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ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN THE REPUBLIC OF SRPSKA

KLINIČKE KARAKTERISTIKE PACIJENATA OBOLJELIH OD AMIOTROFIČNE LATERALNE SKLEROZE U REPUBLICI SRPSKOJ

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a rare, fatal and progressive neurodegenerative disease which begins due to selective damage to motor neurons. The disease begins as spinal (spinal cervical, spinal lumbosacral and spinal thoracic form) and bulbar form. The diagnosis is set by using revised El Escorial criteria.
Aim: Aims of the paper were determining demographic characteristics of ALS patients, category of the disease and functional disability of patients using Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).
Material and methods: In this cross-sectional study, medical histories of ALS patients, which were diagnosed at the Clinic of Neurology of the University Clinical Center of the Republic of Srpska, were examined. Demographic characteristics, initial form of the disease, category of disease (using revised El Escorial criteria), functional disability (using ALSFRS-R) and dia-gnostic delay were analyzed.
Results: This study included 30 patients, 20 (67%) were male, 10 (33%) were female. The ALS began at 57 ± 12 years, and average diagnostic delay was 10 months. The disease started as a spinal form in 26 (87%) patients, out of which 13 (43%) had spinal cervical, 12 (40%) spinal lumbosacral and 1 (3%) spinal thoracic form of disease. The initial bulbar form was reported in 4 (13%) patients. The average ALSFRS-R score was 33,5. Patients with a spinal lumbosacral form of the disease had statistically significant lower score of ALSFRS-R ($p = 0.048$) which indicates bigger functional motoric disablement, compared to other forms of disease. Low values of ALSFRS-R are correlated with more accurate diagnosis, according to the revised El Escorial criteria.
Conclusion: Results of this study showed that ALS is more frequent and occurs earlier in men. The disease most commonly started as spinal cervical form. Patients with spinal lumbo-sacral form of the disease had significantly lower values of ALSFRS-R which indicates a faster progression of the disease. As patients acquire lower ALSFRS-R scores and greater disability, they progress to the definite ALS category.

Keywords:
ALS,
ALSFRS-R,
El Escorial criteria,
diagnostic delay

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Sažetak

Uvod: Amiotrofična lateralna skleroza (ALS) je rijetko, fatalno, progresivno neurodegenerativno oboljenje koje nastaje usljed selektivnog oštećenja motornih neurona. Bolest počinje kao spinalna (spinalna cervikalna, spinalna lumbosakralna i spinalna torakalna) i bulbarna foma. Dijagnoza se još uvijek postavlja na osnovu revidiranih *El Escorial* kriterijuma.

Cilj: Ciljevi rada su utvrđivanje demografskih karakteristika ALS bolesnika, utvrđivanje kategorije bolesti u kojoj se bolesnici nalaze primjenom revidiranih *El Escorial* kriterijuma na početku bolesti, utvrđivanje funkcionalne onesposobljenosti oboljelih primjenom Revidirane skale funkcionalne procene amiotrofične lateralne skleroze (engl. *Revised Amyotrophic Lateral Sclerosis Functional Rating Scale*, ALSFRS-R).

Materijal i metode: U ovoj studiji presjeka izvršen je uvid u medicinsku dokumentaciju oboljelih od ALS, dijagnostikovanih na Klinici za neurologiju Univerzitetskog kliničkog centra Republike Srpske. Analizirane su demografske karakteristike, početna forma bolesti, kategorija bolesti (primjenom revidiranih *El Escorial* kriterijuma), funkcionalna onesposobljenost (primjenom ALSFRS-R) i dijagnostičko kašnjenje.

Rezultati: U studiju je uključeno ukupno 30 bolesnika, 20 (67%) muškog, 10 (33%) ženskog pola. Amiotrofična lateralna skleroza se u prosjeku javljala kod pacijenata starih 57 ± 12 godina. Prosječno dijagnostičko kašnjenje je iznosilo 10 mjeseci. Bolest je počela kao spinalna forma kod 26 (87%) bolesnika, od čega je 13 (43%) bolesnika imalo spinalnu cervikalnu, 12 (40%) spinalnu lumbosakralnu i 1 (3%) spinalnu torakalnu formu bolesti. Bulbarni početak bolesti evidentiran je kod 4 (13%) bolesnika. Prosječan skor ALSFRS-R je 33,5. Bolesnici sa spinalnom lumbosakralnom formom imali su statistički značajno niži ALSFRS-R ($p = 0,048$), što ukazuje na veću motornu onesposobljenost u odnosu na druge forme bolesti. Niske vrijednosti ALSFRS-R u korelaciji su sa sigurnijom dijagnozom po revidiranim *El Escorial* kriterijumima.

Zaključak: Rezultati sprovedene studije ukazali su da se ALS javlja češće i počinje ranije kod muškaraca. Bolest je najčešće počinjala kao spinalna cervikalna forma. Bolesnici sa spinalnom lumbosakralnom formom bolesti imali su značajno niže vrijednosti ALSFRS-R, što ukazuje na bržu progresiju bolesti. Napredovanje bolesnika ka kategoriji sigurne ALS uslovljava niže ALSFRS-R skorove i veću funkcionalnu onesposobljenost.

Ključne reči:
ALS,
ALSFRS-R,
El Escorial kriterijumi,
dijagnostičko kašnjenje

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that occurs due to damage to upper motor neuron (UMN) and lower motor neuron (LMN) in the brain, brainstem, and spinal cord (1). Its name is derived from the word amyotrophic, which refers to the atrophy of muscle fibers, which are denervated as their corresponding anterior horn cells degenerate. It leads to weakness of affected muscles and visible fasciculations, and lateral sclerosis, which refers to hardening of the anterior and lateral corticospinal tracts as motor neurons in these areas degenerate and are replaced by gliosis (2).

The disease occurs in 90% of cases sporadically, while in 5-10% of patients the disease is genetically conditioned. The risk factors include age over 50 years, male sex and family history of motor neuron disease (3).

The incidence of ALS is 1-2 per 100 000 population, and due to that, the ALS is classified in Orphan base in a group of rare diseases (3). The etiology of ALS is unknown. The disease can develop as a spinal form (80%) and bulbar form (20%). Spinal form can begin as spinal cervical, spinal lumbosacral and spinal thoracic with involvement of respiratory musculature (2%) (3). If the first signs of the disease are difficulties to swallow and speak, this indicates bulbar form. Weakness and atrophy of muscles of the arms or legs, with the appearance of fasciculations and cramps of the muscles, indicate a spinal cervical or lumbosacral form of the disease. The valid diagnostic criteria are revised El Escorial (1,4).

The aim of this study was to:

[1)] Determine the demographic characteristics of the patients (age, sex, education, marital status, habits);

[2)] Identify the disease category by applying the revised El Escorial criteria at the onset of the disease;

[3)] Determine the functional disability of patients with the application of ALSFRS-R; and

[4)] Determine the duration of the disease between the onset of symptoms and the time of diagnosis.

Material and methods

This cross-sectional study included ALS cases collected by analyzing inpatient medical records from the Clinic of Neurology of the University Clinical Center of the Republic of Srpska in 2018. Patients who fulfilled the diagnostic criteria for possible, probable or definite ALS, according to the El Escorial revised criteria, were included

in the study (5). The data were taken from the Clinical Information System. The demographic characteristics of patients (sex and age at the beginning of the disease, marital status, education, habits), the initial form of the disease, diagnostic delay, i.e. the time from the onset of the first symptoms and signs of the disease until the diagnosis, were analyzed.

Functional disability of patients was determined using the ALSFRS-R, which is used to determine the quality of: speech, salivation, swallowing, handwriting, presence of gastrostomy, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea and respiratory insufficiency. Maximal number of points is 48, which indicate full functional ability, and low ALSFRS-R may indicate earlier discussions with patient about respiratory support, supplemental feeding and end-of-life care (6).

The data were analyzed using the descriptive statistical methodology (mean, standard deviation, median), two-tailed Student-T-Test and two-sided Fisher's Exact Test for Count Data for independent variables. The results were presented as mean ± standard deviations (SD), and statistically significant difference was considered if the value of $p < 0.05$.

Statistical analyzes were carried out using the data processing application *SPSS version 21.0*, SPSS Inc., an IBM Company Headquarter Chicago, IL. The results are shown both in text and in tables.

Results

The study included 30 patients, out of which 20 (67%) were men and 10 (33%) were women. By analyzing distribution of sex, age and sociodemographic features, we obtained the following results (**Table 1**).

In the examined group of patients, women were slightly older than men (58.6 ± 11.7 vs. 56.3 ± 12.4), but statistically significant difference was not established ($p = 0.311$). The age range for men is from 32 to 77 years, and for women from 37 to 73 years. The average age at onset of ALS for both sexes is 57 ± 12 years. In the examination of socio-epidemiological characteristics, we found that most patients were married - 21 (70%). A total of 9 patients (30%) consumed alcohol, while 26 (87%) were smokers.

The highest number of patients had completed secondary education 19 (63.3%), 6 (20%) completed elementary school, while 5 (16.7%) finished university. Head and spinal column trauma were found in 8 (26.7%) of patients.

Spinal form was found in 26 (86.7%) patients, of which 13 (43%) had spinal cervical, 12 (40%) spinal lumbosacral and 1 (3%) spinal thoracic form. The bulbar form was found in 4 (13%) patients. When comparing the disease pattern: bulbar vs spinal, patients with bulbar form were older (67.3 ± 9 vs. 55.5 ± 11.8), and statistically significant difference ($0 = 0.066$) was not registered (**Table 2**).

When comparing spinal forms of the disease: cervical vs lumbosacral, patients with cervical form were older (54.6 ± 13.1 vs. 54.6 ± 9), and statistically significant difference was not registered ($p = 0.99$) (**Table 3**).

The average value of ALSFRS-R for all forms of illness was 33.5. In spinal form, the average value for ALSFRS-R was 33.3, and in bulbar form was 34.7 (**Table 4**). A statistically significant difference was not found between ALSFRS-R score between spinal and bulbar forms of disease ($p = 0.818$).

Table 1. Main sociodemographic features of investigated ALS patients

Sex		Male	Female	Total
Number		20 (67%)	10 (33%)	30 (100%)
Age	mean	56.3	58.6	57
	SD	12.4	11.7	12
	min	32	37	32
	max	77	73	77
	median	58.5	61	59.5
	p value	0.311		
Marital status	Married	13 (43%)	8 (27%)	21 (70%)
	Not married	7 (23%)	2 (67%)	9 (30%)
Alcohol consumption	Yes	8 (27%)	1 (3%)	9 (30%)
	No	12 (40%)	9 (30%)	21 (70%)
Cigarettes consumption	Yes	17 (57%)	9 (30%)	26 (87%)
	No	3 (10%)	1 (3%)	4 (13%)

Table 2. The initial form of the disease in relation to sex and age at onset of ALS

Initial form of ALS	Male	Female	Total	%	Age					
					mean	SD	min	max	median	p value
Bulbar	2	2	4	13.3%	67.3	9.1	54	73	71	0.066
Spinal	18	8	26	86.7%	55.5	11.8	32	77	58.5	

Table 3. Review of spinal forms of the disease by sex and at onset of ALS*

Spinal forms of ALS	Male	Female	Total	%	Age					
					mean	SD	min	max	median	p value
Spinal cervical	9	4	13	43.3%	54.62	13.1	32	76	58	0.990
Spinal lumbosacral	8	4	12	40%	54.58	9.1	41	68	58.5	

* Only one patient had spinal thoracic form, a man of 77 years.

Table 4. ALSFRS-R in spinal and bulbar form

Initial form of ALS	N	%	ALSFRS-R					
			mean	SD	min	max	median	p value
Bulbar	4	13.3%	34.8	10.7	22	45	36	0.818
Spinal	26	86.7%	33.4	10.1	5	45	35.5	

The average ALSFRS-R for the spinal cervical form of the disease was 36.9, while for the spinal lumbosacral form it was 28.8 (**Table 5**). When comparing spinal forms of the disease: cervical vs lumbosacral, patients with lumbosacral form had statistically significant lower score ALSFRS-R (28.8 ± 11.9 vs. 36.9 ± 6.6), (p = 0.048).

The average diagnostic delay for the spinal form was 10.2 months, and for bulbar 9.3 months (**Table 6**). Observing the diagnostic delay, statistically significant difference was not found (p = 0.686) between spinal and bulbar forms.

Diagnostic delay for the spinal cervical form of the disease ranged from 6 to 36 months, and for the spinal lumbosacral form from 5 to 24 months, with no statistically significant difference (p = 0.459) (**Table 7**).

Most patients (13 of them) had ALSFRS-R values ranging from 38 to 48. The clinical category of definite ALS, according to the revised El Escorial criteria, involved 13 patients, in the probable category were 10 patients, and only 3 patients belonged to the category of clinically possible ALS (**Table 8**). Categories of more accurate ALS diagnosis had lower functional scores.

Table 5. ALSFRS-R in spinal forms of disease*

Spinal forms of ALS	N	%	ALSFRS-R					
			mean	SD	min	max	median	p value
Spinal cervical	13	43.3%	36.9	6.6	24	44	39	0.048**
Spinal lumbosacral	12	40%	28.8	11.9	5	45	31	

* Only one patient had spinal thoracic form, his ALSFRS-R was 43.

** p<0.05

Table 6. Review of the initial forms of the disease and diagnostic delay

Initial form of ALS	N	%	Diagnostic delay					
			mean	SD	min	max	median	p value
Bulbar	4	13.3%	9.3	3.2	6	12	9.5	0.686
Spinal	26	86.7%	10.2	7.4	2	36	8	

Table 7. Diagnostic delay in spinal forms of the disease*

Spinal forms of ALS	N	%	Diagnostic delay					
			mean	SD	min	max	median	p value
Spinal cervical	13	43.3%	11.5	9.1	6	36	8	0.459
Spinal lumbosacral	12	40%	9.3	5	5	24	9	

* The spinal thoracic form was found in only one patient, and diagnostic delay for him was 2 months.

Table 8. Relation of ALSFRS-R values to clinical categories by revised El Escorial criteria

ALSFRS-R	N	Clinically possible ALS	Clinically probable ALS	Clinically definite ALS
(38-48)	13	3	6	4
(27-37)	9	0	4	5
(16-26)	6	0	0	6
(5-15)	2	0	0	2
(0-4)	0	0	0	0
p value	0.059			

Discussion

Amyotrophic lateral sclerosis is a fatal, progressive neurodegenerative disease characterized by combined lesions of UMN and LMN. Muscle weakness at the onset of the disease can manifest itself in bulbar muscles only, leading to disturbance of speech and swallowing, or in the spinal musculature, leading to weakness in the upper and lower extremities. Regardless of how it begins, weakness of the musculature gradually expands and ultimately leads to weakness in respiratory muscles, which leads to a fatal outcome within two to four years (7,8).

The cause of the disease is still unknown, although there are numerous studies that look at the possible cause from different aspects. The FDA has approved a pharmacological treatment with Riluzole which modestly prolongs survival, since it slows down the deterioration of motor neurons (9).

Making an earlier diagnosis would allow patients to have multidisciplinary care, with the possibility of being included in clinical studies in order to find an adequate treatment for the disease (5,10).

There is still no laboratory test that would easily and accurately confirm the diagnosis of ALS in its early stages. Currently, the diagnosis is based on a combination of clinical and electrophysiological criteria known as the Airlie House criteria, set up by the consensus of experts in 1997 when the original El Escorial criteria were revised (11). Criteria in practice show good specificity, but limited sensitivity (4,12).

Analyzing the data on the prevalence of gender, men were found to get the disease earlier and twice as likely than women, with no significant differences with other studies (13-16).

The largest number of patients in our study had a completed secondary education (40%) and a spouse (70%). Most patients consumed cigarettes (90%), while alcohol was consumed by a third of patients (30%), with the possible relationship between smoking and ALS, as shown in the results of other studies (17).

The average diagnostic delay was 10 months for both genders, which was somewhat shorter for women. In relation to the study conducted by Paganoni et al., the diagnosis in our study was set faster (18).

At the onset of the disease, spinal forms of the disease were most represented, of which the spinal cervical and spinal lumbosacral form of the disease were almost equally represented. We registered only one case of spinal thoracic form. Bulbar disease was present in 13% patients whose symptoms began with speech impairment and swallowing. In comparison to the sexes, the bulbar form is equally present. Spinal cervical and spinal lumbosacral forms were more frequently present in men, which did not deviate from the literature results (15).

There was no statistically significant difference between spinal and bulbar onset. Also, we did not find a statistically significant difference between the spinal cervical and spinal lumbosacral forms of the disease, according to the diagnostic delay.

In the analysis of ALSFRS-R values in the initial forms of the disease, the average value of the bulbar form was found to be 34.8, and in spinal 33.4, with no statistically significant difference.

Statistically significant difference ($p = 0.048$) was found between ALSFRS-R for the spinal cervical and spinal lumbosacral form of the disease, where patients with a spinal lumbosacral disease had lower ALSFRS-R.

According to the revised El Escorial criteria, the clinically possible ALS group of patients had high ALSFRS-R values (38 to 48). The clinically definite ALS group had ALSFRS-R values ranging from 5 to 48, most of them ranging from 16 to 26. These data could indicate that the ALSFRS-R values are correlated with clinical categories according to the revised El Escorial criteria, meaning that as clinical diagnosis gets more definite, the functional score gets lower and prognosis worse. A study conducted by Stevic et al. showed that longer survival was observed in patients with early onset, longer diagnostic delay, less

functional impairment at the time of diagnosis (higher ALSFRS-R), and Riluzole treatment (19).

Our study showed that men were more likely to get the disease earlier than women. The majority of patients had a spinal form of ALS, with the spinal cervical form of the disease being the most common. There are no significant differences between the form of ALS in relation to the diagnostic delay. In our study, patients with spinal lumbosacral form of the disease had lower ALSFRS-R ($p < 0.05$), indicating a greater functional disability and faster progression of the disease.

References

1. Kostić V. Neurologija za studente medicine. Beograd: Medicinski fakultet. 2016.
2. Rowland LP, Shneider NA: Amyotrophic lateral sclerosis. N Engl J Med 2001, 344(22):1688-1700.
3. Collins D, Goodfellow J, Silva D, Dardis R, Nagaraja S. Neurology and Neurosurgery. UK: JP Medical Ltd. 2016.
4. Sorenson EJ, Stalker AP, Kurland LT, Windebank AJ. Amyotrophic lateral sclerosis in Olmsted County, Minnesota, 1925 to 1998. Neurology 2002;59(2):280-282. doi: 10.1212/wnl.59.2.280
5. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 2000;1(5):293-299.doi:10.1080/146608200300079536
6. Cedarbaum J, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. Journal of the Neurological Sciences. 1999;169(1-2):13-21.
7. Norris F, Shepherd R, Denys E, U K, Mukai E, Elias L, Norris H. Onset, natural history and outcome in idiopathic adult motor neuron disease. Journal of the Neurological Sciences 1993;118(1):48-55. doi: 10.1016/0022-510x(93)90245-t
8. Miller R, Mitchell J, Lyon M, Moore D. Riluzole for amyotrophic lateral sclerosis. Cochrane Database Syst Rev. 2007;24
9. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. Journal of Neurology, Neurosurgery and Psychiatry 2003;74(9):1258-1261. doi: 10.1136/jnnp.74.9.1258
10. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Woolley SC. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American. Neurology 2009;73(15):1227-1233. doi: 10.1212/wnl.0b013e3181bc01a4
11. Makki AA, Benatar M. The electromyographic diagnosis of amyotrophic lateral sclerosis: Does the evidence support the El Escorial criteria. Muscle and Nerve 2007;35(5):614-619. doi: 10.1002/mus.20748
12. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman OM. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria: a population based study. Archives of Neurology 2000;57(8):1171. doi: 10.1001/archneur.57.8.1171
13. Huisman MHB, de Jong SW, van Doormaal PTC, Weinreich SS, Schelhaas HJ, van der Kooi AJ, van den Berg LH. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. Journal of Neurology, Neurosurgery and Psychiatry 2011;82(10):1165-1170. doi: 10.1136/jnnp.2011.244939
14. Kurtzke J. Epidemiology of amyotrophic lateral sclerosis. Adv Neurol 1982 36:281-302.
15. Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, Beghi E. Incidence of amyotrophic lateral sclerosis in Europe. Journal of Neurology, Neurosurgery and Psychiatry 2010;81(4):385-390. doi: 10.1136/jnnp.2009.183525
16. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano P, Chinea A. A comprehensive review of amyotrophic lateral sclerosis. Surgical Neurology International 2015;6(1):171. doi: 10.4103/2152-7806.169561
17. Oskarsson B, Horton DK, Mitsumoto H. Potential Environmental Factors in Amyotrophic Lateral Sclerosis. Neurologic Clinics 2015;33(4):877-888. doi: 10.1016/j.ncl.2015.07.009
18. Paganoni S, Macklin EA, Lee A, Murphy A, Chang J, Zipf A, Atassi N. Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2014;15(5-6):453-456. doi: 10.3109/21678421.2014.903974
19. Stevic Z, Kostic-Dedic S, Peric S, Dedic V, Basta I, Rakocevic-Stojanovic V, Lavrnic D. Prognostic factors and survival of ALS patients from Belgrade, Serbia. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(7-8):508-514.