ELECTROPHYSIOLOGICAL FEATURES OF HIRAYAMA DISEASE

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ABSTRACT: *Introduction:* The purpose of this study was to compare the pattern of hand muscle involvement in Hirayama disease (HD) and amyotrophic lateral sclerosis (ALS). *Methods:* We reviewed findings of upper limb nerve conduction studies of 46 HD patients and 60 ALS patients. The findings from 54 healthy subjects were used for comparison. *Results:* In HD, the ulnar compound muscle action potential (CMAP) amplitude was more severely reduced than the median one, and the reverse pattern was observed in ALS. The mean ulnar/median (U/M) CMAP amplitude ratio was significantly lower in HD (0.64 ± 0.79) and abnormally higher in ALS (2.15 ± 1.77) compared with normal subjects (0.89 ± 0.23). An abnormally low U/M CMAP amplitude ratio (<0.6) was encountered in 34 patients with HD and in 1 with ALS. A U/M CMAP amplitude ratio ≥4.5 or absent median motor response was found only in ALS. *Conclusion:* Our findings demonstrate different patterns of hand muscle involvement between these two diseases.

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Hirayama disease (HD) is a form of juvenile-onset spinal muscular atrophy characterized by slowly progressive distal amyotrophy of the upper limbs. It is usually monomelic or asymmetric and mainly affects the C7–T1 myotomes.[1–3] Although muscle weakness and wasting in patients with this disease is most pronounced in distal muscles of the upper limb, proximal weakness in the arm is also observed.[4] Progression of amyotrophy in HD usually arrests within a few years. This disease is considered to be a benign focal motor neuron disease. One recent report showed that bilateral symmetric involvement occurred in about 10% of patients with HD.[5]

Amyotrophic lateral sclerosis (ALS) is a progressive, devastating disease resulting from variable degeneration of the upper motor neurons (UMNs) and lower motor neurons (LMNs).[6] Its clinical features include limb spasticity, hyperreflexia, focal or multifocal limb weakness and atrophy, fasciculations, dysarthria, dysphagia, and difficulty in mastication. In sporadic ALS, initial involvement of the arms occurs in about 40% of patients and, in most cases, features of combined UMN and LMN involvement are present.[6] Limb weakness is usually asymmetric in early ALS, and initial manifestations may include either UMN or LMN involvement.[7] Distinguishing between ALS and HD is extremely important, because the former will relentlessly progress to quadriplegia with respiratory failure, whereas the latter will not.

The purpose of this study was to compare the findings of nerve conduction studies of the upper limbs in patients with HD and those with ALS, and to investigate the usefulness of these findings for discrimination between the two disorders.

METHODS

We retrospectively reviewed the results of nerve conduction studies of 46 patients (40 males and 6 females) who attended our neuromuscular clinics with a diagnosis of HD, as well as 60 patients (38 males and 22 females) with ALS, between 1995 and 2007.

Diagnostic criteria for HD included: (1) onset before the age of 25 years; (2) unilateral or bilateral distal predominant weakness and wasting of the upper limbs without sensory impairment; (3) static clinical course after slowly insidious progression; (4) no lower limb involvement; and (5) no history of syringomyelia, spinal cord tumor, cervical vertebral abnormality, multifocal motor neuropathy, congenital muscular dystrophy, trauma, inflammation, infection, or any other cause for the clinical findings.[1,8–11] Dynamic cervical magnetic resonance imaging (MRI) study with neck flexion disclosed posterior dural shifting anteriorly and engorged venous plexus in the posterior dural space in 43 (93%) of the 46 patients with HD.

The diagnosis of ALS was based on the El Escorial criteria,[12] with features of progressive muscle weakness, atrophy, fasciculation, and pyramidal signs, in the absence of sensory deficits and sphincter disturbance.

The mean onset age of the 46 patients with HD and 60 patients with ALS was 17.0 ± 3.0 (range 12–24) and 54.6 ± 13.0 (range 31–78) years, respectively. The mean age at the time of nerve conduction studies of the HD and ALS groups was 21.8 ± 6.3

Abbreviations: ADM, abductor digiti minimi; AE, above the elbow; ALS, amyotrophic lateral sclerosis; APB, abductor pollicis brevis; BE, below the elbow; CMAP, compound muscle action potential; CSA, cervical spondylotic amyotrophy; CV, conduction velocity; HD, Hirayama disease; LMN, lower motor neuron; MRI, magnetic resonance imaging; SNAP, sensory nerve action potential; UMN, upper motor neuron; U/M, ulnar/median

Key words: amyotrophic lateral sclerosis, compound muscle action potential, Hirayama disease, split hand syndrome, ulnar/median ratio

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Table 1. Results of motor conduction studies.

	Median nerve		Ulnar nerve		U/M ratio	
	Amp (mV)	CV (m/s)	Amp (mV)	CV (m/s)	Amp	CV
HD patients	8.1 (3.8)‡,§	57.1 (4.5)*,§	3.7 (2.7)‡	56.7 (5.8)†	0.64 (0.79)*,§	0.99 (0.10)
ALS patients	3.2 (2.8)‡	53.1 (5.1)‡	4.8 (3.3)†	54.9 (6.2)‡	2.15 (1.77)‡	1.04 (0.13)
Normal subjects	10.3 (2.0)	59.0 (4.6)	8.9 (1.6)	60.3 (6.9)	0.89 (0.23)	1.03 (0.12)

Data are presented as mean (standard deviation). Conduction velocities in the forearm segment were used for analyses. The amplitude values were recorded as zero if motor responses were absent. U/M ratio, ratio of the ulnar to the median nerve; Amp, negative peak amplitude; CV, conduction velocity; HD, Hirayama disease; ALS, amyotrophic lateral sclerosis.
$^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.001$, vs. normal subjects; $^{\S}P < 0.001$, vs. ALS group (unpaired Student's t-test).

(range 16–42) and 56.0 ± 12.3 (range 32–78) years, respectively. The mean duration of progression in patients with HD was 28.6 ± 17.8 (range 3–60) months. The mean duration between onset of disease and performance of nerve conduction studies in patients with ALS was 11.4 ± 9.7 (range 3–60) months; at the time of the investigation, muscle weakness was still progressing in all patients.

Nerve conduction studies were performed according to standardized procedures.[3] Motor conduction studies consisted of stimulating the median and ulnar nerves and recording the compound muscle action potentials (CMAPs) from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM), respectively. The median nerve was stimulated at the wrist and elbow, whereas the ulnar nerve was routinely stimulated at the wrist, below the elbow (BE), above the elbow (AE), and in the axilla. The distance of the BE–AE segment was 10 cm with the elbow in moderate flexion. Surface electrodes were used for recording, with the active electrode placed over the belly of the muscles and the reference electrode over the tendon of those muscles. Any patient with motor nerve conduction block, defined by a decline of CMAP amplitude of >40% between distal and proximal stimulation, in either the median or ulnar nerve, suggestive of multifocal motor neuropathy with conduction block, was excluded.[3] Median and ulnar sensory conduction studies consisted of stimulating the nerves at the wrist, and recording the sensory nerve action potentials (SNAPs) on the second and fifth digits, respectively. If the median sensory conduction velocity (CV) of the wrist-to-digit segment was slower than 50 m/s, then another electric stimulation at the midpalm would be given. In these cases, CVs of both the wrist-to-palm and palm-to-digit segments were also calculated. Surface electrodes were used for recording; they were placed at the proximal and distal interphalangeal joint of the digit as the active and reference electrodes, respectively. For those patients with bilateral involvement at the time of nerve conduction studies (9 patients with HD, and most patients with ALS), only data from the most affected hand were included for analysis. For comparison, results of nerve conduction studies were obtained from 56 healthy volunteers (31 men and 23 women, ages 18–68 years, mean 36.7 years). All these normal subjects received a screening history and physical examination to exclude any neuromuscular disease or relevant systemic condition.

Negative peak amplitudes of CMAPs and SNAPs, and motor and sensory CVs of the median and ulnar nerves were recorded. For the ulnar nerve, only motor CV of the forearm segment was used for analysis; for the median nerve, only sensory CV of the wrist-to-digit segment was used for analysis. The ulnar/median (U/M) ratio for each parameter was calculated. Any U/M CMAP amplitude ratio that was <0.6 or >1.7 was considered abnormal.[13] Presence of ulnar motor nerve entrapment at the elbow was defined by an ulnar motor CV across the elbow segment that was slower than that of the forearm segment by ≥10 m/s.[14] Median neuropathy across the wrist was defined by a median sensory CV across the wrist of <43 m/s.[15]

The two-sample *t*-test and Pearson's correlation coefficients were used for statistical analyses. This retrospective study was approved by the institutional review board of the Chang Gung Memorial Hospital (96-1168B).

RESULTS

Table 1 shows the results of motor conduction studies. In normal subjects, the median CMAP amplitudes were slightly larger than those of the ulnar CMAP, and the mean U/M CMAP amplitude ratio was 0.89 (range 0.61–1.66). The median and ulnar CVs were similar, and hence the U/M CV ratio was near 1.0.

In patients with HD, the ulnar CMAP amplitudes were moderately reduced, whereas the median CMAP amplitude was slightly reduced compared with normal subjects. The HD mean U/M CMAP amplitude ratio was 0.64 (range 0–4.00), which was significantly lower than that of normal subjects. The HD mean median–ulnar CMAP amplitude difference was 4.5 ± 0.23 mV (range −4.0 to 14.2 mV). In the HD group, an abnormally low median CMAP

Table 2. Results of the ulnar/median CMAP amplitude ratio.

	Ulnar/median CMAP ratio			
	<0.6	0.6–1.7	>1.7	Median nerve = no response
Forearm–Eb ulnar MCV difference <10 m/s				
HD	23	6	4	0
ALS	1	26	23	3
Normal subjects	0	54	0	0
Forearm–Eb ulnar MCV difference ≥10 m/s				
HD	8	2	0	0
ALS	0	3	0	2
Ulnar nerve = no response				
HD	3			0
ALS	0			2
Total	35	91	27	7

CMAP, compound muscle action potential; Eb, across the elbow segment; MCV, motor conduction velocity; HD, Hirayama disease; ALS, amyotrophic lateral sclerosis.

amplitude (<6.0 mV) was found in 10 (22%) patients, and an abnormally low ulnar CMAP amplitude (<5.5 mV) was found in 36 (78%).

In patients with ALS, the median CMAP amplitudes were markedly reduced, and the ulnar CMAP amplitudes were moderately reduced compared with normal subjects. The ALS mean U/M CMAP amplitude ratio was 2.15 (range 0.33–7.80), which was significantly higher than that of normal subjects. The ALS mean median–ulnar CMAP amplitude difference was -1.6 ± 2.2 mV (range -7.6 to 4.1 mV). In the ALS group, an abnormally low median CMAP amplitude was found in 47 (78%) patients, and an abnormally low ulnar CMAP amplitude was found in 38 (63%).

The median and ulnar motor CVs of patients with HD and those with ALS were slower than those of normal subjects. The degree of CV slowing was similar in both the median and the ulnar nerves of both groups. Therefore, the mean U/M CV ratios remained closed to 1.0 in both the HD and ALS groups. In the HD group, abnormally slow median and ulnar motor CV (<50 m/s) was noted in 3 (6.5%) and 2 (4%) patients, respectively. Of the 60 patients with ALS, abnormally slow median and ulnar motor CV was found in 8 (13%) and 6 (10%) patients, respectively.

There was a correlation ($R = 0.398$, $P = 0.003$, with Pearson's correlation) between the ulnar CMAP amplitude and ulnar motor CV in the ALS group. No statistically significant correlation was found between the median CMAP amplitude and median motor CV in the ALS group, or between the CMAP amplitudes and motor CVs of both the median and ulnar nerve in the HD group.

Table 2 shows detailed results of the U/M CMAP amplitude ratio, and Figure 1 shows the distribution of the U/M CMAP amplitude ratio. Of the 35 patients with an abnormally low U/M CMAP amplitude ratio (<0.6), including 3 with absent ulnar CMAPs (hence, the ratio was 0), 34 (97%) had HD. Thus, 74% of patients with HD and only 1 (1.6%) with ALS had an abnormally low U/M amplitude ratio.

As shown in Table 2, abnormal focal slowing of the ulnar motor CV across the elbow was found in 10 (23%) patients with HD. Of these 10 patients, 8 (80%) had an abnormally low U/M CMAP amplitude. Of the 33 HD patients without ulnar motor nerve entrapment at the elbow, 23 (70%) had abnormally low U/M CMAP amplitude. The median and ulnar CMAP amplitudes as well as the U/M CMAP amplitude ratio of the 10 patients with ulnar motor nerve entrapment at the elbow were not statistically different from those of the 33 patients without ulnar nerve entrapment (Table 3). Absence of ulnar CMAP was found in 3 patients with HD, and hence it was not possible to know whether ulnar motor nerve entrapment was present in these patients.

Abnormal focal slowing of the ulnar motor CV across the elbow was found in 5 (9%) patients with

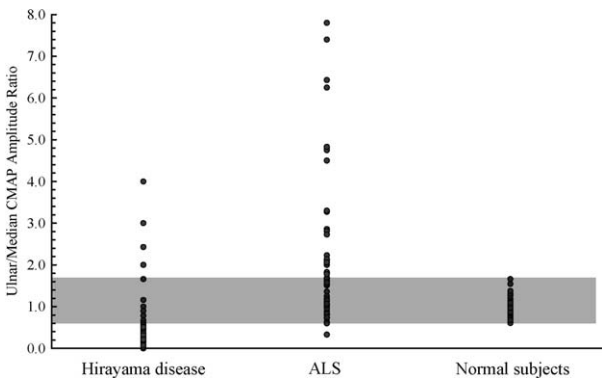

FIGURE 1. Distribution of ulnar/median CMAP amplitude ratio in patients with Hirayama disease and amyotrophic lateral sclerosis (ALS), and in normal subjects. Shadowed areas indicate normal range (0.6–1.7).

Table 3. CMAP amplitudes of patients with and without ulnar motor nerve entrapment.

	HD			ALS		
	Median nerve	Ulnar nerve	U/M ratio	Median nerve	Ulnar nerve	U/M ratio
Forearm–Eb ulnar MCV difference <10 m/s	7.7 (4.1)	3.8 (2.7)	0.75 (0.89)	3.4 (2.8)	5.2 (3.2)*	2.24 (1.79)
Forearm–Eb ulnar MCV difference ≥10 m/s	9.5 (2.8)	4.2 (2.3)	0.47 (0.28)	2.1 (2.3)	2.1 (1.4)*	0.76 (0.05)

Data indicate negative amplitude of CMAP (mV) or its ratio, and are presented as mean (standard deviation). CMAP, compound muscle action potential; HD, Hirayama disease; ALS, amyotrophic lateral sclerosis; U/M ratio, ratio of CMAP amplitude of the ulnar to the median nerve; Eb, across the elbow segment; MCV, motor conduction velocity.
**$P < 0.05$ (unpaired Student's t-test).*

ALS. The ulnar CMAP amplitudes of these 5 patients were significantly lower than those of the 53 ALS patients without focal slowing of the ulnar motor CV across the elbow (Table 3). Absence of an ulnar CMAP was found in 2 patients with ALS.

An abnormally high U/M CMAP amplitude ratio (>1.7) was encountered in 23 (38%) patients with ALS, and 4 (9%) with HD (Table 2). A U/M CMAP amplitude ratio of ≥4.5 was found in 8 (13%) patients, all with ALS. As a result, the U/M CMAP amplitude ratio was more widely distributed in the ALS group than in the HD group (Fig. 1). An absent median CMAP was found in 7 (12%) patients with ALS and none with HD. Accordingly, one quarter of our ALS patients had either a U/M CMAP amplitude ratio of ≥4.5 or an absent median CMAP.

Table 4 shows the results of sensory conduction studies. An abnormally low median SNAP amplitude (<13 μV) was found in 1 patient. This patient who had HD also had abnormally slow median sensory CV (37 m/s) across the wrist segment, as well as a markedly low median CMAP amplitude (1.1 mV). Hence, his abnormally high U/M CMAP amplitude ratio (4.0) could be at least partially attributable to median nerve entrapment at the wrist. Electrophysiological evidence of median neuropathy at the wrist was found in another patient with HD. Both the median CMAP amplitude (7.0 mV) and U/M CMAP amplitude ratio (0.60) of this patient were normal.

Electrophysiological evidence of median neuropathy at the wrist was detected in 8 patients with ALS. Their mean median SNAP amplitude was 28.8 ± 11.0 μV (range 15.1–50.0 μV); none of them had abnormally low median SNAP amplitudes. The mean U/M CMAP amplitude ratio of these patients was comparable to that of the ALS patients who did not have median nerve entrapment at the wrist (2.1 ± 1.4 vs. 2.2 ± 1.8).

None of our patients had abnormally low-amplitude ulnar SNAPs (<12 μV). In the HD group, the mean median SNAP amplitude was slightly greater compared with that of the normal subjects. In the ALS group, the median sensory CV was slightly slower compared with those of the HD group and normal subjects.

DISCUSSION

In our normal subjects, the median CMAP amplitudes were slightly higher than the ulnar CMAP amplitudes. These findings are comparable to previous studies.[16,17] Kuwabara et al.[16] reported that the mean APB/ADM CMAP ratio of their normal subjects was 1.22, which was similar to that of our normal subjects.

Although both the thenar and hypothenar muscles originate from the C8/T1 myotomes, a different degree of muscle weakness and wasting has been noted in patients with ALS. Thenar muscles are more severely affected than the hypothenar muscles in some patients with ALS. Motor unit loss was also found to be far greater in the APB than in the ADM in ALS.[16] One prospective study showed that, in ALS, the mean APB–ADM amplitude difference was −1.7 mV, and the mean APB/ADM CMAP

Table 4. Results of sensory conduction studies.

	Median nerve		Ulnar nerve		U/M ratio	
	Amp (μV)	CV (m/s)	Amp (μV)	CV (m/s)	Amp	CV
HD patients	48.7 (15.2)‡,§	62.6 (6.9)§	41.9 (14.8)	59.5 (7.5)	0.88 (0.49)	0.95 (0.11)§
ALS patients	39.1 (17.3)	57.0 (9.2)†	37.4 (18.6)	56.6 (7.9)	0.99 (0.36)	1.02 (0.12)*
Normal subjects	37.8 (19.2)	60.5 (4.4)	36.1 (15.7)	57.2 (7.9)	1.02 (0.36)	0.96 (0.11)

Data are presented as mean (standard deviation). U/M ratio, ratio of the ulnar to the median nerve; Amp, negative peak amplitude; CV, conduction velocity; HD, Hirayama disease; ALS, amyotrophic lateral sclerosis.
**$P < 0.05$, †$P < 0.01$, ‡$P < 0.005$, vs. normal subjects; §$P < 0.005$, vs. ALS group (unpaired Student's t-test).*

amplitude ratio was 0.7. An abnormally low APB/ADM amplitude ratio was noted in 41% of patients.[13] In our ALS group, the mean median–ulnar (i.e., APB–ADM) CMAP amplitude difference was −1.6 mV, and the mean U/M (i.e., ADM/APB) CMAP amplitude ratio was 2.15. In addition, an abnormally high U/M amplitude ratio (>1.7) was noted in 23 (38%) patients. Hence, our results confirm that the thenar muscles are more severely affected than the hypothenar muscles in ALS. However, it is worth noting that an abnormally high U/M amplitude ratio was also found in 4 (9%) patients with HD. Based on the results of sensory conduction studies, such an abnormally high U/M CMAP amplitude ratio could be attributable to median nerve entrapment at the wrist, except in 1 patient with HD.

"Split hand syndrome" was first used by Wilbourn et al. to describe a type of hand muscle atrophy observed in patients with ALS, in which the muscles of the lateral aspect of the hand were affected more severely than the muscles of the medial aspect.[18] Although this phenomenon was primarily observed in patients with ALS, Wilbourn et al. pointed out that not every ALS patient with hand muscle wasting shows such dissociation, and this phenomenon is not limited to ALS.[18] They observed this type of hand muscle atrophy in patients with spinal muscular atrophy, "benign" focal motor neuron disease, and remote poliomyelitis. As a result, they concluded that this phenomenon seemed to be specific for anterior horn cell disorders.[18]

The mechanism of the split hand in ALS is unclear. By comparing the CMAPs elicited by peripheral stimulation and cortical motor response evoked by magnetic stimulation, Weber et al.[19] found that the cortical/peripheral ratios for the thenar muscles were significantly lower in ALS patients compared with those of healthy control subjects. Such a reduction was not observed for the hypothenar muscles. Accordingly, they concluded that the split hand in ALS is of cortical origin.[19] However, others have suggested that split hand syndrome could be of spinal origin, because the same phenomenon is observed in diseases with different pathophysiological mechanisms.[20] The results of our study show that the typical split hand syndrome could be encountered in patients with HD. Because HD is primarily an LMN disorder, the observation of the split hand phenomenon in patients with this disease provides evidence to support the theory of a spinal origin of split hand syndrome.

Therefore, electrophysiological features of a split hand syndrome could not be used as evidence suggestive of a diagnosis of ALS. Based on our results, the distinctive electrophysiological findings for ALS rather than HD are either a U/M CMAP amplitude ratio ≥4.5 or an absent median motor response. These were encountered in 25% of our ALS patients.

In contrast to dissociated hand muscle atrophy with predominant thenar muscle involvement in ALS, 74% of our patients with HD showed a reverse pattern of involvement; that is, the hypothenar muscles were more severely involved than the thenar muscles. This reverse pattern of hand muscle involvement was found in only 1 ALS patient. Hence, this could be a useful clue to distinguish between HD and ALS; a U/M CMAP amplitude ratio of <0.6 strongly suggests the diagnosis of HD rather than ALS.

Electrophysiological evidence of ulnar motor nerve entrapment at the elbow was not uncommon in our patients. This occurred in 10 (23%) patients with HD and 5 (9%) with ALS. In HD, such findings were encountered in a similar incidence in patients with and without an abnormally low U/M CMAP amplitude ratio. In addition, the mean U/M CMAP amplitude ratio was not significantly different between these two groups. Therefore, an abnormally low U/M CMAP amplitude ratio in HD cannot be attributable to entrapment of the ulnar motor nerve at the elbow. Observation of subclinical ulnar motor nerve entrapment at the elbow in our patients is of clinical importance. Unnecessary surgical exposure of the elbow in young patients with progressive hand muscle atrophy should be avoided even if electrophysiological studies have suggested ulnar motor nerve entrapment at the elbow, unless the diagnosis of HD had been carefully excluded.

The electrophysiological characteristics observed in HD reflect the clinical pattern of muscle weakness in this disorder. In HD, the ADM and first dorsal interosseous were the weakest and most frequently involved muscles, followed by the APB.[3] Nevertheless, this pattern of asymmetric intrinsic hand intrinsic involvement is also non-specific. It can also be found in patients with cervical spondylotic amyotrophy (CSA). Kuwabara et al. reported that, in 28 patients with CSA, the mean APB–ADM amplitude difference was 2.6 mV, indicating that the hypothenar muscles were more severely involved than the thenar muscles.[13]

The underlying pathophysiology of HD remains unclear. Cervical MRI studies with neck flexion have shown anterior shifting of the posterior dura and engorged venous plexus in the posterior dural space in most patients.[3] Focal ischemia of the anterior horn area in the cervical cord was observed in one autopsy case.[21] Hence, the presence of dynamic changes induced by neck flexion, with subsequent ventral spinal cord compression and local circulatory insufficiency resulting in anterior

horn cell dysfunction, has been hypothesized to be the pathophysiological mechanism for HD.[22] In cervical spondylotic myelopathy, a decreased vascular supply due to compression of the anterior spinal artery by the posteriorly herniated cervical disks was thought to play an important role in the pathophysiology of the motor dysfunction.[23] Similarly, in CSA, the atrophic hand muscles could also be due to a vascular insult of the corresponding anterior horn cells. Therefore, dissociated hand muscle atrophy in both HD and CSA may share similar mechanisms of chronic ischemic injury of the anterior horn cells. The results of our electrophysiological studies provide evidence to support this hypothesis. However, it remains unexplained as to whether such vascular insufficiency was the pathological mechanism for HD and why clinical features of lateral column dysfunction were not observed in these patients.

In our studies, slightly slower median sensory CV was noted in patients with ALS. This was probably due to the older age of these patients as compared with normal subjects and those with HD. The cause of the larger median SNAP amplitude found in our HD patients is unclear. The younger age of the HD group is a possible explanation. As shown in Table 4, the ulnar SNAP amplitude was also slightly higher in the HD group, although not to a statistically significant degree, compared with that in the ALS group and in normal subjects.

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