Original Article

Repetitive Nerve Stimulation in Amyotrophic Lateral Sclerosis

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Abstract

Background: Nowadays, it is widely known that decremental responses in low-frequency repetitive nerve stimulation (LF-RNS) are frequently observed in patients with amyotrophic lateral sclerosis (ALS). The pathological mechanism of this phenomenon remains unknown. This study aimed to illuminate the features of RNS in Chinese patients with ALS.

Methods: Clinical and electrophysiological data of 146 probable and definite ALS patients who underwent RNS were retrospectively enrolled and analyzed. LF-RNS (3 Hz) was performed in trapezius, deltoid, abductor digiti minimi (ADM), quadriceps femoris, and tibialis anterior. High-frequency RNS (HF-RNS, 10 Hz) was performed only in ADM. The two-sample *t*-test and Chi-squared test were used for statistical analysis.

Results: Decremental responses to LF-RNS (≥10%) in at least one muscle were detected in 83 (56.8%) of the cases and were most commonly seen in trapezius and deltoid. The incidence of decremental response was higher in patients with upper limb onset. Incremental responses to HF-RNS (≥60%) in ADM were observed in 6 (5.6%) of the cases. In 106 muscles with decremental response, 62 (57.4%) muscles had a continuous decremental pattern, more than a U-shape pattern (37 cases, 34.3%). Nineteen cases showed definite decrements in LF-RNS tests in trapezius, while no abnormalities were found in the electromyography and neurological examination of the sternocleidomastoid muscle, supplied by the accessory nerve as well.

Conclusions: Decremental responses in the RNS are commonly observed in ALS patients. The findings regarding the trapezius indicated that some ALS onsets could be initiated by a "dying back" process, with destruction of neuromuscular junctions (NMJs) before motor neurons. Incremental responses in the ADM implied damage of the NMJs involved both the post and presynaptic membranes.

Key words: Amyotrophic Lateral Sclerosis; Decremental Response; Dying Back; Repetitive Nerve Stimulation

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease of the motor neuron (MN) system,[1] with a median survival period of 3–5 years. The etiology of ALS remains unknown. Repetitive nerve stimulation (RNS) was originally widely applied in the functional evaluation of neuromuscular junctions (NMJs), where it became a routine examination of the NMJ diseases such as myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome.[2] Since the first description by Mulder *et al.* in 1959,[3] it is known that decremental responses in low-frequency RNS (LF-RNS) are frequently observed in patients with ALS. However, the pathological mechanism and the clinical implications of this phenomenon remain elusive.[4-10] Immature sprout, due to denervation and innervation after MN loss, is typically considered a possible mechanism. The animal experiments demonstrated the possibility of NMJs defection occurring before any loss of MNs, termed the "dying back" theory.

In this study, we investigated the clinical and electrophysiological data of 146 Chinese patients with ALS, focusing on features of RNS decrements, in the hope of novel discoveries that would lead to a better understanding about the mechanisms of the disease.

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Methods

Ethics approval

Chinese People's Liberation Army General Hospital Ethics Committee approved the study. All patients were involved in the study based on the voluntary principle and signed informed consent forms. We maximized the protection of the interests of patients and did not harm any patients.

Subjects

Clinical and neuroelectrophysiological data of patients diagnosed with ALS were recruited from the Neurology Department, Chinese People's Liberation Army General Hospital, between April 2016 and December 2017. All patients were examined and diagnosed by experienced senior neurologists. According to the revised El Escorial criteria,[11] the cases were further categorized as clinically definite ALS, clinically probable ALS, clinically probable-laboratory supported ALS, or clinically possible ALS. Patients that met the following conditions were excluded: (1) under the diagnostic degree of clinically probable-laboratory supported ALS, (2) positive response toward anticholinesterase, (3) obvious improvement after clinical follow-up, (4) incomplete clinical data. The patients with progressive muscular atrophy were included in this study, categorized as lower MN disease (LMND) ALS.[12-14] A total of 146 cases were enrolled in this study (91 men, mean age: 54.3 ± 10.8 years, range: 22–78 years). The diagnostic categories by data collection were 93 clinically definite ALS, 33 clinically probable ALS, 8 clinically probable-laboratory supported ALS, and 12 LMND ALS.

Repetitive nerve stimulation methods

The electrodiagnostic studies, including RNS, electromyography (EMG), and nerve conduction studies, were performed in a keypoint workstation machine (31A06, Alpine Biomed ApS, Denmark). Skin temperature over the examined muscle was maintained at 32°C or above throughout the entire measurement. Surface electrodes were used to record the belly-tendon compound muscle action potential (CMAP). At least one muscle was examined in each patient. RNS was performed in the following muscles: deltoid for the axillary nerve (n = 51), trapezius for the accessory nerve (n = 149, both sides tested in 5 cases), abductor digiti minimi (ADM) for the ulnar nerve (n = 110), quadriceps femoris (QUA) for the femoral nerve (n = 25), tibialis anterior (TIB) for the common peroneal nerve (n = 50), and orbicularis oculi (ORB) for the facial nerve (n = 8, both sides tested in 2 cases). A low frequency of 3 Hz train of the 10 stimuli was delivered to the nerves and recorded. A decrement of the peak-to-peak amplitudes of the CMAP of the 4th–1st responses was measured. Based on the conventional criterion, a decremental response of 10% or greater was considered positive, in accordance with the suggestions of the American Academy of Emergency Medicine Quality Assurance Committee.[15] A high frequency of 20 Hz train of 100 stimuli was given to only ADM in 108 participants, after considering tolerance. An incremental response of 60% or greater was considered positive, because of its high diagnostic sensitivity and specificity, in accordance with previous study recommendations.[16] We investigated decremental patterns in 108 muscles with positive decrements, to determine if the U-shape pattern in the MG was commonly found in ALS patients.

Statistical analysis

Statistics calculations were performed using SPSS 22.0 software (SPSS, Chicago, IL, USA). The significance level was set at $P < 0.05$. Descriptive statistics satisfying the normal distribution were performed using means and standard deviations. Enumeration data, such as frequency of decrements, were compared using Chi-squared test and measurement data, such as decremental percentage, were compared using two-sample t-tests.

Results

The EMGs showed diffuse neurogenic changes in all the cases. A significant decremental response was observed in at least one muscle in 83 (56.8%) patients. Clinical features between patients with and without decremental response are summarized in Table 1. Age, age of onset, disease duration,

Table 1: Comparison of clinical features between ALS patients with or without LF-RNS decremental responses

Clinical features	LF-RNS (+)	LF-RNS (−)	Statistics	*P*
Age (years)	53.9 ± 11.2	54.8 ± 10.4	−0.487*	0.627
Age of onset (years)	52.8 ± 10.8	53.7 ± 10.3	−0.475*	0.636
Disease duration (months)	16.2 ± 12.2	14.2 ± 14.9	0.914*	0.362
ALSFRS-R score	3.0 ± 5.1	39.1 ± 5.0	−1.301*	0.196
Disease progression rate	0.99 ± 1.10	0.93 ± 0.70	0.321*	0.749
Region of onset (n)				
Limb	74	47	5.345†	0.021
Medulla	9	16		
Upper limb	56	28	7.772†	0.005
Lower limb + medulla	27	35		
Lower limb	18	19	1.359†	0.244
Upper limb + medulla	65	44		

*t value; †χ^2 value. +: With decremental response; -: Without decremental response. LF-RNS: Low frequency repetitive nerve stimulation; ALS: Amyotrophic lateral sclerosis; ALSFRS-R: ALS Functional Rating Scale-Revised.

ALS Functional Rating Scale-Revised score, and disease progression rate showed no statistical difference. The decremental responses were more frequently seen in upper limb onset cases and less common in bulbar-onset cases.

Distributions of decrement in the different muscles are illustrated in Table 2. Decremental responses were most frequently seen in the trapezius (55.0%) followed by the deltoid (52.9%). Decrements in ADM, QUA, and TIB seemed rare with a frequency of 5.5%, 4.0%, and 2.0%. There was no decrement seen in the obicularis oculi.

In the 106 patients who underwent the 20 Hz stimulation for ADM, 6 (5.6%) had incremental response greater than 60%, while no decremental response in the 3 Hz stimulation was found in the same muscle. EMG in ADM showed neurogenic change in all the cases. 3 Hz RNS of trapezius and TIB was performed in the 6 participants, where 5 of them had decremental responses in the trapezius at the same time.

In electrophysiological images of the 108 muscles with decremental responses, 62 (57.4%) showed a continuous decrease [Figure 1a], while only 37 (34.3%) showed a classical U-like recovery [Figure 1b]. There were also 9 (8.3%) atypical cases [Figure 1c]. Unlike the MG, the distinct U-shape pattern did not dominate in ALS cases.

The electrophysiological results showed that 19 patients had a definite decremental response in the trapezius, yet there was no sign of spontaneous potential or neurogenic motor unit potentials in the EMG of the sternocleidomastoid muscle, which is supplied by the accessory nerve as well. The clinical data were reviewed. The neurological examination showed no weakness in the flexing, turning of the neck, or shoulder shrugging, indicating a normal muscle strength of trapezius and sternocleidomastoid muscle.

Discussion

There are a number of reports stating that decremental responses are commonly observed in patients with ALS, beginning with the first description from Mulder *et al.* in 1959.[3] Our study found decremental responses in at least one muscle in more than half of the patients enrolled (83 patients, 56.8%). In Table 3, the incidence and distribution of decremental responses of the present and previous reports[4-10] are summarized, as a comparison. The deltoid and trapezius showed decremental responses more frequently than the other muscles, indicating that proximal muscles were more sensitive than distal muscles in the RNS in ALS patients, which was in line with previous reports.[4,6]

Some researchers have stated that the incidence of decremental responses in RNS in ALS patients with the rapidly progressing patients is significantly higher than in the slowly progressing patients.[5,17-19] Other studies,[7,10] as well as the current study, did not report this correlation. The incidence of decremental response was significantly higher in patients with upper limb onset and lower in patients with bulbar onset when compared to patients with other onset regions. This was in agreement with a Japanese report[9] and two Chinese reports. The cause of these phenomena remains unknown.

The cause of decremental responses in ALS patients remains controversial, but it is typically attributed to immature sprout,

Table 2: Frequency and distributions of LF-RNS decremental responses in each muscle in patients with ALS (n = 146)

Muscle (nerve)	Examined (n)	Positive (n)	Frequency* (%)	Decremental percentage† (%), mean ± SD (range)
TRA (ACE)	149	82	55.0	19.5 ± 9.1 (10–50)
DEL (AXI)	51	27	52.9	24.0 ± 8.9 (10–40)
ADM (ULN)	110	6	5.5	15.9 ± 3.7 (12–22)
QUA (FEM)	25	1	4.0	15.0
TIB (CP)	50	1	2.0	21.0
ORB (FAC)	8	0	0	–

*Frequency: Positive nerve/examined nerve; †Decremental percentage: Only for patients with decremental response (decremental percentage × 100%≥10%). -: Not described. LF-RNS: Low frequency repetitive nerve stimulation; ALS: Amyotrophic lateral sclerosis; TRA: Trapezius; DEL: Deltoid; ADM: Abductor digitiminimi; QUA: Quadriceps femoris; TIB: Tibialis anterior; ORB: Orbicularis oculi; ACE: Accessory nerve; AXI: Axillary nerve; ULN: Ulnar nerve; FEM: Femoris nerve; CP: Common peroneal nerve; FAC: Facial nerve; SD: Standard deviation.

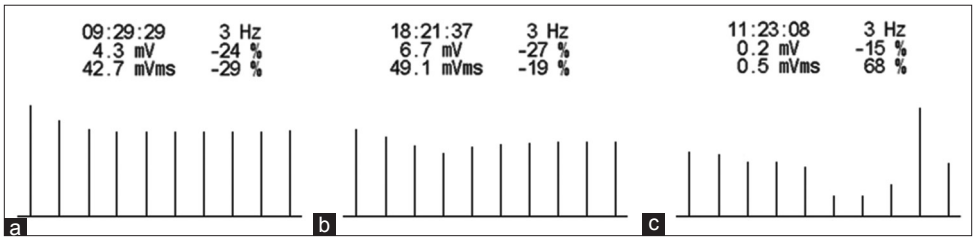

Figure 1: Different decremental patterns in muscles with LF-RNS (3 Hz) decremental response performed on ALS patients by keypoint workstation machine (a) continuous decrease (62/108, 57.4%), (b) U-shape pattern (37/108, 34.3%), and (c) atypical without fixed pattern (9/108, 8.3%). Muscles with decremental response and complete RNS images are included in the study of decremental pattern (n = 108). LF-RNS: Low-frequency repetitive nerve stimulation; ALS: Amyotrophic lateral sclerosis.

Table 3: Comparison of previous reports and the present study on frequency and distribution of decremental responses in patients with ALS

Studies	Time	Patients number	Mean age (years)	Dec* (%)	TRA (%)	DEL (%)	ADM (%)	APB (%)
Present study	2017	146	54.3 ± 10.8	56.8	55.0	52.9	5.5	–
Killian *et al*.	1994	192	55.0	29.0	52.0	–	–	–
Wang *et al*.	2001	15	57.0 ± 9.0	53.0†	–	–	–	–
Iwanami *et al*.	2011	48	62.6 ± 10.8	77.0	52.0	67.0	17.0	29.0
Yamashita *et al*.	2015	51	64.2 ± 14.5	–	–	–	0	34.4
Hatanaka *et al*.	2017	61	65.8 ± 13.8	–	38.0	54.0	–	24.0
Wang *et al*.	2017	54	–	42.6	61.0	–	2.0	10.0
Zheng *et al*.	2017	35	53.5 ± 13.0	71.4	37.1	54.3	22.9	29.0

*Decrement ≥10%; †Only examined in thenars. –: Not described; Dec: Frequency of decremental response in total; ALS: Amyotrophic lateral sclerosis; TRA: Trapezius; DEL: Deltoid; ADM: Abductor digitiminimi; APB: Abductor pollicisbrevis.

due to progressive denervation and chronic innervation at early stage of the disease, resulting from MN loss.[20] This is also termed the "dying forward" theory.

In the present study, 19 cases showed a definite decremental response in the trapezius during LF-RNS. The sternocleidomastoid muscle – which is supplied by accessory nerve as well as the trapezius – appeared completely normal, without weakness in the neurological examination or neurogenic damage in EMG. This has never been reported before. This is interesting as it seems to be clinical proof for the "dying back" theory, which was only seen in animal models.[21] This suggested that the NMJs destruction and axon degeneration of the accessory nerve occurred before MN cell loss. Contrary to the dying forward theory, Fischer *et al*. performed quantity of pathological experimentation on $SOD1^{G93A}$ mice model. He found that end plates denervation and ventral root axons loss occur before any loss of MNs in the spinal cord anterior corn. An autopsy on a single ALS patient showed denervation and reinnervation changes in muscles, where the MNs remained structurally intact.[21] These results demonstrated that the MN pathology begins with NMJs and distal axons, then proceeds in reverse, as a ''dying back'' pattern. A similar pathological pattern is reported in several animal models of MN disease such as the motorneuron degeneration model and the progressive motor neuronopathy model.[22] Even a complete rescue of the MN cells cannot effectively delay muscle denervation and only moderately suspends the mSOD1 mice death.[23-25]

The mechanism of the "dying back" pattern remains unclear. Nutritional status is positively correlated with prognosis and survival time, in both human and transgenic mice.[26] Nardo *et al*.'s study in $SOD1^{G93A}$ mice detected different progression rates and life spans in models of various genetic backgrounds.[27] The fast-progressing mice that had a higher basal metabolic rate,[28] seem to have NMJs innervation more than the slow-progressing mice at onset, while MN loss was equal to the latter. Energy deficits, resulting from hypermetabolism and malnutrition of ALS, could give rise to muscle-initiated NMJs dysfunction. NMJs could be more vulnerable to metabolic demand gap since they are the most distal region of the axon and therefore display an alteration ahead of all.[29] The NMJs dismantlement contributed to muscle denervation and MN death. Another possible explanation is that sublethal damage to the cell body, such as accumulation of insoluble complexes of mutant SOD1 protein[30] or chronic glutamate toxicity,[31] causes the deficient transport of component to NMJs, which are necessary for maintaining synaptic activity. This undernourishment results in degeneration of the distal axons, while the structural integrity of the cell body remains unaffected.[21,32]

The "dying back" pattern in electrophysiological tests was observed other than in the sternocleidomastoid muscle. Additional cases should be enrolled for novel discovery and further research. If this phenomenon is observed in the deltoid as well, it would be reasonable to perform a muscle biopsy. Beside routine observation under a light microscope, morphological changes of the NMJ structures, such as synaptic membrane and mitochondria, as well as dysfunction of the voltage-generated calcium channels, could be observed through electron microscope, to see if these occur ahead of the MN damage. The "dying back" theory could become even more persuasive and valuable for understanding the underlying pathogenesis of ALS.

A recovery after the decrement reaches the bottom is seen in patients with MG, as the U-shape pattern.[33] Some authors have stated that U-shape has also been seen in ALS patients[34] although partially with recoveries less than in MG.[6] In this study, unlike classical postsynaptic destruction, such as MG, the U-shape was not seen much in the RNS tests of ALS patients (37 cases, 34.3%), when the stimulus reached the 6^{th} or 7^{th} wave. This likely resulted from decreased release and storage of acetylcholine in synaptic vesicles, which could not be supplemented and renewed as MG, resulting in continuous dropping safety threshold of the NMJs.[35] The results revealed that the NMJs destruction in ALS was not limited to postsynapse. The incremental responses in the HF-RNS of ADM were found in 6 (5.6%) cases in the current study, without decremental responses in the LF-RNS in the same muscle. Five of the cases were combined with decrements in LF-RNS in the trapezius. The remaining case had an increment in ADM, which was the only abnormality in the RNS, suggesting exclusive presynaptic destruction in

the NMJs. The findings above implied a coexistence of pre and postsynaptic changes, which favored the theory stating that more than one component of the NMJ could be involved in the pathological process.

The decremental responses in LF-RNS are often seen in patients with ALS, yet the pathophysiological mechanism remains unclear. Our results might suggest a "dying back" process in some ALS patients, in accordance with evidence in previous animal experiments. The NMJs dysfunction likely played an important role in initiating the disease, before the MN loss. The NMJs changes in ALS were more likely an overall involvement of the synapse and not restricted to a certain region. However, features revealed from the electrophysiological examination varied with disparate nerves or individuals. The multiple mechanisms made a contribution to the RNS decremental responses in ALS patients. The mechanism underlying could be rather complex.

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Conflicts of interest

There are no conflicts of interest.

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肌萎缩侧索硬化患者的重复神经刺激的研究

摘要

背景：肌萎缩侧索硬化患者中低频神经刺激递减现象较常见。至今这一现象出现的原因仍存在争议。本研究旨在总结中国肌萎缩侧索硬化（ALS）患者重复神经刺激（RNS）的特点。

方法：研究收集了146例拟诊级别以上的ALS患者的临床资料及针极肌电图和重复神经刺激的数据，进行回顾性研究。副神经、腋神经、尺神经、股神经、腓总神经行低频神经刺激（3Hz），尺神经行高频神经刺激（10Hz）。统计学分析采用t检验和卡方检验。

结果：83（56.8%）例患者至少一根神经出现低频刺激递减（≥10%），其中以副神经和腋神经最为常见。在上肢起病的患者中低频递减阳性率更高。6（5.6%）例患者尺神经高频刺激出现递增（≥60%）。在106根低频刺激递减的神经中，62（57.4%）根神经RNS图像呈现持续递减的波型，37（34.3%）根神经呈现U型回升的波型。19例患者副神经低频重复刺激≥10%，副神经支配的胸锁乳突肌针极肌电图及肌力检查正常。

结论：中国ALS患者中RNS异常现象较常见；ALS患者中可能存在逆向死亡的发病过程，在神经元丢失之前神经肌肉接头已经出现功能障碍；ALS患者的神经肌肉接头损害可能同时波及整个突触包括前膜和后膜。