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The rostral to caudal gradient of clinical and electrophysiological features in sporadic amyotrophic lateral sclerosis with bulbar-onset

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Abstract

Objective: Amyotrophic lateral sclerosis (ALS) with bulbar-onset (BO-ALS) tends to propagate to the adjacent anatomical regions symptomatically. However, the spreading pattern of clinical and electrophysiological features is not well documented.

Methods: This retrospective study enrolled consecutive patients with sporadic BO-ALS. The clinical progression and electrophysiological data by electromyography examination were retrospectively analysed based on information from the medical records.

Results: The study enrolled 57 patients: 43 presented with contiguous (37 of 57) or non-contiguous (6 of 57) progression clinically; and 14 patients did not present with symptomatic propagation to other spinal segments. Lower motor neuron dysfunction was more frequently involved in the bulbar and cervical segments and less in the thoracic and lumbosacral segments. As a result, a small proportion of patients had intact thoracic paraspinal or leg muscles or both by electromyography examination. Furthermore, the patients with diagnostic latency $\leq$6 months

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showed a significantly lower incidence of neurogenic changes in the lumbosacral spinal cord compared with those with diagnostic latency > 6 months.
Conclusion: This current study demonstrated a relative rostral–caudal descending gradient of lower motor neuron dysfunction in patients with BO-ALS. These results suggest that follow-up EMG might be necessary for a proportion of patients.

Keywords
Amyotrophic lateral sclerosis, bulbar-onset, diagnostic latency, electromyography

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurological disorder, which is characterized by combined upper motor neuron (UMN) and lower motor neuron (LMN) involvement leading to progressive muscle weakness and atrophy.[1] The region of onset and speed of progression in ALS are highly variable, with a spreading pattern to adjacent anatomical sites (contiguous anatomical propagation) being more likely than non-contiguous symptom development (skipping pattern).[2–4] In particular, ALS with bulbar-onset (BO-ALS), constituting up to 25% of the ALS population,[5] is featured by initial symptoms of bulbar involvement such as dysarthria or dysphagia; and progresses more rapidly with poorer prognosis than ALS with limb-onset.[5,6] Thus, a full recognition of BO-ALS is indispensable in clinical practice.

Electromyography (EMG) is an important tool used for the diagnosis of ALS, often revealing abnormalities preceding clinical features.[7,8] Though neurophysiological abnormalities in terms of spreading pattern in ALS have been reported,[9] it is not well documented in BO-ALS especially when disease duration is considered. The widespread neurogenic involvement of no less than three regions is the typical EMG finding in ALS.[10] However, in our opinion, the neurogenic involvement of thoracic and lumbosacral segments may be lacking at the early stage of BO-ALS due to variable disease progression, which can lead to diagnostic uncertainty in some cases. Thus, clarification of the abnormal electrophysiological features and distribution in BO-ALS is required.

The present study aimed to clarify the distributive patterns of clinical and electrophysiological features in patients with BO-ALS, which might help provide insight into understanding the mechanism of LMN degeneration and thus early recognition with the respect to electrodiagnosis.

Patients and methods

Study population

This retrospective study enrolled consecutive patients with sporadic BO-ALS in the Department of Neurology, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong Province, China between January 2009 and December 2018. By initial and subsequent investigations, all patients were diagnosed according to the Awaji ALS criteria proposed in 2008 and more widely applied in 2012, which were defined by the number of regions that represents UMN and LMN involvement.[11–13] All of the patients were re-evaluated with the criteria when included in the study. Diagnostic categories included

probable and definite diagnosis, but a category of 'possible diagnosis' that could be confused with another aetiology was not included. Diagnostic latency was defined as the time course from symptom onset to probable or definite diagnosis, which was also similar to the disease duration when EMG was performed in this study. Patients with other neurological conditions were excluded, including parkinsonism, previous stroke or spinal lesions, brain tumour, myasthenia gravis, peripheral nerve disorders or diseases potentially affecting peripheral nerves.

This retrospective study complied with the principles of the Declaration of Helsinki and was approved by the local clinical trial committee of the First Affiliated Hospital of Sun Yat-Sen University (no. [2020]263). As a retrospective study, patient consent was exempted by the local clinical trial committee. All patient data were anonymized so that the identity of the patients could not be ascertained in any way.

Clinical investigation

Patients diagnosed as ALS with initial dysarthria or dysphagia were defined as BO-ALS. Clinical symptoms and neurological signs were assessed at the discretion of physician-in-charge according to standard medical practice. During a physical examination, muscle weakness, fasciculation and amyotrophy with or without hyporeflexia were categorized as LMN dysfunction; while hyperreflexia, pathological reflex, spasticity, clonus and preserved reflexes in the weak wasted limbs as UMN dysfunction.[14,15] The contiguous spreading pattern refers to involvement of one adjacent segment after mono- or multi-focal onset. The 'non-contiguous' pattern was defined as spread to distant sites, thereby skipping adjacent anatomical sites, and two situations were included: (i) the patient directly progressed to the lumbosacral segment right after onset in the bulbar region; (ii) the patient had onset in both the bulbar and lumbosacral segments. Because the respiratory muscles are innervated by both the cervical and thoracic segments of the spinal cord, symptoms of dyspnoea were not specifically analysed and clinical involvement in the thoracic segment was less well recorded. Clinical generalization was defined as LMN or UMN dysfunction in no less than three regions of the bulbar, cervical and lumbosacral segments. Sensory examinations of touch, pin-prick, vibration and position sense were normal in all patients. The revised ALS functional rating scale (ALSFRS-R),[16] which is a widely used instrument to measure bulbar, fine motor, gross motor and respiratory function, was applied to determine the severity of symptoms. Cognitive function was not specifically evaluated because it was not reported to be a problem by either the patients themselves or their families.

Electrophysiological examination

All patients underwent nerve conduction studies and needle EMG for diagnosis. Electrophysiological examinations were performed by physicians and technicians in the EMG lab using a Dantec® Keypoint® G4 EMG/NCS/EP Workstation (Alpine Biomed, Skovlunde, Denmark) and a 26G concentric needle electrode (37 mm recording surface; Natus Europe, Gort, Ireland). Skin temperature was maintained above 32°C. Needle EMG was performed in at least one muscle for the bulbar (sternocleidomastoid or tongue muscle) and thoracic spinal segments (T8 or T10 paraspinal muscle), two muscles in the cervical (abductor digiti minimi and deltoid or biceps) and lumbosacral spinal segments (tibialis anterior and quadriceps femoris) (band-pass: 20 Hz–10 KHz). The EMG investigation

was unilateral, but when the finding was normal, bilateral limbs were examined.

Spontaneous activity (SA) was studied at 10 different sites of each muscle (sensitivity: 0.1 mV/D; scanning speed: 10 ms/D), which included fasciculation potential, fibrillation potentials and positive sharp waves, as the evidence of acute or progressive denervation. For fibrillation potentials and positive sharp waves, only regularly firing potentials lasting more than 3 s were accepted as abnormal SA. These activities were considered pathological only when presenting at least two different sites within one muscle. The duration, amplitude and phases of motor unit potentials (MUPs) on gentle muscular contraction (sensitivity: 0.3 mV/D; scanning speed: 10 ms/D) as well as the recruitment pattern on full contraction were simultaneously recorded, and quantitatively analysed according to the laboratory standards for the Chinese population. The following observed EMG features were considered as neurogenic changes: abnormal SA and MUPs with broadened duration. Electrophysiological generalization or widespread neurogenic involvement was considered as neurogenic changes in no less than three regions (bulbar, cervical, thoracic and lumbosacral).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± SD or *n* of patients (%). χ^2-test or McNemar test followed by Bonferroni adjustment was used to compare categorical data when appropriate. Student's *t*-test was used to compare continuous data. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

This retrospective study enrolled 57 patients with sporadic BO-ALS. All patients suffered from initial symptoms in the bulbar region including dysarthria ($n = 52$) or dysphagia ($n = 37$). One patient showed emotional lability at onset. Of the 57 enrolled patients, 41 (71.9%) were diagnosed with definite ALS and 16 (28.1%) with probable ALS at their last visit. The mean ± SD age of the study cohort was 56.5 ± 10.7 years (range, 35.0–83.0 years), with a mean ± SD onset age of 55.4 ± 7.6 years (range, 33.0–83.0 years). The female/male ratio was 1:1.85. The mean ± SD duration from onset to recruitment was 13.6 ± 8.5 months (range, 1.0–38.0 months). The mean ± SD diagnostic latency was 11.3 ± 7.6 months (range, 1.0–32.0 months), which was similar to the disease duration when EMG was performed. The mean ± SD ALSFRS-R score was 38.9 ± 6.5 (range, 24.0–47.2). Five patients manifested breathing difficulty at

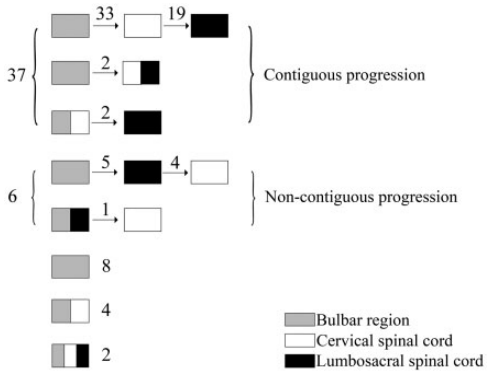

Figure 1. Clinical progression of 57 patients with sporadic amyotrophic lateral sclerosis with bulbar-onset (BO-ALS) according to the medical records. The first column refers to the onset region, the second column refers to the second involved region and the third column refers to the third involved segment. The number shown indicates the number of patients. The colour coding of the blocks indicates which region had clinical manifestations. Blocks with multiple colour codes indicate the involvement of different segments at the same time.

the onset and six patients developed respiratory symptoms as the disease progressed.

The majority of the patients (48 of 57, 84.2%) had a single-site onset, while nine of 57 (15.8%) manifested with a multifocal onset. The clinical progression of 37 patients showed a contiguous spreading pattern (Figure 1): (i) the symptoms starting from the bulbar region progressed to the upper limbs in 33 patients and then successively to the lower limbs in 19 of them; (ii) the clinical manifestations occurred in both the upper and lower limbs at the same time in two patients after bulbar onset; (iii) leg weakness developed after simultaneous occurrence of dysarthria or dysphagia and arm weakness in two patients. In contrast, six patients progressed with non-contiguous patterns: (i) five patients showed leg symptoms right after bulbar-onset, with four of them subsequently presenting with symptoms in the arms; (ii) in one patient, the symptoms were initially in both bulbar and lumbosacral segments, then progressed to the cervical segment. Among the 43 patients that progressed after onset, the mean $\pm$ SD interval between onset and involvement of the second segment was 8.2 ± 6.6 months (range, 0.3–32.0 months). The other 14 patients did not show clinical progression to other segments in the recorded period.

The distribution of LMN dysfunction including weakness, fasciculation and amyotrophy was significantly different in muscles innervated by bulbar and lumbosacral segments ($P < 0.001$). Despite the non-contiguous pattern of spread observed in some patients as shown in Figure 1, the most frequent LMN involvement was found in the bulbar region, followed by that in the upper limbs and then in the lower limbs (Figure 2a). When frequency of the regional symptoms was evaluated, a descending gradient of LMN dysfunction from rostral to caudal regions in BO-ALS was observed. In contrast, UMN signs were found in the majority of patients and there was no significant difference among the different regions: 48 of 57 (84.2%) in the corticobulbar tract, 53 of 57 (93.0%) in the upper limbs and 51 of 57 (89.5%) in the lower limbs. Similarly, the rostral to caudal pattern was also observed in electrophysiological features. Neurogenic changes were more frequently detected in muscles innervated by the bulbar and cervical

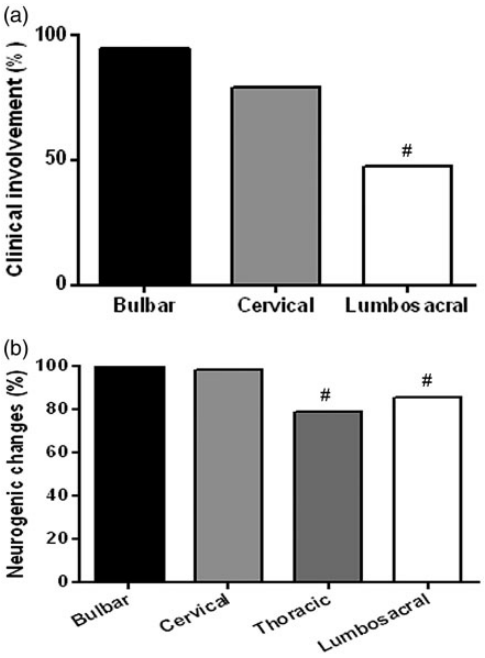

Figure 2. Lower motor neuron (LMN) dysfunction shown as manifestations by clinical investigation and neurogenic changes by electromyography testing in patients ($n = 57$) with sporadic amyotrophic lateral sclerosis with bulbar-onset: (a) occurrence of LMN dysfunction in different spinal segments. Bulbar refers to symptoms of dysarthria, dysphagia or choking; whereas cervical or lumbosacral refers to upper or lower limb symptoms, respectively. $^{\#}P < 0.05$ versus cervical segment, χ^2-test or McNemar test followed by Bonferroni adjustment; (b) frequency of electrophysiological neurogenic changes in muscles innervated by different regions. $^{\#}P < 0.05$ versus bulbar and cervical segments, χ^2-test or McNemar test followed by Bonferroni adjustment.

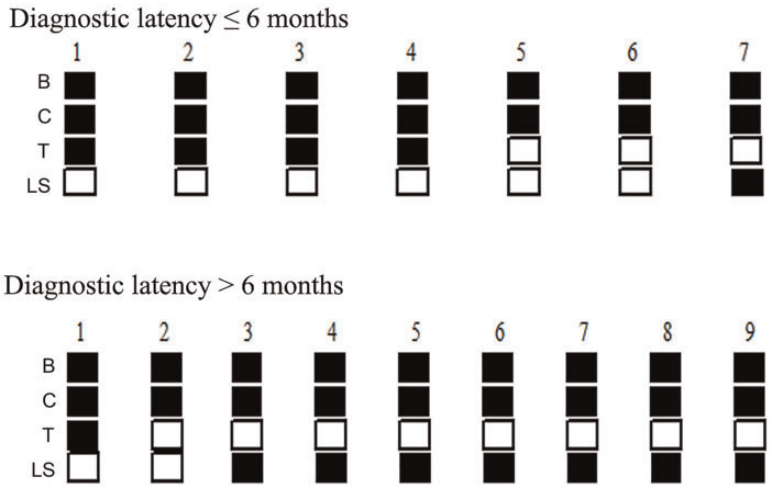

Figure 3. Illustration of electrophysiological neurogenic changes in patients ($n = 16$) with sporadic amyotrophic lateral sclerosis with bulbar-onset whose involvement was less than the full four segments (bulbar region, cervical spinal cord, thoracic and lumbosacral spinal cord). Black squares indicate neurogenic injury and white squares indicate spared segments. Each numbered column shows one patient. B, bulbar; C, cervical; T, thoracic; LS, lumbosacral.

segments compared with those innervated by the thoracic and lumbosacral segments (Figure 2b).

The EMG test showed that a small proportion of patients (16 of 57) presented with neurogenic injury in only the bulbar and cervical segments, sparing the thoracic or lumbosacral segment or both (Figure 3). These patients manifested relatively better neurological function as assessed by the ALSFRS-R score compared with the other patients (41 of 57) with neurogenic injury in all four segments as shown by an EMG test (mean ± SD ALSFRS-R score: 41.31 ± 4.42 versus 37.13 ± 6.82, respectively; $P = 0.028$).

In the present study, patients were grouped by diagnostic latency of 6 months, which was a relatively short but reasonable period of time to make an early diagnosis in clinical practice. The diagnostic latency was ≤6 months in 17 patients and was >6 months in 40 patients. Of the 17 patients with diagnostic latency ≤6 months, 10 (58.8%) were male and 7 (41.2%) were female; with a mean ± SD age of 54.53 ± 11.84 years and a mean ± SD onset age of 53.88 ± 11.77 years. Correspondingly, of the 40 patients with diagnostic latency >6 months, 27 (67.5%) were male and 13 (32.5%) were female; with a mean ± SD age of 57.23 ± 10.18 years and a mean ± SD onset age of 56.05 ± 10.14 years. There was no significant difference in baseline characteristics (sex, age and age of onset) or in the ALSFRS-R score between the two groups. Interestingly, the time interval from onset to the second involved segment was significantly shorter in patients with shorter diagnostic latency (3.66 ± 7.60 months in patients with diagnostic latency ≤6 months versus 7.25 ± 6.10 months in patients with diagnostic latency >6 months; $P = 0.017$), which might contribute to the early definite or probable diagnosis. In patients with a diagnostic latency ≤6 months, a lower incidence of neurogenic changes in the lumbosacral segment was detected compared with the patients with a diagnostic latency >6

Table 1. Electrophysiological features in patients ($n = 57$) with sporadic amyotrophic lateral sclerosis with bulbar-onset stratified according to diagnostic latency.

Electrophysiological features	Diagnostic latency		Statistical analysis[a]
	≤6 months $n = 17$	>6 months $n = 40$	
Neurogenic changes			
Bulbar	17 (100)	40 (100)	–
Cervical	17 (100)	39 (97.5)	–
Thoracic	13 (76.5)	32 (80.0)	NS
Lumbosacral	11 (64.7)	38 (95.0)	$P = 0.009$
Electrophysiological generalization	14 (82.4)	39 (97.5)	NS

Data presented as *n* of patients (%).
[a]Data were analysed with χ^2-test; NS, no significant between-group difference ($P \geq 0.05$).

months, indicating that neurogenic involvement in the lumbosacral segment progressed with time in BO-ALS (Table 1). In addition, as expected, electrophysiological generalization was more common in BO-ALS with a diagnostic latency >6 months.

Discussion

The present retrospective study demonstrated a distinct descending spread of clinical and electrophysiological manifestations from the rostral to the caudal regions in patients with BO-ALS. Furthermore, the study revealed a pattern of LMN degeneration using the neurophysiological techniques, characterized by the distribution of neurogenic involvement correlated with the diagnostic latency.

Since it was suggested that symptoms in ALS develop most often in adjacent anatomical sites during disease progression,[17] clinical propagation has been investigated in recent studies. There was an obvious gradient of clinical manifestations in ALS with more frequent subsequent involvement of adjacent anatomical sites compared with remote sites, indicating contiguous anatomical propagation.[4,6,17,18] However, a non-contiguous pattern of progression in clinical manifestations in ALS was also reported in previous studies; and the difference has been attributed to variable onset subtypes of ALS.[19,20] In a study with a large cohort, ALS patients with bulbar UMN or LMN onset showed progression more frequently to the upper limbs than to the lower limbs and to the lower limbs more frequently than to the thoracic region,[5] although there are no sensitive clinical or functional signs of thoracic region involvement. In the present study on patients with BO-ALS, a large proportion of patients showed a contiguous progression and the highest involvement was in the bulbar region and the lowest in the lower limbs innervated by the lumbosacral segment in clinical investigation, suggesting a descending pattern from the rostral to the caudal regions along the anatomical structure from the brainstem to the spinal cord in the majority of patients. Meanwhile, a minority of patients presented symptoms in the lower limbs after bulbar onset, skipping the upper limbs for a period of time. It has been suggested that ALS spreads in a prion-like fashion with misfolded protein aggregates transmitting to the adjacent cells or via synapses,[21,22] contributing to the organized development of symptoms in contiguous anatomical propagation; whereas a non-contiguous pattern of progression appears to be correlated with

other mechanisms including multifocal onset and selective vulnerability.[3]

This current study further investigated the electrophysiological features in patients with BO-ALS, which was an important part of their diagnosis. For the evaluation of the bulbar region, the tongue or sternocleidomastoid muscles were used as both of them are currently considered alternative muscles for testing the bulbar region.[23,24] A descending pattern in electrophysiological features similar to the clinical propagation was revealed, with neurogenic injury in the lumbosacral segment being involved relatively late. In addition, a significantly lower prevalence of neurogenic involvement in the lumbosacral segment was observed in patients with a diagnostic latency $\leq$6 months compared with those >6 months; and electrophysiological generalization was more common in the latter group. Denervation and reinnervation of muscles in ALS have been found in a dynamic process and LMN dysfunction could remain in a subclinical state without apparent weakness or amyotrophy even if loss of MUPs was up to 50–80%.[10,25,26] Indeed, in this current study, the neurogenic injury in the lumbosacral segment was detected as early as within 6 months after the onset, much earlier than the occurrence of clinical manifestations in lower limbs reported as 14 months.[18] It is well-established that electrophysiological examination such as needle EMG would be more sensitive than clinical investigations to assess motor unit microanatomy and identify regions of LMN degeneration, thus contributing toward an accurate diagnosis. Nonetheless, in some patients with BO-ALS that have a shorter disease duration or occasionally in patients with longer disease duration as in this study, LMN degeneration in the lower limbs was not detected by needle EMG, supporting the necessity of follow-up EMG studies in some patients. In contrast, consistent with previous studies,[3,19] this current study also found a skipping pattern in the electrophysiology features in a small proportion of patients. In addition, inside of the cervical or lumbosacral segment, the muscles innervated by different roots were not always equally affected, or not affected according to the anatomical sequence, i.e. muscles innervated by the C8–T1 roots are more vulnerable than those innervated by the C5–C6 roots, so are the muscles innervated by the L5 than those by L2–L4.[3] These results are in favour of mechanisms other than neural connectivity.

This current study had several limitations. First, it was a retrospective study undertaken in a single centre with a small patient number. Secondly, nearly all of the patients received only one EMG test, so the study was not able to analyse the changes in electrophysiological features over time. Thirdly, only one or two paraspinal muscles innervated by the thoracic segment were evaluated. As there is overlapping innervation from adjacent thoracic roots, there might have been false negative results interfering with the analysis. Nonetheless, as a pilot study, it has demonstrated a relative rostral–caudal spreading pattern of BO-ALS in clinical manifestations and especially electrophysiological features.

In conclusion, the present study found a descending gradient from the rostral to caudal regions in both clinical manifestations and electrophysiological profiles in patients with BO-ALS. As a result, neurogenic injury in the lumbosacral segment was significantly less frequent in patients with shorter diagnostic latency. These results may help understand the clinical and electrophysiological progression of BO-ALS and suggest that follow-up EMG might be necessary for at least a proportion of patients.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

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