F Wave Study in Amyotrophic Lateral Sclerosis: Assessment of Segmental Motoneuronal Dysfunction

Jia Fang, Li-Ying Cui, Ming-Sheng Liu, Yu-Zhou Guan, Xiao-Guang Li, Bo Cui, Qing-Yun Ding

Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Background: Dysfunctional spinal circuit may play a role in the pathophysiology of amyotrophic lateral sclerosis (ALS). The purpose of this study was to use F waves for assessment of segmental motoneuronal excitability following upper motor neuron (UMN) dysfunctions in ALS.

Methods: We studied the F waves of 152 ulnar nerves recorded from abductor digiti minimi in 82 patients with ALS. Two groups of hands were defined based on the presence or absence of pyramidal signs in the same upper limb. The group with pyramidal signs in the upper limbs was designated as the P group, and the group without pyramidal signs in the upper limbs was designated as the NP group.

Results: The mean (P < 0.001), median (P < 0.001) and maximum (P = 0.035) F wave amplitudes, mean (P < 0.001), median (P < 0.001) and maximum (P = 0.003) F/M amplitude ratio, index repeating neuron (P < 0.001) and index repeater F waves (P < 0.001) of the P group were significantly increased compared with the NP group. No significant differences were identified for F wave chronodispersion (P = 0.628), mean F wave latency (P = 0.151), minimum F wave latency (P = 0.211), maximum F wave latency (P = 0.199), F wave persistence (P = 0.738), F wave duration (P = 0.152), F wave conduction velocity (P = 0.813) and number of giant F waves (P = 0.072) between the two groups.

Conclusions: In this study, increased F wave amplitude, F/M amplitude ratio and number of repeater F waves reflected enhanced segmental motoneuronal excitability following UMN dysfunctions in ALS.

Key words: Amyotrophic Lateral Sclerosis; Excitability; F wave; Segmental Motoneuron; Upper Motor Neuron

F waves may serve as an objective measure of pathophysiological changes in segmental motoneuronal excitability in ALS. F waves, produced by antidromic activation of a limited number of motor neurons, reflect activity at the interface between the peripheral nerves and the spinal cord. Inhibitory activity of the spinal interneuronal circuits, which may be among the earliest affected in ALS, may be reliably assessed by F waves. The purpose of the present study was to use F waves to investigate the pathophysiological changes in segmental motoneuronal excitability in ALS and interpret these F wave abnormalities in the context of upper and lower motor neuron (UMN and LMN) dysfunction.

METHODS

Subjects

Eighty-two patients, 54 males and 28 females with mean age 51.5 ± 10.0 years (range 27–72 years) diagnosed as having definite, probable, or laboratory-supported probable ALS according to the revised El Escorial criteria, were recruited.
into the study. At the time of the investigation, the mean duration from symptom onset was 15 ± 11 months (range 3–72 months). The strength of the examined muscles was estimated by manual muscle testing, using the standard Medical Research Council (MRC) rating scale. Only abductor digiti minimi (ADM) muscles with strength of MRC 3 or higher were studied. Patients with cervical myelopathy, pseudobulbar palsy of vascular origin, diabetes mellitus, alcohol abuse and other systemic or neurological diseases were excluded from the study by appropriate examinations. At the time of the investigation, none of the patients were taking riluzole or any antispasticity drugs.

Corticospinal tract signs in the upper limbs were defined by the presence of increased muscle tone in hands and digits, increased tendon reflexes or positive Hoffman signs. The ADM was evaluated in our study, because the abductor pollicis brevis is predominantly affected in ALS patients, whereas the ADM is relatively preserved. Two groups of hands were defined, based on the presence or absence of pyramidal signs in the same upper limb. The group with pyramidal signs in the upper limbs was designated as the P group, and the group without pyramidal signs in the upper limbs was designated as the NP group.

**Nerve conduction studies**

The examination was performed in a warm room, and the temperature of the investigated limb was kept at or above 32°C using a heater or blanket if necessary. All the electrophysiological studies were performed on a Viking IV EMG machine (Nicolet Biomedical, Madison, Wisconsin, USA). Both ulnar nerves were studied in each ALS patient. For measurements of the ulnar nerve, a surface electrode was placed on the belly of the ADM for recording and on the tendon for the reference. A ground electrode was placed between the recording and stimulating electrodes. Stimulation was performed at the wrist (7 cm from the recording electrode). Motor conduction parameters included measurements of peak-to-peak amplitude of compound muscle action potential (CMAP), distal motor latency (DML) and motor conduction velocity (MCV). Tests to exclude the possibility of conduction block were performed by applying the proximal stimulation of the ulnar nerves in the axilla and Erb’s point and by comparing the amplitudes of the CMAP between different stimulation sites. Sensory conduction examinations were performed to exclude peripheral neuropathies that may affect sensory nervous system, such as carpal tunnel syndrome, diabetic neuropathy, etc.

**F wave study**

The subjects were instructed to keep the hands relaxed during the investigation. In all subjects, the ulnar nerves were bilaterally stimulated using bipolar surface electrodes with a proximal cathode. Supramaximal stimuli that were 20% higher than the level necessary to obtain a maximum M response at a frequency of 1 Hz and duration of 0.1 ms were delivered at the wrist to the ulnar nerves. A total of 100 stimuli were considered appropriate to explore the full potential of F waves. The bandpass was set at 20 Hz to 10 kHz, the sweep speed was 5 ms per division, and the amplifier gain for F waves was set to 0.5 mV per division. The recordings were obtained using surface electrodes placed on the ADM. A peak-to-peak deflection from baseline of at least 40 μV was accepted as an F wave. Nerves without CMAP or F waves were excluded from the analysis. A wave defined as identical late responses in ≥8 of 20 traces with a constant latency was excluded from the F wave measurements. For each of the 100 stimuli, we assessed the minimum, mean and maximum F wave latencies, F wave chronodispersion, F wave persistence, mean, median and maximum F wave amplitudes, mean, median and maximum F/M amplitude ratios, F wave duration, F wave conduction velocity, and number of repeater F waves and giant F waves. F wave latency was measured from the start of the stimuli to the onset of the response. F wave amplitude for each trace was measured from peak to peak. F wave amplitude was not normally distributed, so median F wave amplitude was used in addition to mean F wave amplitude. F wave duration was determined from the onset of the response to the end of the F wave in which the last contiguous part of the response returned to the baseline. The difference between minimum and maximum latencies in a series of F waves, termed F wave chronodispersion, was a measure of the range of F wave conductions. Mean, median and maximum F/M amplitude ratios were mean, median and maximum F wave amplitudes divided by the corresponding maximum CMAP amplitudes. F wave conduction velocity was calculated using the following formula: 2D/(F − M − 1), where D was the surface distance measured from the stimulus point to the C7 spinous process in the ulnar nerve, and F and M were the mean F wave and CMAP latencies, respectively. F wave persistence was defined as the number of F waves per 100 stimuli. Repeater F waves, which were waves with identical latency, amplitude, and waveform, were detected by visual inspection. The presence of a notch or an extra phase disqualified the signal as a repeater F wave. We assessed the repeater F waves using the following indices: Index repeating neurons = 100 × number of repeating neurons/number of traces with different F wave shapes in a series of 100 stimuli, and index repeater F waves = 100 × total number of repeater F waves/total number of traces with F waves in the same nerve. The first formula represented the number of individual repeater F waves, whereas the latter formula represented the number of F waves that repeat. The cut-off amplitude for a giant F wave was 1.2 mV in the upper limb nerves.

The research protocol was approved by the Local Research Ethics Committee and adhered to the principles of Declaration of Helsinki. All subjects gave their written informed consent to participate in the study.

**Statistical analyses**

Descriptive statistics was generated for all variables. Kolmogorov-Smirnov tests were used to assess normality of individual parameters. The homogeneity of variance was tested using a Levene test. We analyzed the differences
between the P and NP groups using the independent samples t-test. For values that were not normally distributed, even after data transformation, the Mann-Whitney U nonparametric test was applied. All tests were two-sided and P < 0.05 was taken as the significance threshold for all tests. Results were expressed as mean ± standard deviation (SD) for parametric data, and median (interquartile range) for nonparametric data. Statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

There was no conduction block or M response temporal dispersion in the 152 ulnar nerves examined. There were 75 ADM muscles in the P group, and 77 ADM muscles in the NP group. The absence of F waves was noted in 12 ulnar nerves. There were no significant differences in the DML (t = -0.818, P = 0.415), CMAP (t = -1.669, P = 0.097) and MCV (t = 0.266, P = 0.791) between the P and NP groups. No sensory conduction abnormalities were disclosed [Table 1].

The absolute mean (t = 3.999, P < 0.001), median (t = 3.851, P < 0.001) and maximum (t = 2.065, P = 0.035) F wave amplitudes in the P group were significantly higher compared with the NP group. The mean (z = -3.978, P < 0.001), median (z = -3.967, P < 0.001) and maximum (z = -3.005, P = 0.003) F/M amplitude ratios of the P group were significantly higher than the NP group. The index repeating neuron (z = -4.366, P < 0.001) and index repeater F waves (z = -4.392, P < 0.001) of the P group were significantly higher than the NP group. No significant differences were identified between the P and NP groups for F wave chronodispersion (t = -0.486, P = 0.628), mean F wave latency (t = -1.444, P = 0.151), minimum F wave latency (t = -1.255, P = 0.211), maximum F wave latency (t = -1.291, P = 0.199), F wave persistence (z = 0.334, P = 0.738), F wave duration (t = 1.438, P = 0.152), F wave conduction velocity (t = 0.363, P = 0.813) and number of giant F waves (z = 0.072, P = 0.072) [Table 2]. Figure 1 exhibits F wave traces from the ulnar nerves of an ALS patient following 100 consecutive stimuli.

DISCUSSION

Previous studies have demonstrated prolonged F wave duration[15] and latency[16] increased F wave amplitude,[17] F wave chronodispersion[18] and F wave persistence[19] in UMN lesions, such as stroke,[20] multiple sclerosis,[21] etc. However, others have argued that no increase in F wave duration was found in spastic state, in contrast, reduced F wave duration has been observed.[22] F wave chronodispersion exhibited a strict peripheral origin for changes.[7] The reason of the discordant findings in the studies may be partially due to technical factors, particularly inadequate stimulation. An adequate sample size

Table 1: Comparisons of nerve conduction measurements between P and NP groups (mean ± SD)

| NCV          | P group | NP group | P       |
|--------------|---------|----------|---------|
| DML (ms)     | 2.41 ± 0.30 | 2.45 ± 0.35 | 0.415   |
| a-CMAP (mV)  | 9.33 ± 3.88 | 10.34 ± 3.55 | 0.097   |
| MCV (m/s)    | 59.73 ± 7.09 | 59.42 ± 7.58 | 0.791   |
| a-SAP (μV)   | 11.55 ± 0.73 | 11.64 ± 1.04 | 0.943   |
| SCV (m/s)    | 56.65 ± 1.29 | 57.05 ± 1.19 | 0.823   |

NCV: Nerve conduction velocity; P group: Limbs with pyramidal signs; NP group: Limbs without pyramidal signs; DML: Distal motor latency; a-CMAP: Amplitude of compound muscle action potential; MCV: Motor conduction velocity; a-SAP: Amplitude of sensory action potential; SCV: Sensory conduction velocity; SD: Standard deviation.

Figure 1: F waves of an amyotrophic lateral sclerosis patient following 100 consecutive stimuli. (a) F wave traces from the ulnar nerve in the right upper limb with pyramidal sign. Letters to the right of record identify repeater F waves on the basis of waveform and latency. Mean F wave amplitude = 1732 μV, median F wave amplitude = 2321 μV, maximum F wave amplitude = 2404 μV, mean F/M amplitude ratio = 36.85%, median F/M amplitude ratio = 49.38%, maximum F/M amplitude ratio = 51.15%, index repeating neuron = 42.86%, index repeater F waves = 86.67%; (b) F wave traces from the ulnar nerve in the left upper limb without pyramidal sign. Mean F wave amplitude = 264 μV, median F wave amplitude = 669 μV, mean F/M amplitude ratio = 1.8%, median F/M amplitude ratio = 1.45%, maximum F/M amplitude ratio = 4.55%, and no repeater F waves were noted. The sensitivity is 0.5 mV and the time-base is 5 ms.
The primary objective of the present study was to ascertain the alterations of segmental motoneuronal excitability and F wave characteristics following UMN dysfunctions in ALS.

Generation of F waves is influenced by the balance of excitatory and inhibitory postsynaptic potentials on spinal motoneurons. In ALS, pathophysiological abnormalities that follow damage to descending motor pathways and to motoneurons and interneurons in the spinal cord result in increased segmental excitation of remaining functional motoneurons. Consequently, large numbers of motoneurons partially activated may be within the critical level of depolarization. In addition, changes in motoneuron ion-channel expression may shorten the refractory period of the initial segment of motoneuron axons.

In the present study, significant increases in the mean, median and maximum amplitudes of F waves were found in the P group compared with the NP group. An increased F wave amplitude was a result of the participation of an increased number of neurons giving recurrent discharge more frequent discharge of the responding neurons that produced F responses and an increased number of large motor units that resulted from axonal sprouting during the process of compensatory reinnervation.

The mean, median and maximum F/M amplitude ratios represented the mean, median and maximum fraction of motoneurons activated by the antidromic stimulation respectively. The increased F/M amplitude ratios in the P group compared with the NP group could be attributed to increased tendency of motoneurons to generate F waves. The mean F/M amplitude ratio may be increased in neuropathies, most characteristically with axonal injury and associated decrease in M waves. Some studies exhibited that changes in M amplitude made the F/M amplitude ratio not as accurate as absolute F wave amplitude. Since there were no differences between the P and NP groups in the amplitudes of the ulnar CMAP, the increased F wave amplitude and F/M amplitude ratio indicated a higher level of segmental motoneuronal excitability.

The repeater F waves indicated the selectivity of motor unit discharge in a series of F waves. Increased repeater F waves in the P group compared with the NP group exhibited an enhanced excitatory state of the motoneuron pool that caused motoneurons to produce more frequent repeated backfiring.

F waves offer a flawed measurement of motoneuronal excitability. Under conditions of motoneuronal activation, it’s likely that a reflex discharge contributes to the size of F wave, though some studies demonstrated that the possibility of F wave contamination by H reflex was eliminated by applying supramaximal stimuli. The observed increase in F wave amplitude might reflect an increase in the F-H complex as well. Of interest in the present study, there were no significant differences in the F wave latency, F wave chronodispersion and F wave duration between the P and NP groups. It was possible that an increase in the excitability of the motoneuron pool produced a larger H reflex and prevented the low-threshold slow conducting motoneurons from participating in F wave activity. Preferential loss of fast-conducting, large caliber α-motoneurons in ALS may also explain the similarities between the two groups.

The absence of differences in F wave persistence between the P and NP groups supported the view that F wave persistence was closely related to the number of functional LMNs and indicates LMN damage. No significant differences were identified between the P and NP groups in the number of giant F waves, which may reflect an increase in the motor unit size during the reinnervation process. Intrinsically, some pathological characteristics in ALS such as changes in distal axon caliber, proximal axonal swellings and ongoing Wallerian degeneration along axons may cause dispersion of the eff erent volley, resulting in a nonsynchronous muscle response, and this potential functional abnormality would make detection of changes of F waves difficult.

F for the present study, it is possible that the number of limbs with UMN involvement would be higher than could be detected by clinical examination. To deal with the potentially confounding issue, the upper limbs of ALS patients in our study were mildly or moderately affected in order to avoid severe muscle weakness and wasting masking UMN signs. The alterations of F wave characteristics need to be verified in
further studies with patients with pure LMN lesions as control groups, such as patients with Hirayama disease, Kennedy disease or spinal muscular atrophy, though such patients with matched age and disease duration are difficult to find.

In the present study, increased F wave amplitude, F/M amplitude ratio and number of repeater F waves indicated hyperexcitability of segmental motoneurons and correlated closely to UMN signs in ALS. Findings from our study suggested an intimate linkage between the UMN degeneration and dysfunctional spinal circuit and indicated transneuronal or anterograde LMN dysfunction following UMN lesions in ALS.[31,32]

In conclusion, F waves have the virtue of being easily undertaken in a wide variety of muscles with standard neurophysiological equipment during routine diagnostic assessment of ALS patients. F wave is suitable as a probe for investigations of F wave parameters following UMN dysfunction with disease progression and modulations of F wave parameters by relevant treatment such as riluzole.

References

1. Vucic S, Ziemann U, Eisen A, Hallett M, Kiernan MC. Transcranial magnetic stimulation and amyotrophic lateral sclerosis: Pathophysiological insights. J Neurol Neurosurg Psychiatry 2013;84:1161-70.
2. Bae JS, Simon NG, Menon P, Vucic S, Kiernan MC. The puzzling case of hyperexcitability in amyotrophic lateral sclerosis. J Clin Neurol 2013;9:65-74.
3. Vucic S, Cheah BC, Yiannikas C, Kiernan MC. Cortical excitability distinguishes ALS from mimic disorders. Clin Neurophysiol 2011;122:1860-6.
4. Vucic S, Kiernan MC. Axonal excitability properties in amyotrophic lateral sclerosis. Clin Neurophysiol 2006;117:1458-66.
5. Turner MR, Kiernan MC. Does interneuronal dysfunction contribute to neurodegeneration in amyotrophic lateral sclerosis? Amyotrophic Lateral Scler 2012;13:245-50.
6. Milanov IG. F‑wave for assessment of segmental motoneurone excitability. Electromyogr Clin Neurophysiol 1992;32:11-5.
7. Fisher MA. Inhibition of motoneuron discharge by peripheral nerve stimulation: An F response analysis. Muscle Nerve 1991;14:120-3.
8. Lin JZ, Floeter MK. Do F‑wave measurements detect changes in motor neuron excitability? Muscle Nerve 2004;30:289-94.
9. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Scler Other Motor Neuron Disord 2000;1:293-9.
10. Shibuya K, Misawa S, Nasu S, Sekiguchi Y, Mitsuma S, Beppu M, et al. Split hand syndrome in amyotrophic lateral sclerosis: Different excitability changes in the thenar and hypothenar motor axons. J Neurol Neurosurg Psychiatry 2013;84:969-72.
11. Fisher MA, Hoffen B, Hultman C. Normative F wave values and the number of recorded F waves. Muscle Nerve 1994;17:1185-9.
12. Kawakami S, Sonoo M, Kadoya A, Chiba A, Shimizu T. A‑waves in Guillain‑Barre syndrome: Correlation with electrophysiological subtypes and antiganglioside antibodies. Clin Neurophysiol 2012;123:1234-41.
13. Chroni E, Tendero IS, Punga AR, Stålberg E. Usefulness of assessing repeater F‑waves in routine studies. Muscle Nerve 2012;45:477-85.
14. Ibrahim IK, el‑Abd MA. Giant repeater F‑wave in patients with anterior horn cell disorders. Role of motor unit size. Am J Phys Med Rehabil 1997;76:281-7.
15. Bischoff C, Schoenle PW, Conrad B. Increased F‑wave duration in patients with spasticity. Electromyogr Clin Neurophysiol 1992;32:449-53.
16. Fisher MA. F response latencies and durations in upper motor neuron syndromes. Electromyogr Clin Neurophysiol 1986;26:327-32.
17. Eisen A, Oudsote K. Amplitude of the F wave: A potential means of documenting spasticity. Neurology 1979;29:1306-9.
18. Tsai CT, Chen HW, Chang CW. Assessments of chronodispersion and tachoeosion of F waves in patients with spinal cord injury. Am J Phys Med Rehabil 2003;82:498-503.
19. Schiller HH, Stalberg E. F responses studied with single fibre EMG in normal subjects and spastic patients. J Neurol Neurosurg Psychiatry 1978;41:45-53.
20. Drory VE, Neufeld MY, Korczyn AD. F‑wave characteristics following acute and chronic upper motor neuron lesions. Electromyogr Clin Neurophysiol 1993;33:441-6.
21. Argyriou AA, Karanasios P, Makridou A, Makris N. F‑wave characteristics as surrogate markers of spasticity in patients with secondary progressive multiple sclerosis. J Clin Neurophysiol 2010;27:120-5.
22. Esposito MG, Lin CS, Burke D. Motoneuron excitability and the F wave. Muscle Nerve 2003;27:720-7.
23. Fang J, Liu MS, Guan YZ, Cui B, Cui LY. Importance of sample size for the estimation of repeater F waves in amyotrophic lateral sclerosis. Chin Med J 2015;128:515-9.
24. Swash M. Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? J Neurol Neurosurg Psychiatry 2012;83:659-62.
25. Fisher MA. F response analysis of motor disorders of central origin. J Neurol Sci 1983;62:13-22.
26. Fisher MA. F/M ratios in polyneuropathy and spastic hyperreflexia. Muscle Nerve 1988;11:217-22.
27. Argyriou AA, Polychronopoulos P, Talelli P, Chroni E. F‑wave study in amyotrophic lateral sclerosis: Assessment of balance between upper and lower motor neuron involvement. Clin Neurophysiol 2006;117:1260-5.
28. Fox JE, Hitchcock ER. F wave size as a monitor of motor neuron excitability: The effect of deafferentation. J Neurol Neurosurg Psychiatry 1987;50:453-9.
29. Van der Graaff MM, de Jong JM, Baas F, de Visser M. Upper motor neuron and extra‑motor neuron involvement in amyotrophic lateral sclerosis: A clinical and brain imaging review. Neuromuscul Disord 2009;19:53-8.
30. Ahdab R, Créange A, Saint‑Val C, Farhat WH, Lefaucheur JP. Rapidly progressive amyotrophic lateral sclerosis initially masquerading as a demyelinating neuropathy. Neurophysiol Clin 2013;43:181-7.
31. Eisen A, Weber M. The motor cortex and amyotrophic lateral sclerosis. Muscle Nerve 2001;24:564-73.
32. Vucic S, Nicholson GA, Kiernan MC. Cortical hyperexcitability may precede the onset of familial amyotrophic lateral sclerosis. Brain 2008;131:1540-50.

Received: 09‑03‑2015 Edited by: Xin Chen
How to cite this article: Fang J, Cui LY, Liu MS, Guan YZ, Li XG, Cui B, Ding QY. F Wave Study in Amyotrophic Lateral Sclerosis: Assessment of Segmental Motoneuronal Dysfunction. Chin Med J 2015;128:1738‑42.

Source of Support: Nil. Conflict of Interest: None declared.