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ORIGINAL ARTICLE

Analysis of clinical and electrophysiological characteristics of 150 patients with amyotrophic lateral sclerosis in China

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Abstract

Objective To explore the relationship between the clinical onset locations and the electrophysiological characteristics of different spinal segments in amyotrophic lateral sclerosis (ALS) patients. To develop a rapid examination method using electromyographs (EMGs) for the diagnosis of ALS.

Methods The clinical symptoms and electrodiagnostic examination results of 150 patients with definite or probable ALS were retrospectively analyzed. The patients were divided into four groups according to the primary onset locations (arms and legs onset, arms onset, legs onset, and bulbar onset groups). The differences between the onset locations and the electrophysiological characteristics revealed the lower motor neuron dysfunction in EMGs.

Results The most affected onset location was the lower limbs (36.7%), particularly in the distal muscles. Nerve conduction showed that the sensory system was damaged in 22 patients (14.7%). The positive diagnostic rate of EMGs varied due to different onset locations. EMG abnormalities were seen in approximately 40% of asymptomatic limb muscles. Distal limb muscles showed higher electrodiagnostic sensitivity (78.4%) than proximal limb muscles. Cervical muscles showed the highest electrodiagnostic sensitivity (86.3%).

Conclusions The sensory system in ALS patients was commonly impaired. Cervical muscles showed the highest electrodiagnostic sensitivity. The highest positive rate was generated from detecting the spinal segment onset and the special distal muscles onset ALS in our optimized test method. Through this improved examination based on the most affected individual muscles, physicians can greatly optimize the test duration and significantly reduce patient discomfort.

Keywords Electromyography · Onset location · Amyotrophic lateral sclerosis · Spinal segment · Lower motor neuron

Introduction

Amyotrophic lateral sclerosis (ALS) is one of the most common motor neuron diseases (MNDs) that damage upper or lower motor neurons (LMNs) [1]. It is a progressive neurodegenerative disease affecting the nerve cells in the brain and spinal cord, which leads to the demise of motor neurons. The dysfunction of the motor nerves makes the brain being incapable of initiation and control of muscle movement including the voluntary muscle actions. The respiratory muscle failure is the lethal cause of death in the last stage in patients with ALS. However, the initial onset positions of ALS are the medulla, arms, and legs. Most of the patients usually experience asymmetrical muscle weakness with atrophy or asymptomatic limbs. In the early stage, different muscles are affected in different degree even the controlling nerves derived from the same spinal segment. For example, in bulbar onset ALS, more evidence of impaired LMNs are found in the tongue than in the sternocleidomastoid, and the tibialis anterior is affected more than the quadriceps femoris. The detection of the most involved muscles in the early stage of ALS is important for the early diagnosis.

The recording of electromyographs (EMGs) is currently the most effective method for the evaluation of the impairments of LMNs. EMGs contribute to the early diagnosis to improve the diagnostic accuracy. However, the long

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duration of the EMG tests often makes the patients suffer from a painful examination experience, especially when the clinicians do not select the tested muscles properly. To shorten the examination duration and relieve the pain, clinicians need to clarify the most possible affected muscles of one ALS spinal segment. However, researches focusing on the distinguishment of the most affected muscles from the same ALS onset location can hardly be found. With the knowledge of the muscles that most likely to show signs of ALS, clinicians can choose the muscles properly for EMG, shorten the examination duration, and reduce the unnecessary pain. In this research, we compared the diagnostic sensitivity of different muscles to explore the relationships between muscles and ALS onset locations. A fast EMG examination method was developed to improve the detection accuracy and reduce the patient discomfort during the examination.

Materials and methods

Ethics statement

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University (Qingdao), China. Written informed consent was obtained from all patients.

Clinical data

According to the El Escorial criteria [2], we collected the basic clinical data and electrophysiological results of 150 patients diagnosed with amyotrophic lateral sclerosis (ALS) in Qingdao Hospital from January 2015 to January 2018. Examinations such as imaging examination, immunological tests, blood tests, and cerebrospinal fluid detections were used to exclude other diseases. For example, the patients with mononeuropathy or spine (cervical, lumbar) diseases were excluded. However, patients with ALS combined with cervical and lumbar spondylosis were not removed as it is difficult to identify from the EMG and it also can be a neurogenic damage of the limb. In our research, definite ALS was defined as at least three segments showing impairment of upper and lower motor neurons (LMNs) in the bulbar, cervical, thoracic, and lumbar regions. Probable ALS was defined as two segments showing innervation. Possible ALS was defined as one segment showing innervation or two or three segments of injury among upper motor neurons [3]. Of all the patients, 100 cases are definite ALS and 50 cases are probable ALS. The patients were divided into four groups according to the onset locations (arms onset, legs onset, arms and legs onset, and bulbar onset groups). The ALS functional rating scale of all patients are shown in Fig. 1 [4].

Electrophysiology

The motor and sensory nerve conduction velocities were evaluated and the needle electromyographs (EMGs) of different muscles in the bulbar, cervical, thoracic, and lumbar spinal cord were measured standardly by using a Dantec Keypoint instrument [5].

Median and ulnar nerves in the upper extremity, as well as sural, peroneal, and tibial nerves in the lower extremity were chosen for the detection of the sensory and motor conduction velocities, as well as the latency and amplitude of the waves. The minimal F latency was detected in F responses. The antidromic sensory method was chosen due to the small sensory nerve action potential. The instrument was set with a sensitivity of 10 μV/D and a scanning speed of 1 ms/D. In the motor nerve tests, the instrument was set with a sensitivity of 2~5 mV/D and a scanning speed of 2 ms/D. In the F response tests, the instrument was set with a sensitivity of 200 μV/D and a scanning speed of 5~10 ms/D.

The positions for needle EMG recording were well specified. In the cervical region, the first dorsal interosseous, abductor pollicis brevis, extensor digitorum communis, biceps brachii, or deltoid was located. In the lumbar region, the quadriceps femoris, tibialis anterior, or gastrocnemius was located. In the bulbar region, the tongue or sternocleidomastoid was selected. In the thoracic region, the paraspinal muscles (T6–T10) were located. The EMGs included assessments of spontaneous potentials during complete relaxation, the duration, and amplitude of the multiple muscle action potential, the percentage of polyphase waves during mild contraction, and the recruitment during gradual contraction. When the spontaneous potentials, measuring motor unit potentials (MUPs) or evaluating recruitment were being measured, the instrument was set with a sensitivity of 100 μV/D, a scanning speed of 10 ms/D, and a bandpass of 20 Hz to 10 kHz.

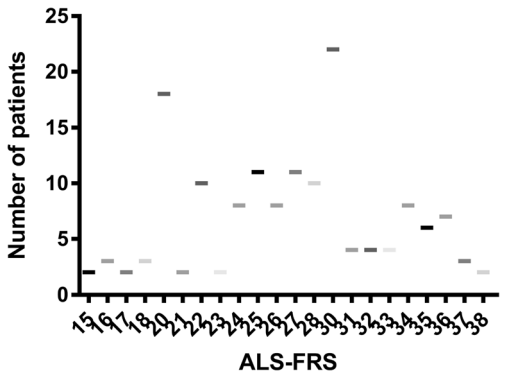

Fig. 1 The clinical severity of 150 patients indicated by ALS-FRS

Electrophysiological evaluation

In the nerve conduction tests, the operations were done standardly and the default values referred to David C. P. et al. [6]. The abnormal needle EMGs included active denervation potentials (fibrillation potentials, positive sharp waves, fasciculations, etc.) and regeneration potentials (increased amplitudes, broadened durations, reduced recruitment, and instable MUPs) [2, 3]. The following phenomena were checked to confirm the abnormality: at least one abnormal muscle in the bulbar region, at least two abnormal muscles in different peripheral nerves and different nerve roots in the cervical or lumbar region, and at least one abnormal muscle in the thoracic T6~T10 region.

Statistical analysis

The statistical analysis was done on the SPSS 17.0 software. Data in the form of percentage were analyzed using the chi-squared test. The data in the form of the mean ± SEM were analyzed with the *t* test. The statistical significance was defined as $P < 0.05$.

Results

General information of different onset location groups

A total of 85 males and 65 females aged from 25 to 86 years (mean age of 60 ± 12 years) were included in our research. There were 55 patients in the legs onset group, 44 in the arms onset group, 34 in the arms and legs onset group, and 17 in the bulbar onset group. The age and gender of the patients distributed even in the four groups.

Most of the ALS cases initiated with limbs being weak. Only 11.3% of the patients exposed to bulbar onset ALS (Fig. 2). The morbidity of ALS significantly increased by the age above 50 which was in accordance with the previous report [7]. Patients aged 51 to 60 sufferd from the highest morbidity. Different from limbs onset ALS, the highest morbidity age of bulbar onset ALS was 61 to 70 (Fig. 2) with the highest incidence of definite ALS (Fig. 3) and the least diagnosis time of 2.0 ± 1.7 years (Table 1). The time for the diagnosis of ALS was mostly more than 3 years. The distal muscles in the majority of limbs onset ALS had been affected; the distal muscles in 58.8% of the arms and legs onset ALS, 65.9% of the arms onset ALS, and 69.1% of legs onset ALS were affected (Table 1).

Nerve conduction

There were 46 cases of abnormal motor nerve conduction: 10 cases of abnormal median nerve conduction, 9 cases of abnormal ulnar nerve conduction, 21 cases of abnormal peroneal nerve conduction, and 6 cases of abnormal tibial nerve conduction. There were 22 cases of abnormal sensory nerve conduction: 8 cases of abnormal median nerve conduction, 6 cases of abnormal ulnar nerve conduction, and 8 cases of abnormal sural nerve conduction; other causes of polyneuropathy had been ruled out in the patients with the alterations of the sural nerve.

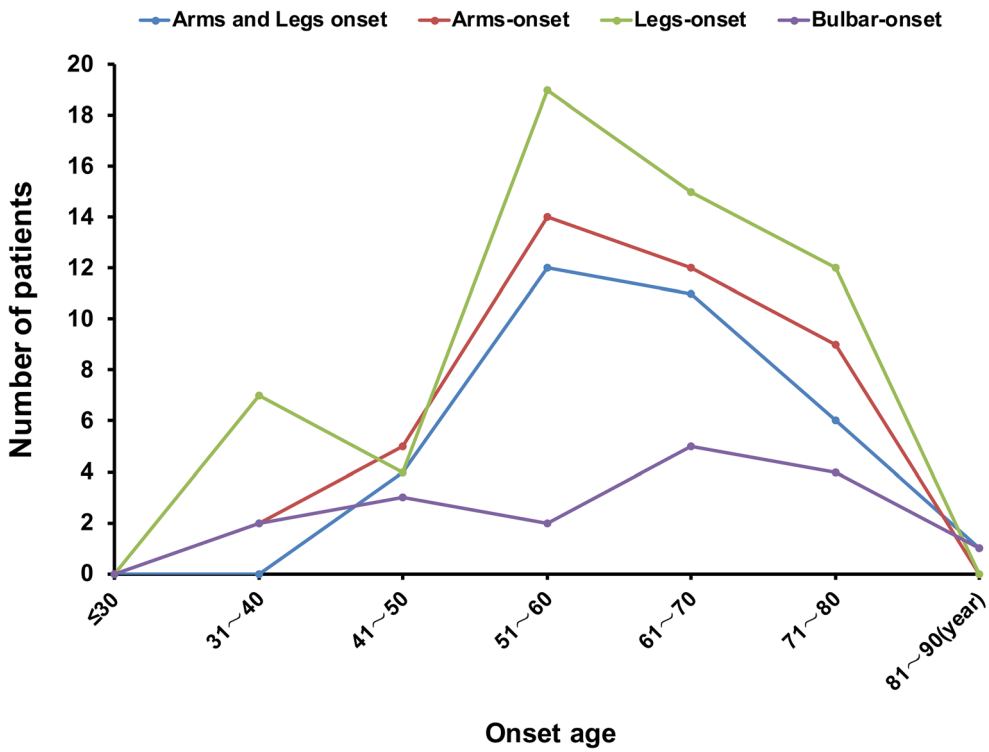

Fig. 2 Comparison of onset ages between the different onset location groups

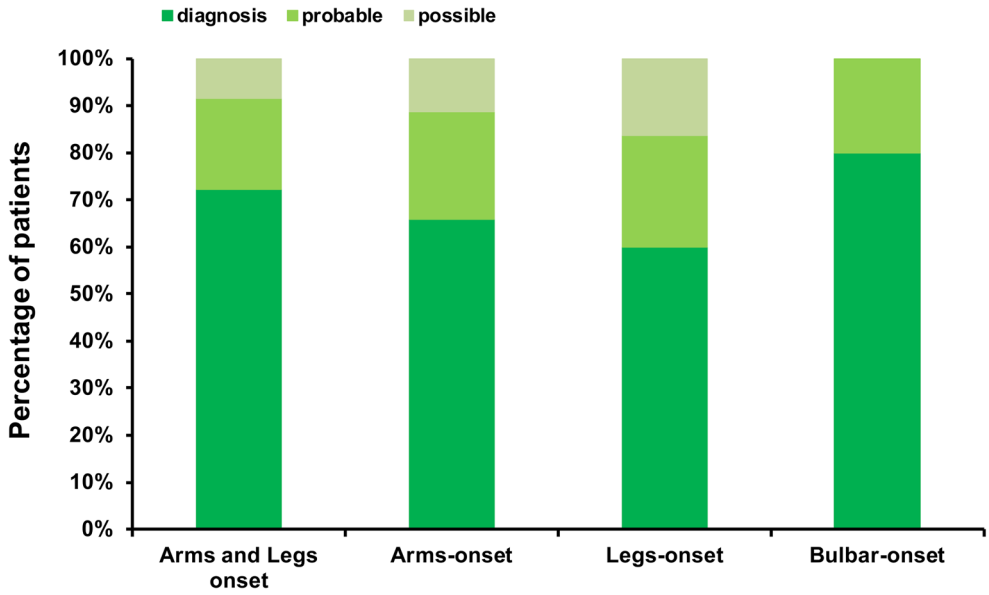

Fig. 3 Distribution of diagnosis levels in the different onset location groups

There were 19 cases of abnormal F waves: 6 cases with a decreased rate of F waves, and 13 cases with a prolonged distal latency of F waves.

The nerve conduction assessment indicated that the motor nerves, especially the axons, were frequently impaired. The main electrophysiological features of the ALS patients included the significant decrease of amplitude, and the slightly prolonged latency or mildly slow conduction velocity in some of the patients. Furthermore, sensory nerves in the axons were mildly impaired in some of the cases.

EMG

EMGs in different onset location groups

In the 466 tested cervical muscles, 402 were abnormal with the highest positive rate of 86.3% ($P < 0.01$). The cervical muscles showed the highest electrodiagnostic sensitivity compared with the other segments. In the arms onset group, the highest positive rate (95.0%) was detected in the cervical segment, followed by 83.6% in the bulbar segment, and 57.4% in the thoracic segment ($P < 0.01$). In the legs onset group, the positive rate (86.8%) was highest in the lumbar segment and lowest (53.8%) in the bulbar segment ($P < 0.01$). In the bulbar onset group, the positive rate in the bulbar segment was 100%, which was significantly higher than that in the lumbar and thoracic segments ($P < 0.01$) (Table 2).

The highest electrodiagnostic sensitivity was observed in the spinal segment onset ALS, especially in symptomatic muscles, whereas the farthest region often had the lowest electrodiagnostic sensitivity. Moreover, abnormalities in EMG were found in approximately 40% of asymptomatic muscles.

EMGs of distal and proximal muscles

Of the 574 distal muscles, 450 muscles were abnormal, with a significantly higher positive rate of 78.4% than for proximal

Table 1 General information regarding the different onset location groups

	Arms and legs onset (34)	Arms onset (44)	Legs onset (55)	Bulbar onset (17)
Age (year)	61.2 ± 10.3	60.8 ± 11.2	58.7 ± 12.8	60.6 ± 16.3
Peasant	12	16	18	9
Subacute onset	2	0	3	1
Diagnosis time (year)	3.5 ± 1.8[#]	3.4 ± 1.5[*]	2.8 ± 1.6	2.0 ± 1.7
Male	19	26	33	8
Distal muscles	20 (58.8%)	29 (65.9%)	38 (69.1%)	–
Abnormal muscles	212 (79.1%)	287 (80.4%)	377 (78.4%)	87 (76.3%)
Histories	2 cases of pesticide and 2 cases of cervical lumbar disease	1 case of fracture, 1 case of cerebral infarction, and 7 cases of cervical lumbar disease	2 cases of surgical and 1 case of cerebral infarction, 3 cases of fracture, 1 case of pituitary adenoma, and 7 cases of cervical lumbar disease	1 case of fracture and 4 cases of cervical lumbar disease

[#]/*Compared with the bulbar onset group, $P = 0.005$

Table 2 Comparison of EMGs in different onset location groups

Onset location	Cervical (466)		Lumbar (408)		Bulbar (192)		Thoracic (154)	
	Normal (64)	Abnormal (402)	Normal (l91)	Abnormal (317)	Normal (50)	Abnormal (142)	Normal (52)	Abnormal (102)
Arms and legs onset (268)	15	91 (85.8%)	19	60 (75.9%)	10	36 (78.3%)	12	25 (67.6%)
Arms onset (357)	7	133 (95.0%)	33	76 (69.7%)^{a1}	10	51 (83.6%)^{a2}	20	27 (57.4%)$^{a3@}$
Legs onset (481)	34	132 (79.5%)^{b1}	25	165 (86.8%)^{b2}	30	35 (53.8%)	15	45 (75.0%)
Bulbar onset (114)	8	46 (85.2%)^{c1}	14	16 (53.3%)	0	20 (100%)^{c2}	5	5 (50.0%)$^{\&}$

Comparison of EMGs of the arms onset group with the other spinal segment groups: compared with the cervical onset group: ^{a1}: $x^2 = 29.0$, $P = 0$; ^{a2}: $x^2 = 7.1$, $P = 0.008$; ^{a3}: $x^2 = 40.2$, $P = 0$; $^{@}$: compared with the bulbar onset group, $x^2 = 9.1$, $P = 0.003$. Comparison of EMGs of the legs onset group: compared with the bulbar onset group: ^{b1}: $x^2 = 15.4$, $P = 0$; ^{b2}: $x^2 = 31.2$, $P = 0$. Comparison of EMGs of the bulbar onset group: compared with the lumbar onset group: ^{c1}: $x^2 = 10.1$, $P = 0.001$; ^{c2}: $x^2 = 13.0$, $P = 0$; $^{\&}$: compared with the bulbar onset group, $x^2 = 13.2$, $P = 0$

muscles ($P < 0.01$) (Table 3). Distal limb muscles showed the highest electrodiagnostic sensitivity regardless of the onset locations.

Discussion

Previous researches have reported that ALS mainly occurs in the middle-aged or elderly people without obvious preference to genders [7, 8]. Our research reached the same etiology conclusions on age and gender bias in ALS patients. The patients in this study were divided into four groups according to onset locations (arms onset, legs onset, arms and legs onset, and bulbar onset groups). No significant difference in age or gender was observed between the four groups of patients.

The Chinese patients generally do not seek medical assistance for symptoms such as limb weakness or mild muscle atrophy if their daily life or the ability to work is not significantly affected. However, speech impairment has a more fearful impact on people, making them feel sick and prompting them to visit a doctor. More severe and faster development of ALS is observed in the bulbar onset group which leads to dysarthria in the patients. Clinical symptoms, such as dysarthria or difficulty swallowing or breathing, can emerge suddenly without clear causes. The neurological impairment of spinal segments 3 or 4 would suddenly be detected in these patients' EMGs with the quick progression of the disease. The highest incidence of definite diagnosis is found in the bulbar onset group. Patients with limbs onset ALS exhibit relatively slower progression and better prognosis.

Table 3 Comparison of EMGs in the distal and proximal groups

Location	Normal (257)	Abnormal (617)	X^2	P
Distal (574)	124	450 (78.4%)	49.0	0
Proximal (300)	133	167 (55.7%)		

Distal locations in the legs onset group are most likely to be affected. In our cohort, there were 55 patients (36.7%) with legs onset ALS, which included 38 cases (69.1%) with distal onset ALS. Only 17 cases were medulla onset. Our data indicated that the lower extremity was mostly affected.

EMG has become an important method for identifying damage in LMNs. EMG can be used not only to verify existing clinical symptoms or signs but also to identify subclinical impairments and provide an electrophysiological basis for the early diagnosis of ALS. The main electrodiagnostic features include normal sensory nerve conduction, the amplitude of normal or abnormal complex muscle action potentials, the prolonged distal latency and F-wave latencies, and the decreased rate of F-waves. Needle EMG reveals extensive neurogenic impairments, including denervated potentials and regeneration potentials in the bulbar, cervical, thoracic, and lumbar muscles [9, 10].

Previous studies reported that the sensory abnormalities were observed in ALS patients [11–13]. Affected sensory fibers could also be detected in 22 patients (14.7%) of this study by the pathological tests, consistent with the previous findings. In ALS patients, sensory impairments are often mild, and there is no significant progression. Some researchers reported that sensory damage was related to the degeneration of the spinal dorsal root ganglia [14]. However, other researchers argued that sensory impairment was caused by peripheral nerve injury, such as immune damage, metabolic disorders, and genetic polymorphisms [15, 16]. Thus, sensory abnormalities cannot be completely excluded in ALS.

There were 19 patients with abnormal F waves, accounting for 12.7% of cases. The preferential loss of fast conduction fibers, axonal degeneration, proximal axonal swelling, or anterior horn cell injury may slow the development of depolarization or F-wave conduction, with F waves potentially disappearing [17, 18].

Of all 1220 muscles, there were 402 abnormal muscles in the cervical segment, possessing the highest positive rate (86.3%). And the lowest positive rate (66.2%) was in the

thoracic segment. Kyuon et al. [19] reported that the thoracic positive rate was 100%, which was significantly higher than what is found in this study. This discrepancy can be explained by the different patient selection criteria in these two researches. The patients' thoracic segment may not be affected during the examination or may be tested less frequently than other segments. In addition, 78 patients (52%) in our study exhibited ALS associated with the upper extremities, which contributed to the highest positive rate in the cervical segment.

In the upper extremity onset group, the positive rate was up to 95% in muscles of the cervical segment, 83.6% in muscles of the bulbar segment, and 57.4% in muscles of the thoracic segment. It is possible that patients with arms onset ALS have neurogenic lesions that can be easily detected by EMGs because of the more common prevalence in the upper extremities. Furthermore, identifying more lesions in other spinal segments requires a greater amount of time. Bulbar muscles were more likely involved than thoracic muscles in arms onset ALS in our study.

The positive rate was higher in the lumbar segment (86.8%) than that in the bulbar segment (53.8%) of patients with lower extremity onset. The lower extremity muscles are most commonly involved in legs onset patients, which is associated with the lumbar spinal cord. The medulla is the farthest segment from the lumbar segment, which takes a longer time to be affected. Thus, the positive rate of ALS diagnosis is very low on muscles associated with the medulla.

In contrast, in bulbar onset patients, the positive rate in the bulbar segment was as high as 100%. In the bulbar segment, we only measured EMGs of the tongue and sternocleidomastoid muscles, as these two muscles are most vulnerable in the segment. Furthermore, patients with bulbar onset were more likely to exhibit involvement of the anterior horn of the cervical cord, which is consistent with the anatomical contiguity.

The spontaneous potentials were greater in patients with a symptomatic tongue which is in accordance with the findings by Preston et al. [20]. The positive rate of spontaneous potentials in the bulbar segment was the highest (100%) in bulbar onset patients, followed by the cervical segment in arms onset patients and the thoracic segment regardless of onset location. However, a study by Kyuno K et al. drawed a conclusion opposite to our findings, where a high positive rate in thoracic muscles than the others was observed [19]. Spontaneous potentials are associated not only with onset locations but also with special muscles. We hypothesized that the low rate of spontaneous potentials in paravertebral muscles might be related to the slow progression or better lateral buds in denervated fibers.

For now, we could not provide an algorithm for muscles to examine in ALS patients, as each patient's condition was different. We have developed a novel testing method for the simplified identification of ALS patients by EMGs. This method is based on the neurogenic impairments detected by EMGs of the most vulnerable muscles corresponding to the spinal cord segments. Further examination of the adjacent areas and the remote locations corresponding to the spinal cord segments greatly improves the detection accuracy. First, check the most severe limbs or muscles (for the brain stem or thoracic segment, a muscle abnormality may indicate the segment is abnormal, and the tongue muscle or the lower thoracic paraspinal muscle is preferred; for the limb, the first is involving the distal end. If there is no obvious damage at the proximal end, two muscles that are controlled by a different nerve root and peripheral nerves at the distal end of the affected limb are preferred). Secondly, the adjacent spinal cord segment is checked. If there is no abnormality, further examination can be stopped to avoid unnecessary pain to the patient. The patient is reviewed several months later to see the condition. By using this method, the majority of the ALS patients can be diagnosed correctly in time. However, the non-contiguous spread of the degeneration in a small portion of patients would lower the detection accuracy of this method. In addition, approximately 40% of patients showed asymptomatic muscle abnormalities in EMGs. As a result, different onset locations would affect the EMGs positive rate distribution of different spinal segments. If a patient's ALS onset location is analyzed recently, the physicians should look for subclinical evidence in the adjacent location during the examination. Finally, it is not necessary to continue to test other muscles if a normal EMG is detected in the nearest spinal cord segment if patients are very sick or unable to tolerate pain. The positive rate (78.4%) in distal limb muscles was higher than proximal muscles, suggesting that the distal muscles were more likely to be involved in ALS, consistent with previous electrophysiological findings [21]. Cappellari et al. [21] also reported that motor neurons with longer axons were more likely to be involved. Thus, if patients had no confirmed proximal muscle impairments, the impairments of the distal muscles should be considered for examination.

There are several limitations in this study. First, we did not examine the motor evoked potentials. Besides, the major ALS-associated genes (i.e., SOD1, TDP43, C9ORF) were not checked in this study. These issues will be studied in our future work.

Conclusion

In this research, we reported a novel examination method for the diagnosis of ALS. We were able to not only greatly shorten the examination time but also significantly relieve patients' pain and improve the quality of their medical care. For patients with serious conditions or special needs, examinations on one or two segments associated with the onset site especially the representative distal muscles can be done for diagnosis. By the application of this improved examination based on the most

affected individual muscles, physicians can greatly optimize the test duration and significantly reduce patient discomfort.

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Compliance with ethical standards

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University (Qingdao), China. Written informed consent was obtained from all patients.

Competing interests The authors declare that they have no competing interests.

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