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ORIGINAL ARTICLE

Nerve Conduction Studies in the Early Diagnosis of Amyotrophic Lateral Sclerosis and the Importance of Split-Hand Phenomenon

Amyotrofik Lateral Skleroz Erken Tanısında Sinir İletim Çalışmaları ve Ayrık El Bulgusunun Önemi

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ABSTRACT

Aim: The heterogeneity of the Amyotrophic Lateral Sclerosis (ALS) clinical phenotypes leads to difficulties in early diagnosis. The split-hand sign is defined by the thenar muscles that are more prominently affected by hypothenar. In this report, the results of the initial nerve conduction study of the patients were compared with those of the controls in order to increase the findings supporting early diagnosis.
Material and Method: Seventy-five patients who were diagnosed with ALS in our clinic were included in the study. The initial ENMG findings of the patients were compared with those of 70 healthy controls: Distal motor latency (DML), the compound muscle action potential (CMAP) amplitude, velocity in the motor conduction of median, ulnar, peroneal, and tibial nerves; distal latency, amplitude, velocity in sensorial conduction were evaluated. Ulnar/median DML and ulnar/median CMAP amplitude ratios were also examined.
Results: In ALS group, DMLs of the median, ulnar, peroneal, and tibial nerves were significantly longer, and CMAP amplitudes were significantly smaller than those of the controls. The sensory conductions of the median, ulnar, and sural nerves were not statistically different between the groups. The ulnar/median DML ratio of the patients was lower than the ratio of the controls (0.73/0.80;p=0.003) while the ulnar/median CMAP amplitude ratio was greater (1.40/1.11; p=0.002).
Conclusion: Prolonged DML and reduced amplitudes were observed in the motor nerve conduction of ALS patients in the early period. The results of the present study also support the presence of split-hand phenomenon even in early period of limb-onset ALS (both upper and lower). These findings suggest that nerve conduction studies and electrophysiologically detected split-hand sign are important clues for the early diagnosis of ALS in case of heterogeneous clinical phenotype.

Keywords: Amyotrophic lateral sclerosis, split-hand, nerve conduction study

ÖZ

Amaç: Amyotrofik Lateral Skleroz' da (ALS) özellikle başlangıç döneminde klinik ve muayene bulgularının heterojenliği erken tanıda zorluklara yol açmaktadır. 'Ayrık-el' işareti, ALS' de tenar kasların hipotenar kaslardan daha belirgin olarak etkilenmesini tanımlamak için kullanılır. Bu çalışmada erken tanıyı destekleyen bulguları artırmak için ALS hastalarının kliniğimizdeki ilk sinir iletim çalışmalarının sonuçları araştırıldı ve kontrol grubuyla karşılaştırıldı.
Gereç ve Yöntem: Kliniğimizde ALS tanısı ile takip edilen 75 hasta çalışmaya dahil edildi. Hastaların ilk elektronöromyografi bulguları 70 sağlıklı kontrol ile karşılaştırıldı: Distal motor latans (DML), bileşik kas aksiyon potansiyeli (CMAP) amplitüdü, median, ulnar, peroneal ve tibial sinirlerin motor iletim hızları; distal latansları, amplitüdleri ve duyusal iletim hızları değerlendirildi. Ayrıca ulnar/median DML ve ulnar/median CMAP amplitüd oranları kontrol grubuyla karşılaştırıldı.
Bulgular: ALS grubunda kontrol grubuna göre median, ulnar, peroneal ve tibial sinirlerin DML' leri anlamlı olarak daha uzundu ve CMAP amplitüdleri anlamlı olarak daha küçüktü (p□0.05). Median, ulnar ve sural sinirlerin duyusal iletimleri gruplar arasında istatistiksel olarak farklı değildi. Hastaların ulnar/median DML oranı kontrollere göre daha düşüktü (0.73/0.80; p=0.003); ulnar/median CMAP amplitüd oranı ise daha yüksekti (1.40/1.11; p=0.002).
Sonuç: ALS hastalarının erken dönemde motor sinir iletimlerinde uzamış DML ve düşük amplitüdler gözlendi. Bu çalışmada sonuçlarımız, ekstremite başlangıçlı ALS' nin (hem üst hem de alt) erken döneminde bile ayrık-el fenomeninin varlığını ve önemini desteklemektedir. Bulgularımız, ALS' nin spesifik muayene ve elektrofizyoloji bulgularının oldukça heterojen olduğu başlangıç döneminde dahi sinir iletim çalışmaları ve ayrık-el işaretinin erken tanıda önemli ipuçları olduğunu düşündürmektedir.

Anahtar Kelimeler: Amyotrofik lateral skleroz, ayrık-el, sinir iletim çalışması

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease characterized by diffuse upper and lower motor neuron degeneration (1,2). The disease is characterized by the progressive degeneration of motor neurons in the primary motor cortex, corticospinal tract, brain stem, and spinal cord. Although hypotheses such as oxidative stress, glutamate excitotoxicity, viral infections, autoimmune mechanisms, genetic predisposition, glial abnormal activity, and decreased trophic factors in its etiopathogenesis are put forward, the exact aetiology of the disease is unknown (2-4). Such neurophysiological abnormalities were also reported to be based on gene mutations, such as SOD1, C9orf72, FUS, and ALS2 (4,5). The clinical findings of the disease may involve generalized fasciculations, progressive atrophy and weakness of muscles, foot drop, spasticity, exercise intolerance, dysarthria, dysphagia, and dyspnoea. Loss of strength is progressive and the disease is fatal within 2–3 years after diagnosis for the patients with bulbar

onset and within 3–5 years after diagnosis for those with extremity onset (3-6).

Patients with ALS have a wide range of heterogeneous phenotypes in the early period; therefore, difficulties are encountered in early diagnosis. The "split hand" sign is defined by the thenar muscles [Abductor pollicis brevis (APB) and first dorsal interosseous (FDI)] that are more prominently affected than the hypothenar muscle (abductor digiti minimi, ADM). The muscles involved in the ''split-hand'' are innervated through the same spinal segments (C8 and T1), and FDI & ADM, which are differentially affected and both ulnar nerve innervated (7-10). This remarkable sign was referred to as 'split-hand' by Wilbourn (11). In this report, the results of the initial nerve conduction study of the patients with ALS were compared with the healthy controls in order to increase the clues for early diagnosis.

Material and Method

In this retrospective archive screening study, the patients diagnosed with ALS who were examined and treated in our clinic between the years 2002 and 2022 were investigated. The study was carried out with the permission of University Noninvasive Clinical Research Ethics Commitee (Decision no: 22-KAEK-090). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patient data were collected with an automated system that enables access to the results of the examination, consultation, background, and other investigations performed in all units including inpatient services, outpatient clinics, laboratories, and the radiology department. The results of the first EMG and nerve conduction studies that were conducted in our own electrophysiology laboratory for the patients who were followed up at our clinic due to diagnosis of ALS were evaluated. These findings were compared with the findings of the control group, patients presenting with a pre-diagnosis of cervical discopathy or entrapment neuropathy, and whose all nerve conduction studies/needle EMG results were reported as normal, and consistent in terms of age and gender at the same laboratory. Seventy-five patients who were diagnosed with limb-onset ALS at our clinic were included in the study. Patients with additional clinical and/or electrophysiological findings such as diabetes mellitus, polyneuropathy, entrapment neuropathy, demyelinating disease, and spondylotic myelopathy were not included in the study. In clinical studies, it has been reported that some of the patients with bulbar-onset only continued as "isolated bulbar involvement" throughout the entire disease period, and extremity involvement was never observed. Therefore, bulbar-onset ALS patients (n= 8) were excluded in this study.

Multiple ENMG examinations were performed in our electrophysiology laboratory during the diagnosis and follow-up of the majority of our patients who were observed for ALS diagnosis. The initial ENMG findings of the patients in our electrophysiology laboratory were compared with those of the 70 healthy controls: Distal motor latency (DML), the compound muscle action potential (CMAP) amplitude, motor conduction velocity of median, ulnar, peroneal and tibial nerves, and sensory distal latency, amplitude, sensory conduction velocity of the same nerves and sural nerve were evaluated. In addition, ulnar/median DML and ulnar/median CMAP amplitude ratios were compared between the two groups.

The Kolmogorov-Smirnov test of normality was used to examine whether or not the continuous variables were normally distributed. Independent two sample t-test was employed to compare continuous variables between ALS and control groups. The variables were displayed as (Mean) and ± standard deviation (SD). When p values were less than 0.05 and deemed as statistically significant. The analysis were carried out via ready-to-use statistical software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

The mean age of ALS patients was 62.43 ± 7.21 years, while the mean age of the control group was 63.27 years (p>0.05). The ALS group had a male/female ratio of 1.77, whereas the control group had a ratio of 1.58. There was no difference between the groups in terms of male/female ratios (p>0.05).

The sensory conductions of the median, ulnar, and sural nerves were not statistically different between the two groups (p>0.05). In ALS group, DMLs of the median, ulnar, peroneal and tibial nerves were significantly longer; CMAP amplitudes were significantly smaller than those of the control group (Tables 1 and 2). Furthermore, ALS patients had significantly prolonged ulnar and tibial F response latencies than the control group (p<0.05) (Tables 1 and 2).

The presence of the split-hand sign was determined by evaluating ratios of the motor distal latencies and the CMAP amplitudes of the ulnar and median nerves. The ulnar/median DML ratios of the ALS patients was lower than the control group (0.73/0.80; p=0.003);while the ulnar/median CMAP amplitude ratios were significantly higher (1.40/1.11; p=0.002) (Fig. 1)

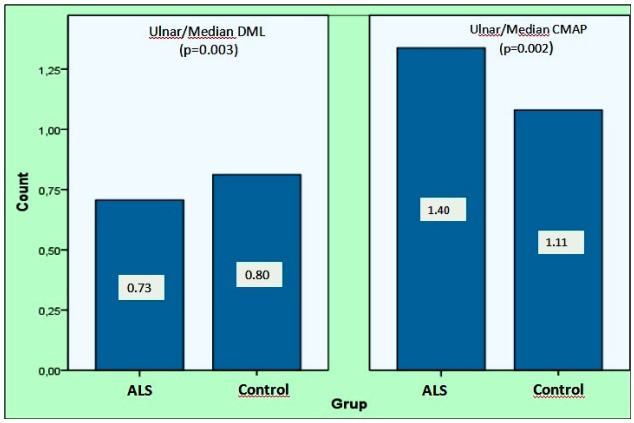

Figure 1: Comparison of Median / Ulnar DML ratios and Median / Ulnar CMAP ratios between ALS patient and control groups. DML: Distal motor latency, CMAP: compound muscle action potential

Table 1: Comparison of median and ulnar nerve conductions in patient and control groups.

	Group	Mean	Std. Deviation	P
Med.mot.dist.lat	ALS	3.76	.80	0.0001
	Control	3.16	.40	
Med.mot.amp	ALS	7.48	3.52	0.0001
	Control	11.0	3.08	
Med.mot.Vel	ALS	56.10	5.97	0.88
	Control	56.25	3.81	
Med.sens.dist.lat	ALS	3.09	.60	0.30
	Control	2.98	.32	
Med.sens.amp	ALS	15.65	5.88	0.14
	Control	17.21	4.32	
Med.sens. Vel.	ALS	43.33	4.78	0.16
	Control	43.98	3.59	
Uln.mot.dst.lat	ALS	2.66	.42	0.001
	Control	2.38	.25	
Uln.mot.amp	ALS	8.82	3.78	0.001
	Control	11.70	2.46	
Uln.mot.Vel	ALS	57.81	5.77	0.97
	Control	58.87	5.47	
Uln.sens.dist.lat	ALS	2.62	.31	0.35
	Control	2.62	.32	
Uln.sens.amp	ALS	12.34	4.65	0.07
	Control	14.18	4.64	
Uln.sens.Vel	ALS	44.19	4.06	0.19
	Control	43.02	4.01	
Ulnar F lat.	ALS	28.34	3.15	0.02
	Control	27.06	2.16	

Table 2: Comparison of Peroneal, tibial, and sural nerve conductions in patient and control groups.

	Group	Mean	Std. Deviation	P
Per. mot. dist.lat	ALS	4.57	1.11	0.008
	Control	4.03	.78	
Per. mot. amp	ALS	5.20	2.76	0.0001
	Control	7.45	2.35	
Per. mot. Vel	ALS	47.93	5.63	0.06
	Control	50.51	4.64	
Tib.mot.dist.lat	ALS	4.33	1.08	0.005
	Control	3.79	.76	
Tib.mot.amp.	ALS	7.80	4.61	0.0001
	Control	11.41	4.63	
Tib. mot.Vel	ALS	45.82	5.41	0.16
	Control	47.18	4.12	
Tib. F lat.	ALS	49.86	6.92	0.021
	Control	47.24	3.46	
Sural dst.lat	ALS	3.38	.53	0.32
	Control	3.64	1.76	
Sural Amp	ALS	10.68	5.24	0.09
	Control	12.32	3.65	
Sural Vel.	ALS	39.78	3.57	0.74
	Control	39.54	3.58	

Discussion

ALS may present with very heterogeneous clinical findings in its early period, resulting in a substantial loss of time until a final diagnosis can be established. Therefore, clinical and electrophysiological clues that facilitate the definitive diagnosis are precious, especially in the early period. The split hand phenomenon has been reported as being a specific clinical marker for ALS and especially limb onset-ALS. Split-hand phenomenon is observed in around 70% of patients with ALS at time of diagnosis and is evident in almost all cases at some stages of the disease (12). The physiological mechanisms underlying the split hand in ALS are exactly understood, but both cortical and spinal/peripheral mechanisms are probably involved. Peripheral axonal excitability studies suggest that APB and FDI motor axons have more distinct, permanent sodium current than ADM axons, resulting in higher axonal excitability and consequently, more readily degeneration (13). Pincer or precision grip is vital to human hand function, and frequent use of thenar complex muscles may lead to greater oxidative stress and metabolic demands at both upper and lower motoneurons innervating APB and FDI (9,14).

Although the aetiology of the split-han phenomenon has not been fully clarified; two hypotheses have been proposed to explain it: Central mechanism and Peripheral mechanism. The central mechanism may lead to more frequent use of the thenar complex muscles, increased metabolic demand and oxidative stress in the upper and lower motoneurons that drive the APB and FDI, and eventually, corticomotor neuronal dysfunction may primarily affect these muscles. The hypothesis is based on cortical hyperexcitability that aggravates motor neuron degeneration. In the peripheral mechanism, the motor axons of the APB and FDI muscles are thought to be exposed to much more sodium current than the ADM, leading to increased axonal excitability and therefore susceptibility to degeneration (9,10,15,16). The axonal excitability of the peripheral nerve of the APB muscle was found substantially longer when compared with the ADM muscle in a study conducted on healthy individuals (7-11). These findings support the hypothesis that split hand' is caused by selective excitotoxicity in motor axons. A recent study found that when compared to patients with cervical spondylotic myelopathy, even ALS patients without a split-hand clinic had a significantly lower ulnar/median DML ratio, and attributed this condition to the prominence of distal axonopathy in the median nerve (15). On the other hand, another study indicated that the difference that was defined in the APB and ADM muscles was not only present in distal motor latency and amplitude, but also in F responses (17). Our ALS patient group consisted of all patients with limb-onset, regardless of the lower or upper extremity, however, the split-hand phenomenon was prominent even in patients' first EMGs. Also, some studies reported that this phenomenon could be observed not only in limb-onset ALS but also in patients

with bulbar-onset (8).

The clinicians may come across ALS patients who exhibit symptoms and findings that can be confused with many different diseases such as entrapment neuropathies, cerebrovascular diseases, demyelinating diseases, cervical myelopathy and multifocal motor neuropathy, especially in the early stages of the disease (6,18,19). Due to these heterogeneous phenotypes, differential diagnosis in the early stages of the disease is quite difficult. The average time between the onset of symptoms and an ALS diagnosis is 12 months. Within this time period, 10%–15% of patients undergo unnecessary operations due to misdiagnosis (20). Likewise in our clinic, 16.2% of the patients had undergone operations for spinal disc hernia or entrapment neuropathies before their ALS diagnosis (21). This causes patients to waste time throughout the diagnostic phase and become physically, psychologically, and financially exhausted from unnecessary surgeries. Electrophysiological studies and specific clues, which are specific to the disease, are therefore critical in diagnosing ALS rapidly(22). We found prolonged DML and reduced amplitudes in the motor nerve conduction of ALS patients even in the early period; because, these values were the results of the initial EMG studies of the patients.

Conclusion

In early ALS, a split-hand sign is a valuable diagnostic tool, and recent objective studies have indicated that it has a high degree of specificity. Our results support the presence of split-hand phenomenon even in the early period of limb-onset ALS (both upper and lower). These findings suggest that nerve conduction studies and electrophysiologically detected split-hand sign are important clues for the diagnosis of ALS in the early period when clinical phenotype is heterogeneous.

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