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RESEARCH

Evaluation of the relationship between clinical findings and F responses and diffusion tensor tractography in patients with amyotrophic lateral sclerosis

Amyotrofik lateral sklerozlu hastalarda klinik bulgular ile F yanıtları ve difüzyon tensör traktografi arasındaki ilişkinin değerlendirilmesi

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Abstract

Purpose: The aim of this study is to show whether radiologically diffusion tractography imaging (DTI) and electrophysiologically F responses methods support clinical examination in Amyotrophic Lateral Sclerosis (ALS). It is to determine the relationships between these two methods.

Materials and Methods: Patients with a definite diagnosis of ALS according to the Revised-El Escorial and Awaji criteria at any stage of the disease, who applied to the Electromyography (EMG) laboratory of the Neurology Clinic of Istanbul University Cerrahpaşa, Cerrahpaşa Medical Faculty, prospectively and cross-sectionally, were included in the study. The revised ALS functional rating scale (ALSFRS-R) was scored. Electrophysiological studies included routine nerve conduction studies, F responses and needle EMG. In radiological examinations, diffusion tractography imaging (DTI) maps were obtained in brain and cervical Magnetic Resonance Imaging (MRI) and diffusivity and fractional anisotropy (FA) values were compared.

Results: The mean age of the 12 volunteer patients included in the study was 55.92±9.68 (43-72), and consisted of 4 female and 8 male individuals. The mean ALSFRS-R score was 35.75±7.86 (24-46). MRI was performed in 11 of the patients, spinal imaging could not be performed in one patient. The mean age of the 11 patients who were imaging was 56.4±9.8 years and the disease duration was 2.7±1.9 years. Low values of DTI-FA

Öz

Amaç: Bu çalışmanın amacı, Amiyotrofik Lateral Skleroz (ALS) hastalığında radyolojik olarak difüzyon traktografi görüntüleme (DTG) ve elektrofizyolojik olarak F yanıtlarının klinik muayeneyi destekleyip desteklemediğini göstermektir.

Gereç ve Yöntem: İstanbul Üniversitesi Cerrahpaşa Cerrahpaşa Tıp Fakültesi Nöroloji Kliniği Elektromiyografi (EMG) laboratuvarına başvuran, hastalığın herhangi bir evresindeki Revize-El Escorial ve Awaji kriterlerine göre kesin ALS tanısı alan hastalar prospektif, kesitsel olarak çalışmaya alındı. Revize ALS fonksiyonel derecelendirme ölçeği (ALSFRS-R) uygulandı. Elektrofizyolojik incelemelerde rutin sinir iletim çalışmaları, F yanıtları ve iğne EMG'si incelendi. Radyolojik incelemelerde, Radyolojik incelemelerde beyin ve servikal manyetik rezonanas görüntülemede (MRG) difüzyon traktografi görüntüleme (DTG) haritaları elde edildi ve difüzyon ve fraksiyonel anizotropi (FA) değerleri karşılaştırıldı.

Bulgular: Çalışmaya alınan 12 gönüllü hastanın yaş ortalaması 55.92±9.68 (43-72) idi ve 4'ü kadın, 8'i erkek bireyden oluşmaktaydı. Ortalama ALSFRS-R puanı 35.75±7.86 (24-46) idi. Hastaların 11'ine MR görüntülemesi yapıldı, bir hastanın spinal görüntülemesi yapılamadı. Görüntüleme yapılan 11 hastanın ortalama yaş 56,4±9,8 ve hastalık süresi 2,7±1,9 yıldı. Düşük DTG-FA değerlerinin, lineer regresyon analizi ile değerlendirildiğinde kötü solunum ve konuşma skorları ile

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were found to be associated with poor respiratory and speech scores as assessed by linear regression analysis. Repeater F responses in the ulnar nerves were also associated with a high ALSFRS-R score.
Conclusion: In our study, we observed that low values of DTI-FA were associated with poor respiratory and speech scores. Showing the correlation of low FA with a vital function such as respiration may indicate that this technique will be helpful in the prognosis and progression of the disease. The increase of repeater F responses in the ulnar nerves in those with high ALSFRS-R scores suggests that it is worth investigating whether ALS can be used in differentiating from other anterior horn diseases. The results of this study suggest that DTI-FA, which is an advanced radiological evaluation, and repeater F responses as an electrophysiological method may support early diagnosis in ALS.
Keywords:.Amyotrophic lateral sclerosis, F response, diffusion tensor imaging, fractional anisotropy

ilişkili olduğu bulundu. Ulnar sinirlerdeki tekrarlayan F yanıtları da yüksek bir ALSFRS skoru ile ilişkilendirildi.
Sonuç: Çalışmamızda düşük DTG-FA değerlerinin kötü solunum ve konuşma skorları ile ilişkili olduğunu gözlemledik. Düşük FA'nın solunum gibi hayati bir fonksiyonla ilişkisinin gösterilmesi, bu tekniğin hastalığın prognozunda ve ilerlemesinde yardımcı olacağına işaret edebilir. ALSFRS-R skoru yüksek olanlarda ulnar sinirlerde tekrarlayan F yanıtlarının artması ALS'nin diğer ön boynuz hastalıklarından ayırıcı tanısında kullanılıp kullanılamayacağını düşündürmektedir. Bu çalışmanın sonuçları, ileri radyolojik bir değerlendirme olan DTG-FA ve elektrofizyolojik bir yöntem olarak tekrarlayan F yanıtlarının ALS'de erken tanıyı destekleyebileceğini düşündürmektedir.

Anahtar kelimeler: Amiyotrofik lateral skleroz, F yanıtı, difüzyon tensor görüntüleme, fraksiyonel anizotropi

INTRODUCTION

ALS is a rapidly progressive disease that causes selective degeneration of motor neurons and causes death within 3-5 years due to respiratory failure. The first symptom of the disease is usually asymmetrical loss of strength and atrophy, which may be localized in a particular region of an extremity and often begins distally. Symptoms start from the upper extremity in 30-50% of the cases, from the lower extremities in 20-40%, and from the bulbar muscles in 20-30%[1]. History, clinical, neurophysiological evaluations and exclusion of other causes are required for diagnosis. Various algorithms have been developed for early diagnosis. Among these algorithms, the Awaji criteria, which define fasciculation potentials as signs of active denervation, were found to be more sensitive in diagnosis without increasing the false-positive rate[2].

While lower motor neuron (LMN) degeneration can be detected by needle electromyography without clinical signs of weakness and atrophy, it is difficult to demonstrate upper motor neuron (UMN) dysfunction in the early stages of the disease. Although neuroimaging and neurophysiological techniques have been explored in the evaluation of UMN dysfunction, there are currently no widely accepted objective tools[3].

A new approach is needed to demonstrate the degeneration of UMN before clinical detection of signs of UMN. In this respect, MR spectroscopy, volume measurement, functional MRI and diffusion tractography imaging (DTI) are the methods investigated in imaging. DTI provides direct assessment of white matter affected by degeneration of motor neurons, including the corticospinal tract. Therefore, many researchers have used the d DTI to detect UMN abnormalities. Fractional anisotropy (FA) is a representative value of DTI[4]. DTI has a great contribution to our understanding of the neurobiological mechanisms underlying ALS. It has proven to be the most reliable MRI technique for evaluating microstructural abnormalities in ALS patients[4-6]. A recent meta-analysis combining the results of 77 DTI studies showed that the major structural abnormalities in ALS disease are localized to the frontal white matter in the corticospinal tract and a small region of the posterior leg of the inner capsule[7].

F responses in ALS patients show increased latency and distribution, and occur with an increased frequency of repeater F responses[8]. The persistence of the F response in ALS has not been systematically investigated, but it can be expected to increase in relation to signs of dysfunction of the corticospinal tract[9]. Since the F responses generate from the LMN cell body, where the LMN and UMN synapse, repeater F response, which can be observed with DTI UMN involvement and dysfunction of the corticospinal pathway, may guide us.

The aim of this study is to show upper motor neuron involvement in ALS, the characteristics of radiological imaging methods, DTI, and the electrophysiological method of F responses, and

whether the relationship between them supports the clinical examination.

MATERIALS AND METHODS

Sample

Twelve volunteer patients who applied to the Electromyography (EMG) laboratory of the Neurology Department of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty and were diagnosed with definite ALS according to the Revize-El Escorial and Awaji criteria at any stage of the disease were included in the study. Voluntary consent was obtained from all participants. The patients who (i)Had a definite diagnosis of ALS according to the Awaji-El Escorial criteria, (ii) Volunteering to participate in the study, and (iii) didn't have any internal or neurological disease other than ALS were included. The patients with clinical respiratory distress were excluded.

Procedure

The study was performed between February 2019-February 2020 at Istanbul University, Cerrahpaşa Faculty of Medicine, Electromyography Laboratory of Electrodiagnostic Neurology Department, and Neuroradiology Department of the Radiology Department. The study was approved by the Ethics Committee of Istanbul University Cerrahpaşa Faculty of Medicine (04.09.2018/83045809).

Clinical evaluation

a) Physical and detailed neurological examination

b) For the evaluation of muscle strength, the strength of the extremity and trunk muscles in the relevant movement plans was evaluated using the Medical Research Council (MRC) scale and recorded over 5 degrees.

c) The revised ALS functional rating scale (ALSFRS-R) was used. This scale was used for speaking, drooling, swallowing, handwriting, using cutlery, dressing and self-care, turning and covering in bed, walking, climbing stairs, dyspnea, orthopnea, respiratory failure It is a scale consisting of 12 parameters and is used in the follow-up and evaluation of ALS patients over a total of 48 points. Each question is evaluated between 0 and 4 points, the functionally normal patient is evaluated with four points, while the scores decrease from four due to functional deterioration, a zero score indicates the worst functional status. In our study, 12 parameters in the scale were evaluated by dividing the total score and subgroups[10].

Electrophysiological examinations

Routine nerve conduction studies in the EMG laboratory, F responses, H reflex and needle EMG were examined. Keypoint portable EMG device with 24 kHz resolution power was used for EMG recording. The skin temperature of all patients who underwent nerve conduction studies was kept between 31 °C and 34 °C.

Nerve Conduction Studies: Median, ulnar, sural and superficial peroneal nerve sensory, median, ulnar, posterior tibial and peroneal motor nerve conduction studies were performed on the volunteers participating in the study. In sensory nerve conduction examinations; screen sweep rate was 1 ms/div, sensitivity was 20 μV/division, and amplifier filter setting was 10Hz-2 kHz. In motor nerve conduction examinations, the screen sweep rate is 5 ms/div., the sensitivity is 2 mV/div. and the amplifier filter setting was set to 5 Hz – 10 kHz, and. F responses were studied in bilateral median, ulnar, peroneal and posterior tibial nerves and H reflex responses were studied from soleus muscle. F response persistence, latency and repeater F responses were noted.

Conventional Needle Electromyography: Needle electromyography was performed on the upper and lower extremities, bulbar and/or trunk muscles using disposable concentric needle electrodes (37mm x 0.46–26G, Spes Medica, Disposable Concentric Needle Electrode Genova, Italy) Needle EMG examinations, spontaneous activity sensitivity 100 μV/div for MUP configuration, sensitivity 200 μV/div for MUP configuration, sensitivity 1 mV/div for interference pattern, amplifier filter setting 5 Hz – 10 kHz, and screen sweep rate, spontaneous activity and 10 ms/div for MUP configuration, It is set to 20 ms/div for the interference pattern.

Radiological evaluation

Brain imaging was performed using 3D T1 and T2 weighted sequences using the head-neck helix system in a 3 Tesla MRI unit in the Neuroradiology Department of our faculty. With the obtained data, it was possible to evaluate cortical gray matter and white matter together or separately. Trace diffusion-weighted images as well as DT maps were obtained by using different b values in diffusion-weighted MRI

examination, and diffusivity and anisotropy values were compared with known normal values in the same age group. Spinal cord thickness, diffusivity, and anisotropy values were compared with diffusion MRI examination of the cervical region.

Statistical analysis

The parameters used in the study were classified as categorical and individual. Numerical data were presented as mean and standard deviation, and categorical data were presented as medians and percentages. Logistic regression analysis was performed to evaluate the effect of repeater F response rates among the ALSFRS-R scores and the F persistence. We carried out Two separate logistic regression analyzes, with ALSFRS-R as the dependent factor in the first analysis, and F persistence of ulnar, median, tibial and peroneal nerves as the independent factors in the second analysis, in which covariate was repeater F response rates of ulnar, median, tibial and peroneal nerves (yes vs. no). The results were presented as odds ratio (OR). Finally, the relationship between MR findings and ALSFRS-R score sub-parameters was analyzed by linear regression analysis. P value was accepted as 0.05, SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis.

RESULTS

The age of the volunteer patients included in the study was between 43-72 (mean age: 55.92±9.68 years), and the patient group consisted of 4 (33.3%) female and 8 (66.7%) male individuals. The mean ALSFRS-R score was 35.75 ± 7.86 (24-46).

Electrophysiological examination findings of nerve conduction and sensory nerve conduction of the patients were within normal limits according to the age group. Motor conduction studies were found to be low amplitude or could not be obtained in atrophic muscles. Needle EMG findings were compatible with the diagnosis of ALS according to the Revised-El Escorial and Awaji criteria.

Table 1. F response findings of our patients

Nerve	Obtaining F response (Right/Left)	F response latency (ms) (Right/Left) (mean±standard deviation)	F response persistence (Right/Left) (mean±standard deviation)	F response loss (Right/Left) (%)	Repeater F response (Right/Left) (%)
Median	8/7	27.41±3.61/25.61±2.57	83.12±23.44/68.97±17.48	33/42	50/33
Ulnar	9/10	25.96±2.29/26.40±2.94	72.22±41.09/78.79±24.80	25/17	50/58
Posterior tibial	8/8	50.95±6.25/51.30±4.21	91.87±22.98/90.62±22.75	33/33	42/42
Peroneal	4/7	54.15±5.37/53.26±6.10	59.25±9.78/65.04±29.92	67/42	33/42

Table 2. Presence of Ulnar repettative F Responses ALSFRS-R: Revised Amyotrophic lateral sclerosis functional rating scale

ALSFRS-R score	Ulnar F latency right (ms)	ulnar F latency left (ms)	ulnar repeater F response right	ulnar repeater F response left
38	none	21,60	none	present
42	none	31,70	none	present
30	none	none	none	none
41	27,90	28,80	present	present
45	24,90	24,90	present	present
46	23,90	26,60	none	present
25	27,00	none	none	none
24	22,30	23,80	present	none
39	26,30	25,80	present	present
41	28,80	28,00	present	none
30	24,00	28,50	none	none
28	28,50	24,30	present	present

Table 3. Logistic Regression Model of F persistence and ALSFRS on the repeater F response (covariate: yes vs no) in patients with ALS. ALSFRS-R: Revised Amyotrophic lateral sclerosis functional rating scale

Dependent factor	N	Odd Ratio	95% Confidence Interval	p
Median F persistence (covariate:repeater F response of median nerve)	15	0.96	0.997-1.026	0.23
Ulnar F Persistence (covariate:repeater F response of ulnar nerve)	19	1.01	0.992-1.010	0.24
Tibial F Persistence (covariate:repeater F response of tibial nerve)	16	0.10	1.003-1.049	0.99
Peroneal F Persistence (covariate:repeater F response of peroneal nerve)	11	0.02	1.019-1.108	0.99
ALSFRS-R scores (covariate:repeater F response of median nerve)	15	0.07	0.100-3.253	0.1
ALSFRS-R scores (covariate:repeater F response of ulnar nerve)	19	0.01	0.002-0.07	0.03
ALSFRS-R scores (covariate:repeater F response of tibial nerve)	16	0.01	-0.039-0.062	0.6
ALSFRS-R scores (covariate:repeater F response of peroneal nerve)	11	0.82	-0.027-0.069	0.34

H reflex was obtained in 11 patients on the right and 9 patients on the left. H reflex latency was 33.45±2.76 ms on the right, 34.27±3.17 ms on the left and the amplitude was 1.30±1.74uV on the right and 1.59±1.06 uV on the left. F response latency, persistence and repeater F response data are summarized in Table-1. Logistic regression analysis showed that repeater F responses in the ulnar nerves were causally associated with a high ALSFRS-R score (p=0.03; OR:0.01, CI: 0.002-0.07) (Table-2). Logistic regression analysis could not establish a causal relationship between persistence of F and repeater F responses (Table-3).

MR imaging was performed on 11 (F/M: 4/7; mean age 56.4±9.8 years) patients with a mean disease duration of 2.7±1.9 years. Our patient number nine did not have spinal imaging. Half of them had corticospinal tract hyperintensity, one patient had precentral gyrus atrophy, one had parietal lobe atrophy, and one had spinal cord anterior column hyperintensity was observed. In 3 of the patients with corticospinal tract hyperintensity, the onset of the disease was in one extremity, in one patient from the bulbar, region and in one patient from both lower extremities while in four of the patients with out corticospinal tract hyperintensity, the disease started simultaneously in both halves of the body, and in one patient form single extremity (Table-4).

Disease duration, age of onset, ALSFRS-R scores, swallowing, speech and respiratory function scores of patients with increased corticospinal tract intensity

were not different from those without increased intensity. (Table-4). With linear regression analysis, low values of DTI-FA were found to be associated with poor respiratory and speech scores (p:0.03). (Table-5).

Table 4. Special MRI findings of our patients MR: magnetic resonance, DTI-FA: Diffusion tractography imaging fractional anisotropy

Variable	MR Imaging(n:11)
Corticospinal tract hyperintensity	5/10 (% 50)
Presentral gyrus atrophy	1/11 (% 9)
Hippocampal atrophy	0/11
Frontal, Thalamus, Caudate Atrophy	0/11
Parietal lobe atrophy	1/11 (% 9)
Corpus Callosum Atrophy	0/11
T2 hypointense precentral gyrus	0/11
Spinal cord atrophy	0/10
Spinal cord T2 /T1 hyperintensity anterior column	1/10 (%10)
Corticospinal tract DTI-FA • Right • Left	 0.496 0.482

Table 5. Corticospinal pathway intensity increase features in the radiological examinations of our patients ALSFRS-R: Revised Amyotrophic lateral sclerosis functional rating scale

	Presence of increase intensity in the corticospinal tract (n:5)	No increase in intensity in the corticospinal tract (n:5)	P* mann withney U test
Disease onset age (years)	55.4	53.6	0.6
Disease duration (years)	3±1.4	2.6±2.6	**0.4**
ALSFRS score	31.8	39	**0.1**
Speaking score	3.4	3.6	0.6
Swallowing score	3.2	3.6	**0.3**
Respiratory score	4	3.6	0.6

DISCUSSION

In our study, in the evaluation of UMN, we found that the intensity of the corticospinal pathway in increased half of our patients in DTI. Low values of DTI-FA were associated with poor respiratory and speech ALSFRS-R scores. In the evaluation of LMN, we found increased repeater F responses in the ulnar nerves in patients with high ALSFRS-R scores.

In our study, we examined the presence of spinal cord atrophy and hyperintensity in the cervical region to show UMN involvement. We did not observe any difference from normal values in the corticospinal pathway intensity in half of our patients in DTI. DTI can be used to predict the random diffusion movement of motor molecules and to quantitatively show the structural and orientational damage of nerve fibers[11]. Previous DTI studies in ALS patients have shown that FA, which is an indicator of axonal impairment, is decreased at various corticospinal pathway levels[12-14]. In addition, correlations between FA values and ALSFRS-R or vital capacity have also been reported[15-17]. However, these studies were conducted within a limited brain region and few studies focused on the cervical spinal cord[18,19].

In the study of Gupta et al., corticospinal pathway hyperintensity was not found as a diagnostic tool in demonstrating UMN involvement, especially for early-stage ALS[20]. In the study of Fukui et al., degeneration of UMN and LMN was observed in 84% of 38 ALS patients, and there was no significant difference in the clinical examination of patients who had abnormal DTI-FA values, in terms of the presence of UMN findings[11]. It has been shown at autopsy that motor cortex hypointensity in ALS patients is associated with iron deposition in microglia in the middle and deep cortical layers and is qualitatively correlated with the severity of the disease[21]. We could not confirm this data in our

study. In our study, we observed that low values of DTI-FA were associated with poor respiratory and speech scores. In various studies, decreased FA in the corticospinal pathway has been associated with a decrease in ALSFRS-R and worsening UMN findings[16,22].

Repeater F responses result from the rebound of the same individual motor neurons. Repeater F responses have also been shown in peripheral neuropathies and polio in addition to ALS[23,24]. F response abnormalities have also been found in UMN diseases. This suggests the presence of altered excitability in the spinal motoneuron pool[25,26]. The amplitudes of F responses were found to be higher in diseases with spasticity, such as multiple sclerosis and myelopathy, than in controls[26]. The spinal excitability level of the motor neuron pool is dependent on multiple excitatory and inhibitory effects from various aspects of the central and peripheral nervous system. Whether a particular motor neuron produces a repeatative discharge depends on the level of depolarization of its soma and its dendrites. The main determinant of F response frequency in ALS is the number of functional LMN rather than their excitability. The spinal excitability level of the motor neuron pool is dependent on multiple excitatory and inhibitory effects from different aspects of the central and peripheral nervous system. Whether a particular motor neuron produces a repeatative discharge depends on the level of depolarization of its soma and its dendrites. The main determinant of F response frequency in ALS is the number of functional LMNs remaining more than their excitability. In addition, LMN impairment markedly affects the amplitude of F responses. Peioglou-Harmoussi et al. showed that the frequency of repeater F-response is higher in ALS and cervical myelo-radiculopathy compared to controls compared to cervical radiculopathy, emphasizing the role of UMN dysfunction in the occurrence of repeater F-response[8].

In our study, there was a loss of F response, although it was more common in the posterior tibial and peroneal nerves. The loss of F response in ALS has also been shown in previous studies[27]. We found that repeater F responses were increased in the ulnar nerves in those with high ALSFRS scores. This finding is worth investigating if it can be used to differentiate ALS from other anterior horn cell diseases.

The limitations of our study are the small number of patients and the inability to perform imaging in all of our patients due to Covid-19 pandemic. In addition, the lack of a control group in imaging is another limitation of our study.

In conclusion, we found that repeater F responses were increased in the ulnar nerves in those with high ALSFRS scores. This finding is worth investigating if it can be used to differentiate ALS from other anterior horn cell diseases. We also observed that low values of DTI-FA were associated with poor respiration and speech scores. Showing the correlation of low FA with a vital function such as respiration shows that this technique will help with the prognosis and progression of the disease. The results of this study suggest that DTI-FA, which is an advanced radiological evaluation, and repeater F responses as an electrophysiological method may support early diagnosis in ALS disease. Further studies with randomized controlled trials are required.

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REFERENCES

1. Pasinelli P, Brown RH. Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nat Rev Neurosci. 2006;7:710-23.
2. Johnsen B, Pugdahl K, Fuglsang-Frederiksen A, Kollewe K, Paracka L, Dengler R et al. Diagnostic criteria for amyotrophic lateral sclerosis: A multicentre study of inter-rater variation and sensitivity. Clin Neurophysiol. 2019;130:307-14.

3. Li W, Wei Q, Hou Y, Lei D, Ai Y, Qin K et al. Disruption of the white matter structural network and its correlation with baseline progression rate in patients with sporadic amyotrophic lateral sclerosis. Transl Neurodegener. 2021;10:35.
4. Sarica A, Cerasa A, Valentino P, Yeatman J, Trotta M, Barone S et al. The corticospinal tract profile in amyotrophic lateral sclerosis. Hum Brain Mapp. 2017;38:727-39.
5. Agosta F, Chio A, Cosottini M, De Stefano N, Falini A, Mascalchi M et al. The present and the future of neuroimaging in amyotrophic lateral sclerosis. AJNR Am J Neuroradiol. 2010;31:1769–77.
6. Chio A, Pagani M, Agosta F, Calvo A, Cistaro A, Filippi M. Neuroimaging in amyotrophic lateral sclerosis: Insights into structural and functional changes. Lancet Neurol. 2014;13:1228–40.
7. Li J, Pan P, Song W, Huang R, Chen K, Shang H. A meta- analysis of diffusion tensor imaging studies in amyotrophic lateral sclerosis. Neurobiol Aging. 2012;33:1833–8.
8. Peioglou-Harmoussi S, Fawcett PRW, Howel D, Barwick DD. F-response frequency in motor neuron disease and cervical spondylosis. J Neurol Neurosurg Psychiatry. 1987;50:593–9.
9. de Carvalho M, Scotto M, Lopes A, M, Swash M. F-Waves and the corticospinal lesion in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2002;3:131–6.
10. Koç F, Balal M, Demir T, Alparslan ZN, Sarica Y. Adaptation to Turkish and reliability study of the revised amyotrophic lateral sclerosis functional rating scale(ALSFRS-R). Noro Psikiyatr Ars. 2016;53:229-33.
11. Fukui Y, Hishikawa N, Sato K, Nakano Y, Morihara R, Shang J et al. Detecting spinal pyramidal tract of amyotrophic lateral sclerosis patients with diffusion tensor tractography. Neurosci Res. 2018;133:58-63.
12. Cardenas-Blanco A, Machts J, Acosta-Cabronero J, Kaufmann J, Abdulla S, Kollewe K et al. Structural and diffusion imaging versus clinical assessment to monitor amyotrophic lateral sclerosis. Neuroimage Clin. 2016;11:408-14.
13. Iwata NK, Kwan JY, Danielian LE, Butman JA, Tovar-Moll F, Bayat E et al. White matter alterations differ in primary lateral sclerosis and amyotrophic lateral sclerosis. Brain. 2011;134:2642-55.
14. Menke RA, Körner S, Filippini N, Douaud G, Knight S, Talbot K et al. Widespread grey matter pathology dominates the longitudinal cerebral MRI and clinical landscape of amyotrophic lateral sclerosis. Brain. 2014;137:2546-55.
15. Rasoanandrianina H, Grapperon AM, Taso M, Girard OM, Duhamel G, Guye M et al. Region-specific impairment of the cervical spinal cord (SC) in amyotrophic lateral sclerosis: A preliminary study using SC templates and quantitative MRI (diffusion tensor imaging/inhomogeneous magnetization transfer). NMR Biomed. 2017;30:e3801.
16. Cosottini M, Giannelli M, Siciliano G, Lazzarotti G, Michelassi MC, Del Corona A et al. Diffusion-tensor MR imaging of corticospinal tract in amyotrophic lateral sclerosis and progressive muscular atrophy. Radiology. 2005;237:258-64.
17. Bartels C, Mertens N, Hofer S, Merboldt KD, Dietrich J, Frahm J et al. Callosal dysfunction in amyotrophic lateral sclerosis correlates with diffusion tensor imaging of the central motor system. Neuromuscul Disord. 2008;18:398-407.
18. El Mendili MM, Cohen-Adad J, Pelegrini-Issac M, Rossignol S, Morizot-Koutlidis R, Marchand-Pauvert V et al. Multi-parametric spinal cord MRI as potential progression marker in amyotrophic lateral sclerosis. PLoS One. 2014;9:e95516.
19. Querin G, El Mendili MM, Lenglet T, Delphine S, Marchand-Pauvert V, Benali H et al. Spinal cord multi-parametric magnetic resonance imaging for survival prediction in amyotrophic lateral sclerosis. Eur J Neurol. 2017;24:1040-6.
20. Gupta A, Nguyen TB, Chakraborty S, Bourque PR. Accuracy of conventional MRI in ALS. Can J Neurol Sci. 2014;4:53-7.
21. Kwan JY, Jeong SY, Van Gelderen P, Deng HX, Quezado MM, Danielian LE et al. Iron accumulation in deep cortical layers accounts for MRI signal abnormalities in ALS: correlating 7 tesla MRI and pathology. PLoS One. 2012;7:e35241.
22. Keil C, Prell T, Peschel T, Hartung V, Dengler R, Grosskreutz J. Longitudinal diffusion tensor imaging in amyotrophic lateral sclerosis. BMC Neurosci. 2012;13:141.
23. Chroni E, Tendero IS, Punga AR, Stålberg E. Usefulness of assessing repeater F-waves in routine studies. Muscle Nerve 2012;45:477-85.
24. Zheng C, Zhu Y, Yang S, Lu F, Jin X, Weber R et al. A study of dynamic F-waves in juvenile spinal muscular atrophy of the distal upper extremity (Hirayama disease). J Neurol Sci 2016;367:298-304.
25. Oguz Akarsu E, Sirin NG, Kocasoy Orhan E, Erbas B, Dede HO, Baslo MB et al. Repeater F-waves in amyotrophic lateral sclerosis: Electrophysiologic indicators of upper or lower motor neuron involvement? Clin Neurophysiol. 2020;131:96-105.
26. Bischoff C, Schoenle P, Conrad B. Increased F -wave duration in patients with spasticity. Electromyogr Clin Neurophysiol 1992;32:449-453.
27. Fang J, Cui L-Y, Liu M-S, Guan Y-Z, Li X-G, Cui B et al. F wave study in amyotrophic lateral sclerosis: assessment of segmental motoneuronal dysfunction. Chin Medical J(Engl) 2015;128:1738-42.