude that a difference

between the median and ulnar nerves with respect to the susceptibility of the CMAP decrement (detected using the RNS test) is a diagnostic marker for ALS. This was because we did not include diseased and healthy controls in our study. Hence, further study would be required to establish the usefulness of the RNS test in the accurate diagnosis of ALS.

Conflict of interest

The authors declare that they have no conflict of interest.

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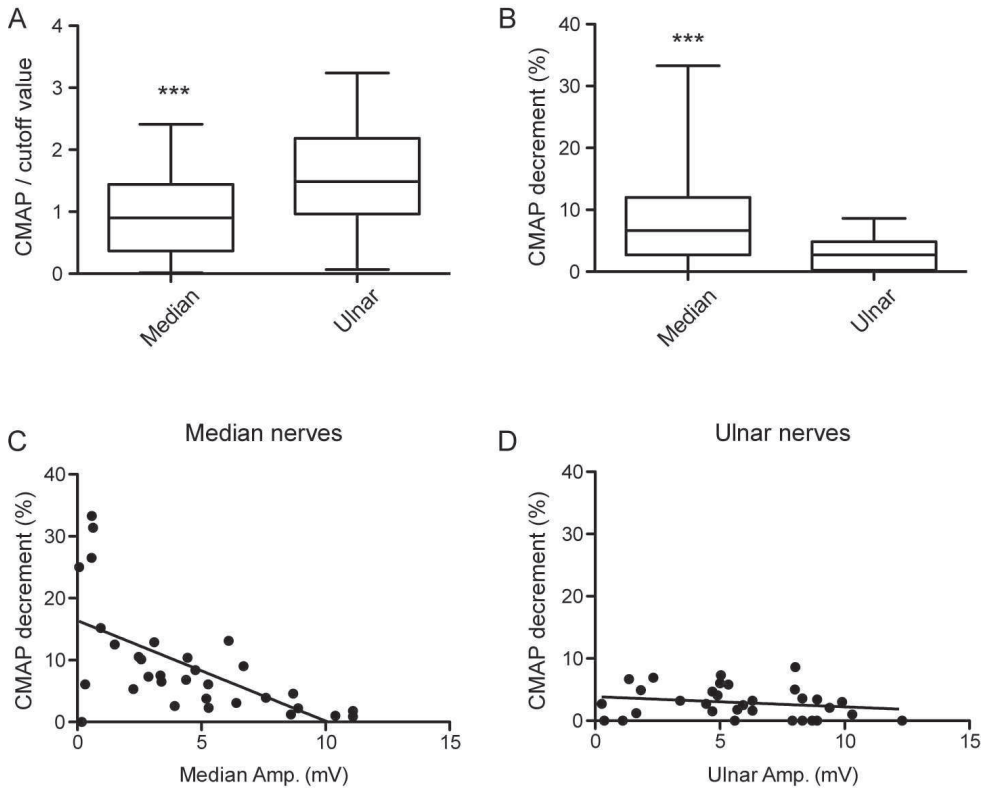
FIGURE LEGENDS

FIGURE 1

(A) Comparison of compound muscle action potentials (CMAP) divided by cutoff values in the median and ulnar nerves. ***, $P < 0.001$. **(B)** Comparison of CMAP decrement in response to 3-Hz repetitive nerve stimulation in the median and ulnar nerves. ***, $P < 0.001$. **(C)** Scatter plot of the decrement and amplitude of the CMAP of the median nerves. R = −0.3824, $P = 0.0002$. **(D)** Scatter plot of the decrement and amplitude of the CMAP of the ulnar nerves. R = −0.0424, $P = 0.2584$.



(A) Comparison of compound muscle action potentials (CMAP) divided by cutoff values in the median and ulnar nerves. ***, P < 0.001. (B) Comparison of CMAP decrement in response to 3-Hz repetitive nerve stimulation in the median and ulnar nerves. ***, P < 0.001. (C) Scatter plot of the decrement and amplitude of the CMAP of the median nerves. R = −0.3824, P = 0.0002. (D) Scatter plot of the decrement and amplitude of the CMAP of the ulnar nerves. R = −0.0424, P = 0.2584.
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