ABSTRACT: Previous studies suggest that in amyotrophic lateral sclerosis (ALS) the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) are more severely involved than abductor digiti minimi (ADM). To elucidate the pattern, frequency, extent, and specificity of such dissociated muscle atrophy in ALS, compound muscle action potentials recorded from APB, FDI, and ADM were analyzed in 77 ALS patients, 171 normal controls, and 196 disease controls. Compared with normal controls, ALS patients had a reduced APB/ADM amplitude ratio ($P < 0.001$) and FDI/ADM ratio ($P < 0.001$), whereas patients with other anterior horn diseases showed similar APB/ADM and FDI/ADM ratios to normal values. Decreased APB/ADM ratio was found in 41% of ALS patients, 5% of normal controls, and 4% of disease controls. Prominent muscle atrophy in APB and FDI, with relatively preserved ADM, appears to be specific to ALS. Dissociated hand muscle atrophy presumably reflects part of the pathophysiology and supports the diagnosis of ALS.


DISSOCIATED SMALL HAND MUSCLE ATROPHY IN AMYOTROPHIC LATERAL SCLEROSIS: FREQUENCY, EXTENT, AND SPECIFICITY

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In patients with amyotrophic lateral sclerosis (ALS), muscle wasting preferentially affects the thenar muscle (abductor pollicis brevis, APB) and first dorsal interosseous (FDI) muscle compared with the hypothenar muscles,5,13,14 and this pattern of dissociated small hand muscle atrophy has been termed the “split hand” by Wilbourn.14 Although a loss of motor neurons has been demonstrated using motor unit number estimates in both APB and the hypothenar muscle (abductor digiti minimi, ADM),1,3,8,15 a previous study comparing the loss of motor unit numbers in APB and ADM showed that the loss in APB is far greater than in ADM.7

APB, FDI, and ADM are innervated by spinal motor neurons of the same segments (C8 and T1), and FDI and ADM have the same ulnar nerve supply. Although it is not known why APB and FDI are preferentially affected compared with ADM, it is also unclear whether the dissociated muscle atrophy is seen specifically in ALS. Previous reports have shown a similar dissociation in disorders affecting lower motor neurons, such as spinal muscular atrophy (SMA) and spinocerebellar ataxia type 3 (SCA-3),9 and even in normal elderly individuals.11 Furthermore, the comparison between APB and FDI involvement has rarely been examined.

We therefore conducted a prospective multicenter study to elucidate the pattern, frequency, extent, and specificity of the dissociated small hand

Abbreviations: ADM, abductor digiti minimi; ALS, amyotrophic lateral sclerosis; APB, abductor pollicis brevis; BSMA, bulbo-spinal muscular atrophy; CMAP, compound muscle action potential; CSA, cervical spondylotic amyotrophy; FDI, first dorsal interosseous; LMND, lower motor neuron disorders; SCA, spinocerebellar ataxia; SMA, spinal muscular atrophy

Key words: amyotrophic lateral sclerosis; compound muscle action potential; nerve conduction study; small hand muscle; split hand

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muscle atrophy in ALS and the results were compared with those of a large number of normal as well as neurological controls.

MATERIALS AND METHODS

Subjects. Seventy-seven consecutive ALS patients, 171 normal controls, and 196 disease controls were prospectively examined between February 1 and September 30, 2007. They were seen at EMG clinics of 11 tertiary medical centers (The Tokyo Metropolitan Neuromuscular Electrodiagnosis Study Group). The ALS patients fulfilled the revised El Escorial criteria for definite, probable, or probable laboratory-supported ALS. There were 43 men and 34 women ranging in age from 45–83 years (mean, 66 years). Disease duration ranged from 4–50 months (mean, 14 months). We excluded coincidental carpal tunnel, cubital tunnel, or Guyon canal syndrome on the basis of clinical examination and nerve conduction studies.

During the same study period, 171 normal volunteers (84 men and 87 women; mean age, 47 years; range, 23–76 years) and 196 patients with small hand muscle atrophy caused by a disorder other than ALS (103 men and 93 women) were also examined. The disease controls included 16 patients with lower motor neuron disorders such as SMA (n = 6), bulbospinal muscular atrophy (BSMA, genetically confirmed; n = 5), and SCA-3 (genetically confirmed; n = 5); 28 with cervical spondylotic amyotrophy; and 152 with polyneuropathy. SCA-3 was included in lower motor neuron disorders because its spinal pathology usually showed loss of motor neurons, and hence it can be regarded as a type of anterior horn disease. Causes of polyneuropathies included chemotherapeutic agents, alcohol abuse, vitamin B1 deficiency, POEMS syndrome, and diabetes. We excluded patients with mononeuropathy or multiple mononeuropathy.

Nerve Conduction Studies. Nerve conduction studies were performed by conventional procedures using EMG machines (Viking 4, Nicolet Biomedical Japan, Tokyo, Japan, or Neuropack, Nihon-Kohden, Tokyo, Japan). Compound muscle action potentials (CMAPs) were recorded from the APB, FDI, and ADM muscles after median or ulnar nerve stimulation at the wrist. For FDI recording the active electrode was placed on its belly and the reference electrode at the medial aspect of the proximal interphalangeal joint of the index finger. Skin temperature on the forearm or palm was monitored and maintained above 33°C. The initial negative-peak amplitudes were measured for all CMAPs. Absolute amplitudes, amplitude ratios of APB/ADM, FDI/ADM, and FDI/APB, and amplitude differences of APB – ADM, FDI – ADM, and FDI – APB were measured. All patients gave informed consent to the study procedures, which were approved by the local ethics committee.

Statistical Analyses. The differences in CMAP amplitudes and amplitude ratios between the normal and patient groups were analyzed using the Mann–Whitney U-test. Regression analyses were performed using Spearman’s rank correlation test.

RESULTS

Normal Subjects. Table 1 shows CMAP amplitudes of APB, ADM, and FDI and their amplitude ratios and differences. In normal controls the mean CMAP amplitude was similar for APB and ADM; therefore, the APB/ADM amplitude ratio was 1.0 and the APB-ADM amplitude difference was nearly zero. The mean FDI amplitude was 50% higher than those of APB and ADM, and the FDI/ADM and FDI/APB ratios were approximately 1.5. When these data were plotted against the subjects’ age, absolute amplitudes declined with age; there were weak inverse

<table>
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<th>Table 1. CMAP amplitude ratios and differences.</th>
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<td><strong>Number</strong></td>
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</tr>
<tr>
<td>Normal</td>
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ALS, amyotrophic lateral sclerosis; LMND, lower motor neuron disease; CSA, cervical spondylotic amyotrophy; *p < 0.05, **p < 0.001 compared with normal values. Data are expressed as mean (SD)
relationships between age and amplitudes of APB \((P = 0.03)\), ADM \((P = 0.046)\), and FDI \((P = 0.04)\). However, there was no significant relationship between age and amplitude ratios of APB/ADM, FDI/ADM, and FDI/APB, and age-dependent changes were not found in analyses of amplitude differences. These findings suggest that absolute CMAP amplitudes decline with age, but the extent of decrease does not significantly differ for APB, ADM, and FDI. Therefore, age-matched normal controls were used for absolute amplitude analyses, and for CMAP amplitude ratios the data of all the normal subjects were compared with those of the patients.

The values of absolute amplitudes and amplitude ratios did not show a Gaussian distribution and considerable variability was noted for each value (SD ranged from 22% to 31% of the mean values). The normal limits were therefore defined as a value outside a 2.5 SD of the mean of the logarithmically transformed values of the normal controls. For amplitude ratios the lower limits were set at 0.6 for the APB/ADM ratio and 0.9 for FDI/ADM ratio. Using these cutoff values, 95%–99% of normal subjects had values within the normal range (Table 2).

To assess interlaboratory variation of amplitude measurements, the mean APB, ADM, and FDI amplitudes were compared among 11 laboratories but the values were not significantly different.

### ALS and Other Forms of Neurogenic Amyotrophy.

Of the 77 ALS patients, three had absent responses from APB \((n = 3)\), ADM \((n = 1)\), or FDI \((n = 2)\). These patients were excluded from amplitude analyses. Figure 1 compares the absolute amplitude of the three muscles in normal controls and in patients with ALS, lower motor neuron disorders (LMND), cervical spondylotic amyotrophy (CSA), and polyneuropathy. Compared with normal values, all the amplitudes were significantly lower in all the patient groups. However, patterns of the amplitude decreases differed among these disorders. The LMND and neuropathy groups showed a pattern similar to that of the normal subjects, CMAP amplitudes being similarly low in APB and ADM, and high in FDI. In contrast, ALS patients had markedly reduced APB and FDI amplitudes. APB/ADM and FDI/ADM ratios, therefore, were the lowest among ALS patients (Table 1). In CSA patients ADM amplitudes were lowest, and therefore the APB/ADM ratio was high. Analyses of amplitude differences showed similar results; ALS patients had greater differences between APB and ADM amplitudes and between FDI and ADM amplitudes. Thus, both amplitude ratio and amplitude difference analyses suggest that in ALS, APB, and FDI are more severely affected than ADM.

In ALS patients there was no significant relationship between disease duration and APB/ADM and FDI/ADM amplitude ratios, suggesting that the dissociated muscle involvement occurs at an early stage of the disease. In subgroups of ALS patients divided according to region of symptom onset (bulbar, upper limb, and lower limb), the CMAP amplitude ratios and differences were similar for the three subgroups (Table 1).

Table 2 shows the percentage of patients with abnormally decreased APB/ADM and FDI/ADM ratios. The ALS group included much higher percentages of patients with abnormal CMAP amplitude ratios, which were rarely found in the other patient groups.
groups. In particular, abnormality of both the APB/ADM and FDI/ADM ratios was found in 20% of ALS patients, none of the 171 normal controls, and only one (0.5%) of the 196 patients with LMND, CSA, or polyneuropathy; only one patient with BSMA had abnormal amplitude ratios of both APB/FDI (0.42) and FDI/ADM (0.88).

**DISCUSSION**

Our results confirmed that in ALS the APB and FDI muscles are preferentially affected compared with ADM, and showed that this pattern of dissociated small hand muscle atrophy is nearly specific to ALS. In our ALS patients the APB/ADM ratio appeared to be more sensitive and specific than the FDI/ADM ratio, as shown in Table 2. These results suggest that the dissociated small hand muscle involvement is supportive of a diagnosis of ALS.

Previous studies demonstrated that dissociated small muscle atrophy is most frequently seen in ALS. However, this phenomenon is reported occasionally in other anterior horn diseases, and even in normal elderly individuals. Our data showed that when cutoff values of CMAP amplitude ratio are set based on data from a large number of normal controls, preferential involvement of both APB and FDI is nearly specific to ALS, although 1 (6%) of the 16 patients with LMND showed decreased APB/ADM and FDI/ADM ratios. The three muscles, APB, ADM, and FDI, were almost equally affected in our patients with LMND or axonal neuropathy. The prominent dissociated hand muscle atrophy, particularly the combination of APB/ADM ratio <0.6 and FDI/ADM ratio <0.9, was rarely found in LMND, CSA, and polyneuropathy. Although exceptional cases may be present, the dissociated involvement among muscles presumably leads to a diagnosis of ALS. Regarding the age-dependent effects, it is reasonable to suppose that absolute amplitudes decline with aging due to the physiological loss of motor units. However, our findings do not provide evidence of age-related changes in amplitude ratio and thereby different age-dependent effects among the small hand muscles. A previous report comparing the age-related changes in the APB, ADM, and FDI muscles suggested that APB and FDI undergo greater age-dependent changes than ADM. However, the study examined the differences, not ratios, in CMAP amplitudes between APB and ADM, or FDI and ADM. We also studied amplitude differences, but our data showed that aging does not appear to be associated with prominent differences in the extent of motor unit loss among the small hand muscles.

It is not clear what mechanisms cause the preferential involvement of APB and FDI in ALS, but several possibilities were raised in a previous study. First, because humans use the thumb and index finger more often than other fingers, the more frequent use of APB and FDI may lead to more oxidative stress or may place more metabolic demand on APB and FDI spinal motor neurons. Second, although the pattern of degeneration of anterior horn cells is random in ALS, APB or FDI cortical motor neurons far outnumber those of ADM. Consequently, the corticospinal connections of APB or FDI motor neurons are much more extensive than those of ADM motor neurons, and this could result in more prominent glutamate excitotoxicity in APB and FDI spinal motor neurons. Further studies will be required to elucidate the mechanisms of vulnerability of APB and FDI in ALS.

The differences in patterns of small hand muscle involvement in ALS and CSA could be of clinical significance because their differential diagnosis is important on clinical practice. In CSA the ADM and FDI seemed to be more preferentially affected than APB. Patients with CSA can have variable patterns according to the affected spinal segments or nerve roots but, as a group, the APB was relatively spared, and this contrasts with the pattern in ALS patients. Again, the reason for the dissociation in CSA patients is unknown, but we speculate that there may be some differences in the spinal segments innervating APB and ADM, or in distribution of APB and ADM/FDI motor neurons in the anterior horn. This issue should be examined in future studies.

A simple comparison of multiple CMAP amplitudes could provide new insights into the pathophysiology of disorders causing neurogenic amyotrophy. The dissociated muscle involvement presumably reflects part of the pathophysiology of ALS. We suggest that when such dissociated amyotrophy is clearly detected during nerve conduction studies in patients with suspected ALS, subsequent needle examination will lead to its diagnosis in most instances.

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REFERENCES