ORIGINAL ARTICLES

UDC: 616.8-07
https://doi.org/10.2298/VSP160115330D

Comparison of diagnostic criteria in patients with amyotrophic lateral sclerosis – the contribution of electromyographic findings

Poređenje dijagnostičkih kriterijuma kod bolesnika sa amiotrofičnom lateralnom sklerozom – doprinos elektromiografskih nalaza

Aleksandra Dominović-Kovačević*, Duško Račić*, Sanja Grgić*, Zoran Vukojević*, Sladjan D. Milanović†, Tihomir V. Ilić‡§

University of Banja Luka, University Clinical Centre of the Republic of Srpska, *School of Medicine, Republic of Srpska, Bosnia and Herzegovina; University of Belgrade, †Institute for Medical Research, Belgrade, Serbia; University of Defence, ‡Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; Military Medical Academy, §Clinic of Neurology, Belgrade, Serbia

Abstract

Background/Aim. Diagnosis of amyotrophic lateral sclerosis (ALS) is based on combination of clinical signs and electrophysiological correlates of pathological process which takes place in general. New electrophysiological criteria Awaji-Shima (AS) additionally qualify the complex fasciculations and neurogenically modified potentials of motor units as signs of active lesions of peripheral motor neuron, contrary to previously valid revised El Escorial criteria (rEE). The objective of this research was to determine the clinical significance and advantages of using the AS criteria in patients with ALS. **Methods.** Thirty patients (59.2 ± 10.9 years, 57% of them with spinal form of the disease) with clinically suspected ALS were monitored from the time of diagnosis until reaching the category of definitive diagnosis or death. The clinical evaluation and electromyographic (EMG) examinations were carried out at 3-month intervals. **Results.** By applying the AS criteria, the category of probable or definite diagnosis was achieved in all patients with ALS, except in one (96.6%), as contrary to the rEE (33.3%), after 6 months of the follow-up period. The subclinical affection in more than two body regions has been defined through detection of denervation potentials (80% of the patients by using the AS, or 67% by the rEE criteria). The complex fasciculations were registered particularly often in small muscles of the feet (37–40%). **Conclusion.** Application of the AS criteria improve the achievment of category of probable or definite diagnosis of ALS by 2.7 months earlier compared to the rEE. This outcome is particularly affected by a higher frequency of positive EMG findings, when the AS criteria were employed. Early determination of diagnosis provides the better perspective and more frequent participation of the ALS patients in pharmacotherapy studies intended to establish new therapeutic options.

Key words:
amyotrophic lateral sclerosis; electrophysiology; electromyography; predictive value of tests; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Dijagnoza amiotrofične lateralne skleroze (LS) zasniva se na kombinaciji kliničkih znakova i elektrofizioloških korelata patološkog procesa koji se odvija u osnovi. Novi elektrofiziološki kriterijumi, Awaji-Shima (AS), dodatno kvalifikuju kompleksne fascikulacije i neurogeno izmenjene potencijale motornih jedinica kao znakove aktivnih lezija perifernog motornog neurona, nasuprot ranije važećim revidiranim El Escorial kriterijumima (rEE). Cilj ovog istraživanja bio je da se utvrdi klinički značaj i prednosti primene AS kriterijuma, kod obolelih od ALS. **Metode**. 30 bolesnika (59,2 ± 10,9 godina, od kojih 57% sa spinalnom formom bolesti) sa klinički suspektnom ALS, praćeno je od vremena postavljanja dijagnoze do postizanja kategorije definitivne dijagnoze ili smrtnog ishoda. Kod bolesnika su obavljane klinička evaluacija i elektromiografski (EMG) pregledi u tromesečnim intervalima. **Rezultati.** Primjenom AS kriterijuma, nakon 6 meseci praćenja, kategorija verovatne ili pouzdane dijagnoze postignuta je kod svih bolesnika sa ALS, izuzev jednog (96,6%), nasuprot rEE kriterijuma (33.3%). EMG nalazi bili su pozitivni u ≥ 2 telesna regiona kod 80% bolesnika primenom AS, odnosno 67% primenom rEE. Kompleksne fascikulacije zabeležene su posebno učestalo u malim mišićima stopala (37–40%). **Zaključak.** Primenom AS kriterijuma kategorija vjerovatne ili pouzdane dijagnoze ALS postiže se za 2,7 meseca ranije, u poređenju sa rEE, na šta

Correspondence to: Tihomir V. Ilić, University of Defence, School of Medicine of the Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 11 3609064. E-mail: tihoilic@gmail.com

posebno utiče veća učestalost pozitivnih EMG nalaza. Ranije utvrđivanje dijagnoze donosi perspektivu veće zastupljenosti obolelih u farmakoterapijskim studijama sa novim terapeutskim agensima.

Ključne reči:
amiotrofijska lateralna skleroza; elektrofiziologija; elektromiografija; testovi, prognostička vrednost; osetljivost i specifičnost.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disease caused by the selective damages of motor neurons of the cerebral cortex, brainstem and anterior horns of the spinal cord. The disease is clinically manifested by the combination of lesions of the central (CMN) and peripheral motor neuron (PMN) with progressive development of muscle weakness and atrophy [1]. The diagnosis of ALS is based on the combination of neurological findings and subclinical signs of PMN lesions, which are revealed by electromyography (EMG) [2].

During the evolution of diagnostic concept in ALS, several diagnostic approaches were applied, starting with Lambert criteria [3]. Over time, a concept of diagnostic categories divided into suspected, probable and definite diagnosis of ALS has been established. Such probabilistic approach is, on one hand, based on a broad differential diagnosis of ALS, which requires high specificity, and on the other hand, on the fact that there is no biological surrogate marker of the disease which would facilitate the diagnosis.

Furthermore, therapeutic options in the treatment of this disease are extremely modest, with a slight exception of a beneficial effect of the antiglutamatergic drug riluzole which affects the length of survival mainly in the categories of probable and definite ALS [4]. Therefore, effective testing of the innovative pharmacological agents, with highly probable diagnosis as imperative, is limited to a small proportion of patients. In this way, the possibility of accepting incorrect diagnosis in the process of testing new drugs is substantially reduced and high credibility of the findings is ensured.

However, by using the restrictive criteria (revised El Escorial – rEE criteria) based on a broad differential diagnosis of ALS, it is easy to understand that the sensitivity is significantly reduced [5, 6]. Therefore, in order to facilitate the diagnosis, in 2006 there was a modification of the rEE criteria, which were proposed to be called Awaji-Shima after the place of the meeting. New criteria, particularly emphasized the phenomena of complex fasciculations and neurogenically modified motor unit potentials which can be detected and analyzed by using the needle electromyography. These indicators, especially the complex fasciculations, as it is suggested, represent the electrophysiological correlates of acute denervation or additional markers of affected PMN. In that way, the number of EMG indicators increases, which in combination with the clinical signs of PMN lesions, increases the sensitivity of Awaji diagnostic criteria [7].

This research compared the difference between two systems of classification by using the rEE and Awaji-Shima criteria in relation to the time required to achieve the category of probable and definitive diagnosis of ALS, and the time of initial evaluation on the reasonable suspicion of ALS (category of suspected diagnosis). In addition to that, the study separately discussed the subclinical aspects of affected body regions based on the evaluation of electromyographic findings and their impact on the achievement of specific categories of the disease according to either the rEE or Awaji-Shima criteria and relation to the time course.

The primary objective of the study was the time necessary to determine the category of probable or reliable diagnosis of ALS, expressed in months.

The secondary objective was the analysis of denervation potential frequency - the complex fasciculation in different body regions at first place.

Methods

Patients

Sixty-eight patients with clinical presentation of progressive muscular weakness suggestive for ALS were examined at the Clinic of Neurology, University Hospital Clinical Centre Banja Luka, the Republic of Srpska, Bosnia and Hercegovina in the period 2012–2014. The suspected ALS was diagnosed in 30 patients (20 men, average age of 59.2 ± 10.9, ranging between 39–75 years). The analysis excluded patients with different forms of neuropathy (primarily those with multifocal motor neuropathy) and the patients with positive family history of motor neuron disease since the progression of sporadic and familiar forms of the disease are not the same. Demographic data of patients is presented in Table 1.

Table 1

Demographic and baseline clinical characteristics of patients with amyotrophic lateral sclerosis (ALS) at study entry

Parameters	Total sample (n = 30)	Spinal form (n = 17)	Bulbar form (n = 13)	*p*
Age (years), mean (SD)	59.2 (10.2)	54.8 (10.8)	64.9 (8.8)	0.01
(range)	39–75	39–71	45–75	
Gender (female)	10	2	8	
Time elapsed from symptom onset (months), mean (SD)	10.2 (4.5)	9.6 (4.8)	10.9 (4.0)	n.s.
(range)	3–18	5–18	4–18	
ALS-FRS, mean (SD)	43.3 (3.6)	41.8 (4.2)	46.1 (3.9)	n.s.

***ALS-FRS – ALS Functional Rating Scale; SD – standard deviation; n.s. – not significant.**

When they entered the study, the patients were subjected to clinical evaluation and electromyographic examination at 3-month intervals, either to achieve a category of definite diagnosis or death, if it occurred before reaching this category.

At each visit to the Clinic, on the basis of the neurologic findings and the EMG examination, currently affected body regions in patients were defined (bulbar region, cervical, thoracic and lumbosacral spinal region) according to clinical signs of CMN and PMN lesions as well as the EMG correlates of the PMN lesions. Based on that evaluation, the patients were categorized in accordance with the rEE and AS criteria (Table 2). Additionally, the assessment of functional score (FS) at each examination and for each patient was made using The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS FRS).[8]

Electromyography

EMG was done with concentric disposable electrodes (TECA, 25 mm × 30G) on the equipment model Medelec Synergy (VIASIS, United Kingdom) by the same researcher under the same environmental conditions (the temperature of extremities 30°C), for muscles in the mentioned body regions, according to the selection as follows: bulbar region – one muscle [*m. mentalis – mMEN* (*n. facialis*)]; cervical spinal region – three muscles [*m. deltoideus – mDEL* (C5-C6*; n. axillaris*)*, m. biceps brachii – mBB* (*C5-C6; n. musculocutaneus*) *and m. abductor digiti minimi – mADM* (*C8-Th1; n. ulnaris*)]*;* thoracic spinal region: muscles in several segments [*mm. paravertebrales toracales – mPV* (Th2–Th10)]; lumbosacral spinal region – two muscles [*m. vastus lateralis – mVL* (L2–L3–L4; *n. femoralis*)*, m. tibialis anterior – mTA* (L4–L5–S1; *n. peroneus*), *m. extensor digitorum brevis – mEDB* (L5–S1; *n. peroneus*) *and m. flexor hallucis brevis – mFHB* (L5–S1; *n. plantaris medialis grana n. tibialis*)].

The signs of PMN lesion were considered to be the occurrence of a denervation potential type of fibrillation, positive sharp waves (PSW) and fasciculations if they were found in the target muscle in two or three locations during the relaxation. The neurogenic lesion was also indicated by the presence of changed motor unit action potential (MUAP) on the increase of amplitude pattern, extended duration and increased number of phases (poly-phases) and with the reduction of an interference pattern. The myotomal distribution was confirmed if the electrophysiological signs of the PMN lesion were registered in the muscles that were differently innervated by the spinal and peripheral nerves.

Statistical analysis

The data were analyzed by the method of descriptive and analytical data processing (Mann-Whitney U test, Chi-square test, Fisher's exact test, Wilcoxon signed-rank test).

The time necessary for the achievement of the specific diagnostic categories of ALS was correlated with a number of EMG positive regions and the pattern of diagnosis (bulbar vs. spinal form) whenever the McNemar test was used. The results were presented as means ± standard deviation. Statistically significant differences were considered if p-value < 0.05.

Statistical analysis was done using the application for the data processing "SPSS" version 16.0, SPSS Inc., USA.

Results

Initial clinical and electrophysiological examination included 68 patients whereby the diagnosis of suspected ALS was confirmed in 30 patients. In other patients who were initially examined, the multifocal motor neuropathy was diagnosed in 5 patients, polyradiculopathy in 24 patients, paraneoplastic neuropathy in 4 patients, spinal muscular atrophy in 3 patients and myositis in 2 patients. The initial clinical presentation of the spinal form of ALS was present in 17 (57%) patients. Comparing the forms of disease in the tested sample, it was found that the patients with the bulbar form of the disease were about 10 years older (64.9 ± 8.8 vs. 54.8 ± 10.8; $p = 0.010$) (Table 1).

Table 2

Comparative overview of the distribution and affected number of body regions necessary to diagnose the categories of amyotrophic lateral sclerosis (ALS) in accordance with rEE and AS criteria

Parameters	rEE criteria	AS criteria
Possible ALS		
CMN	1	1
PMN	1*	1
Probable – laboratory supported ALS		
CMN	1	
PMN	1*	
Probable ALS		
CMN	2	2
PMN	2*	2
Definite ALS		
CMN	3	
PMN	3	

CMN – central motor neuron; PMN – peripheral motor neuron; *The level of PMN lesion must be rostral in relation to CMN lesion along the neural axis (neuraxis); rEE – revised El Escorial criteria; AS – Awaji-Shima criteria.

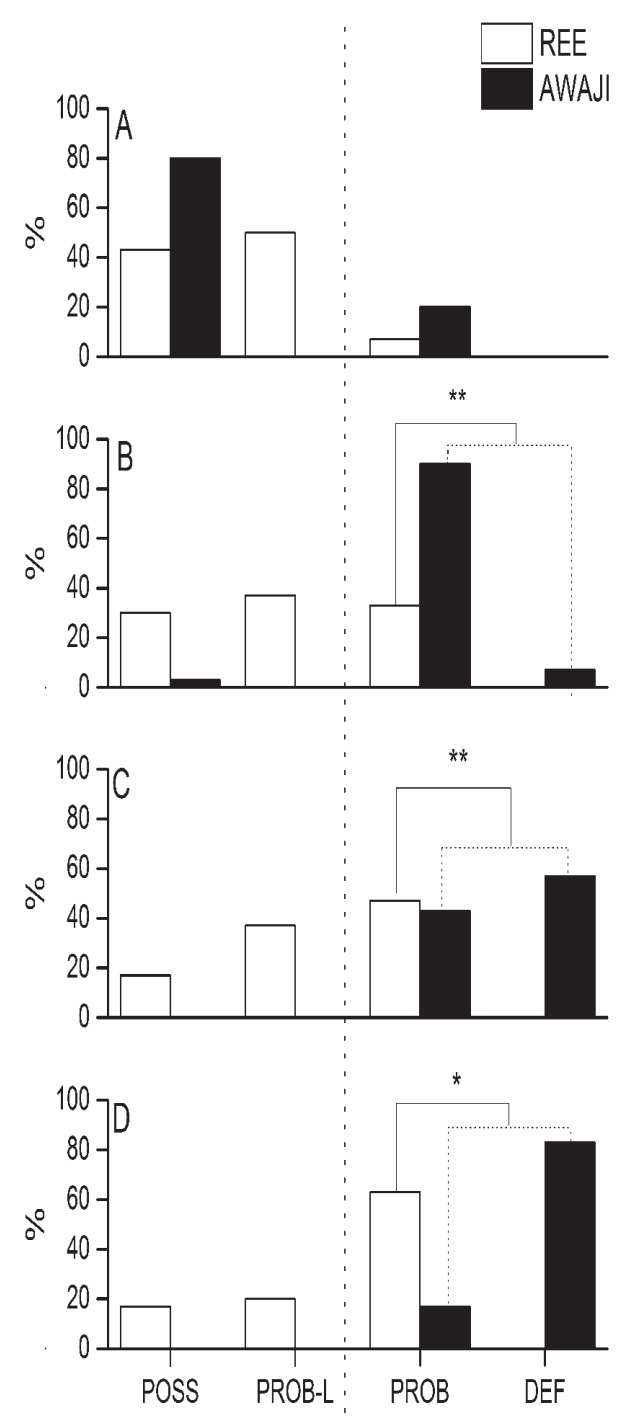

Fig. 1 – Distribution of diagnostic categories by using the rEE or AS criteria according to the time intervals in which repeated evaluations were done (A – 3 months; B – 6 months; C – 9 months; D – 12 months). * $p < 0.05$, ** $p < 0.01$ (indicates the level of statistical significance); rEE – revised El Escorial criteria; AS – Awaji-Shima criteria; POSS – possibly; PROB – probably; DEF – definitely.

Body regions in which the initial difficulties in the spinal form of the disease were expressed, were evenly represented – there were 9 patients with the cervical and 8 with the lumbosacral clinical presentation.

During the period of monitoring, 7 out of 30 patients diagnosed with ALS died in the interval between 10 and 14 months after the first examination, so, after 12 months, it was possible to analyze 26 patients in total, and after 15 months, only 23 patients.

According to the data obtained from an anamnestic interview, the patients (> 2/3 examinees) took the first examination in the period between 6 and 24 months from the time of the subjective perception of symptoms, which were subsequently confirmed as the correlates of lesions of the CMN and/or PMN (Table 1).

The primary objective of the study, the time necessary to achieve the category of probable or definite diagnosis of ALS, was achieved in all patients in the period between 9 and 15 months of monitoring, or after 4 or 6 repeated examinations (including the initial). By using the rEE criteria, the average period necessary to achieve the category of probable and definite diagnosis was 9.4 months, while for the AS criteria, it was 6.7 months which created a difference of 2.7 months.

Accordingly, the target diagnostic categories (probable or definitive) by using rEE and AS criteria was achieved at different rates at successive time points as shown in Figure 1 and Table 2. The key difference was generated in the second control examination (6 months after the initial evaluation), when applying rEE category probable (or definitive) diagnosis was achieved only in 1/3 of patients, as opposed to 96.6% when AS criteria were applied. This was also the key findings of the study.

However, when we analyzed the time required to achieve the target diagnostic categories in relation to the disease form (bulbar vs. spinal), the key difference was detected on the third examination (6 months after the initial one) showing that the AS reached the target for all ALS patients with bulbar form compared to less than half patients with spinal form (46.2%) (Figure 2).

In an attempt to define the contribution of number of positive body regions, in which the contribution in the detection of PMN lesions was achieved by using the EMG for diagnostic categories of probable and definite diagnosis, there were distinguished findings – at the third examination (after 6 months) of the patients classified by using the rEE criteria, 67% had positive EMG findings in 2 or more body regions, in contrast to 80% of patients classified by the AS criteria ($p = 0.031$) (Figure 3). A similar difference was determined by a number of patients, who at the fourth examination (in the ninth month of monitoring) showed the positive EMG findings in three or more body regions according to the used criteria (rEE = 42% vs. AS= 71%, $p < 0.05$) (Figure 3).

The denervation potentials (fibrillation, PSW and complex fasciculations) were present in the patients with ALS with different frequency. The complex fasciculations were particularly frequent in small foot muscles, mEDB and mFHB (40% and 37% respectively) at the third examination (in the sixth month of monitoring). Contrary to that, fibrillation and PSW were registered in arm and hand muscles (*mDEL, mBB* and *mADM*) as well as in the paravertebral musculature of thoracic region (*mPV*) more frequently (Figure 4).

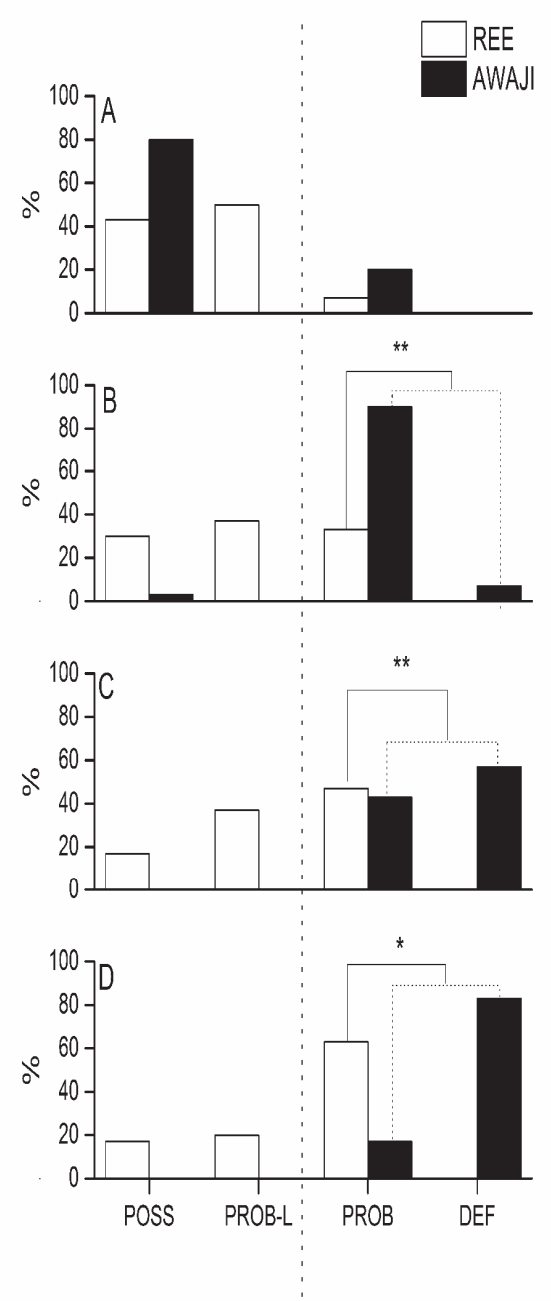

Fig. 2 – Distribution of diagnostic categories by using the rEE or AS criteria according to the forms of the disease, spinal vs. bulbar according to the times of evaluation.
Marks are the same as in Fig. 1 (A – 3 months; B – 6 months; C – 9 months; D – 12 months), so as abbreviations (POSS – possibly; PROB – probably; DEF – definitely).

Finally, we tried to determine whether the degree of functional deficits measured by the FS in the patients who achieved the criteria of diagnosis by using the rEE or AS was different, which proved to be true only for the study "breakpoint" – the third examination at the sixth month of monitoring when the FS median of the AS was 34, or 30.5 of the rEE ($p = 0.017$).

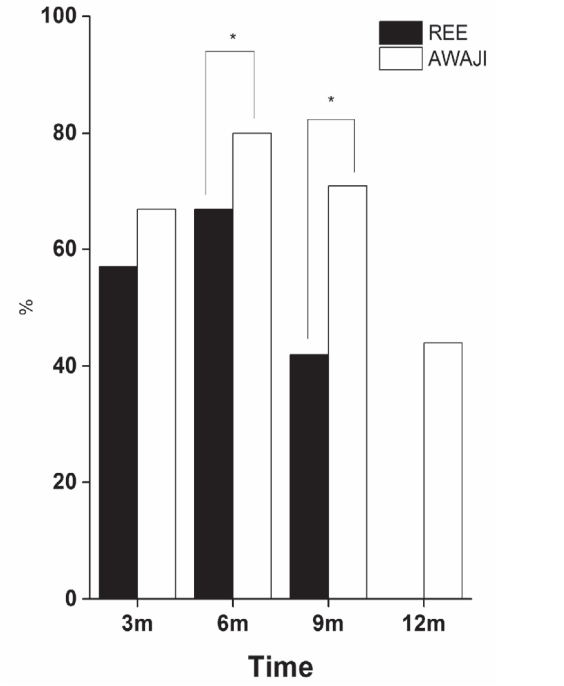

Fig. 3 – Representation of affected 2 or more body regions, in the categories of probable and definite diagnosis of ALS and according to positive EMG findings as correlates of PMN lesions. The abscissa includes the times of evaluation in months.
***$p < 0.05$ (indicate the level of statistical significance); REE – Revised Ed Escorial criteria; AWAJI – Awaji-Shima criteria.**

Discussion

The key finding of this prospective study refers to the time required to make a definite diagnosis of ALS, which, by using the AS criteria, is shortened on average for less than 3 months. By using the AS criteria the definite diagnosis is made on average 9.81 ± 1.81 months from the initial examination, while in the period of 12 months from the initial examination none of the patients were diagnosed with definitive ALS by using the rEE criteria. The difference between this study and previous similar ones refers to the absence of monitoring the evolution and contribution of the criteria during the longitudinal observation of patients.

Namely, the diagnosis of amyotrophic lateral sclerosis significantly complicates the complex clinical picture with numerous overlappings clinical presentations with other diseases of the peripheral motor neuron as well as the absence of a reliable biological marker. Therefore, the diagnostic protocol requires both the clinical and electrophysiological signs of the disease, which eventually resulted in three (AS) or four (rEE) categories of diagnosis among which the reliability increases with a number of body regions.

Therefore, significant acceptance of electrophysiological signs of denervation activity extends the possibility of determining the affected body region from which the findings arose in our and similar studies.

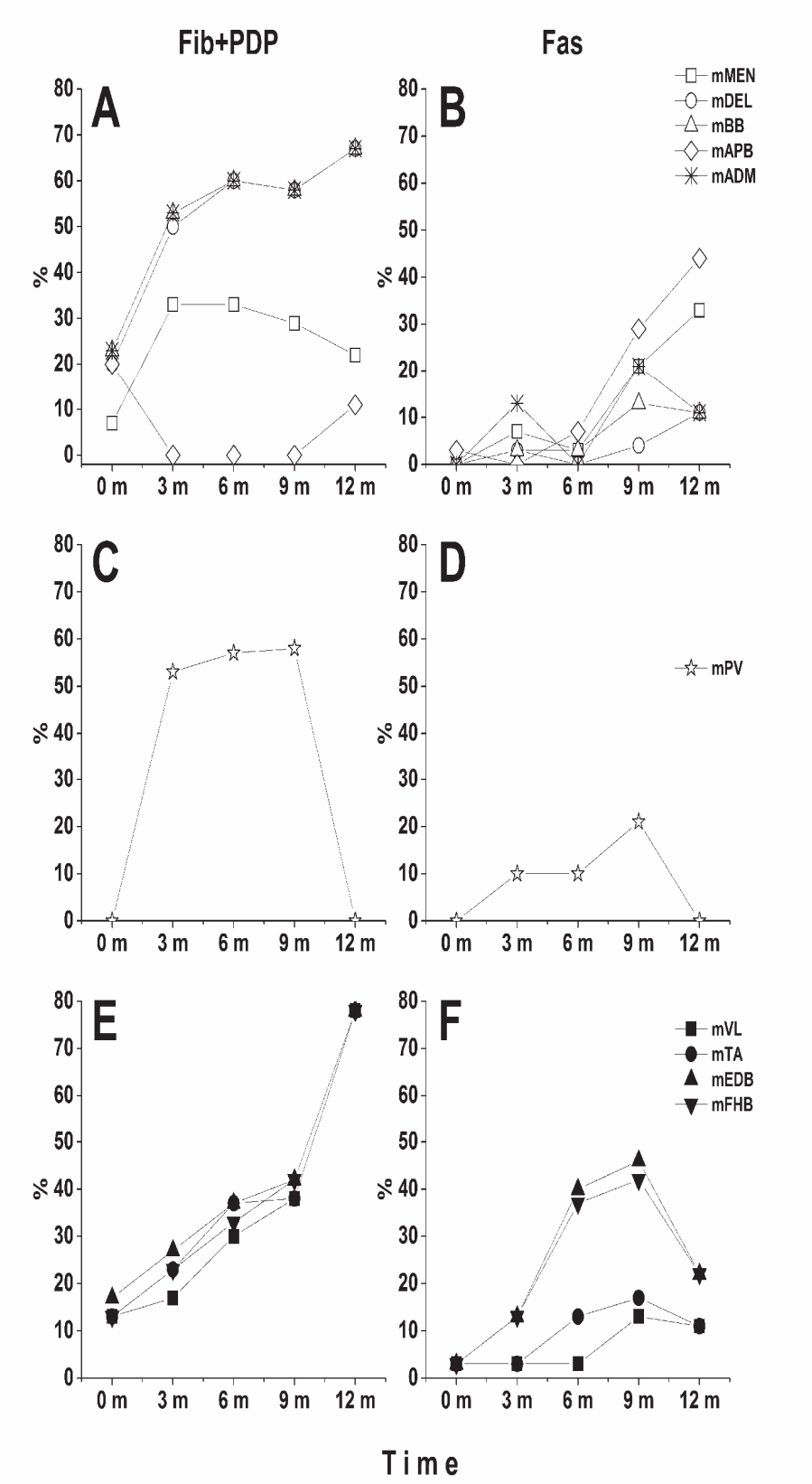

Fig. 4 – Temporal and spatial distribution of the frequency of denervation activity in patients with amyotrophic lateral sclerosis.
Fib – fibrillation; PDP – progressive denervation; FAS – fasciculations.
mMEN – ***m. mentalis;*** **MDEL –** ***m. deltoideus;*** **mBB –** ***m. biceps brachii;*** **mAPB –** ***m. abductor pollicis trevis;***
mADM – ***abductor digiti minimi;*** **mVL –** ***m. rastus lateralis;*** **mTA – m. tibialis anterior; mEDB –** ***m. extensor digitorum brevis;***
mFHB – ***m. flexor mallucis brevis.***

The findings in our study are slightly weaker in comparison to the study of Okita et al. [9], since in their study the disease was diagnosed about 6 months earlier by using the AS criteria, but if the time was measured from the onset of symptoms. This difference may be partly due to the known effects of a relative delay between the onset of symptoms and refers to the tertiary center [10] in our study (Banja Luka, the Republic of Srpska), which was 10.2 ± 4.5 months.

Furthermore, after 3 examinations (6 months after entering the study), 28 of 30 patients (96%) met the AS criteria for probable or definite diagnosis, contrary to 33.3% when applying the rEE criteria. Also, using the AS criteria did not result in the loss of specificity, while the sensitivity was improved in categories of probable and definite diagnosis of ALS to 6.7% in the third month by using the rEE, contrary to 20% by using the AS. Moreover, the AS criteria provided the sensitivity of 100% for the mentioned above diagnostic categories in the ninth month of the monitoring, while the sensitivity according to the rEE in the twelfth month was only 60%. This is consistent with findings of de Carvalho and Swash [11] in one of the first publications dealing with similar issue, but at the same time, which is significantly better than some other studies [12, 13]. However, regarding the two last studies, it is necessary to emphasise that it is difficult to make the direct comparison due to the methodological differences; the study of Noto et al. [12] was about an ethnic group of Asians, while in the study of Boekestein et al. [13], the design was a retrospective study. In addition to that, fewer muscles were examined electromyographically, which could certainly influence the sensitivity of the approach.

The assumption that a set of the AS criteria is particularly sensitive to defining the category of the disease in the patients with bulbar form [12–14] was not confirmed in our case probably due to the relatively small number of examinees, since only 13 patients with ALS suffered the bulbar form of the disease.

In terms of detecting the denervation activity in general, the key point in the AS approach refers to the acceptance of specific types of the fasciculations, which are complex and unstable, as equivalent to current denervation changes [14]. However, it is necessary to emphasize that the fasciculations, at the same time, are not the specific occurrence in ALS, but they can be seen extensively in other diseases of the peripheral motor neuron as poliomyelitis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy [15]. Regarding the mechanism of the genesis of fasciculations, it is now known that the fasciculations can occur at any level of a peripheral motor neuron, and the complex fasciculations are particularly frequent in the region of distal axon arborisation [16]. There is an observation in patients with ALS that the fasciculations more often occur in an early phase of the disease when the muscular strength is relatively preserved. However, eliminating carefully other diseases and by the electrophysiological examination, the importance is given to fasciculations in early diagnosis of ALS, so de Carvalho and Swash [17] fasciculation as "very early marker of ALS".

This research showed that already after six months of monitoring using the AS criteria, more EMG affected regions can be detected, which is consistent with the research of Schrooten et al. [18] who showed that about half of the patients (46.4%) have for at least one more affected region by using the AS criteria in relation to the patients categorised in accordance with the El Escorial criteria.

Having in mind that there are no strict protocols of electrophysiological evaluation related to the number of muscle examinations, or their selection by additional analysis we tried to provide commentary on the significance of this issue. In our sample, fibrillations and PSW are particularly often registered in mBB and mADM in upper extremities in only 2 examinations in a row, where the ADM showed somewhat more frequent presence of fasciculations. Contrary to this, the analysis of the examination of lower extremity muscles showed the particular importance of the small muscles of the feet (mEDB and mFHB) in detecting fasciculations.

In summary, prospectively analyzing the use of new AS criteria for the diagnosis of amyotrophic lateral sclerosis, the preservation of specificity is confirmed, with the additional increase in the sensitivity of this approach. A study like this does not represent a special affirmation of electrophysiological evaluation, having in mind that the approach is unavoidable was derived from the Lambert criteria. However, the AS criteria affirm a different importance of electrophysiological indicators enabling a faster determination of the categories of definite diagnosis and at the same time better accessibility to innovative forms of treatment of this acute fatal disease for the patients.

Conclusion

Application of the AS criteria improve the achievement of a category of probable or definite diagnosis of ALS by 2.7 months earlier compared to the rEE. This outcome is particularly affected by a higher frequency of positive EMG findings, when the AS criteria were employed. Early determination of diagnosis provides the better perspective and more frequent participation of ALS patients in the pharmacotherapy studies intended to establish new therapeutic options.

Acknowledgment

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article.

The work of TVI was supported by the following grants: Ministry of Education and Science of the Republic of Serbia (Project No. 41014) and the Ministry of Defense of the Republic of Serbia (Project MFVMA/12/13-15). The work of SDM was supported by the grant of Ministry of Education and Science of the Republic of Serbia (Project No. 175012) and the Ministry of Defense of the Republic of Serbia (Project MFVMA/12/13-15).

REFERENCES

1. *Mitchell JD, Borasio GD*. Amyotrophic lateral sclerosis. Lancet 2007; 369(9578): 2031–41.
2. *Ryberg H, An J, Darko S, Lustgarten JL, Jaffa M, Gopalakrishnan V*, et al. Discovery and verification of amyotrophic lateral sclerosis biomarkers by proteomics. Muscle Nerve 2010; 42(1): 104–11.
3. *Lambert EH, Mulder DW*. Electromyographic studies in amyotrophic lateral sclerosis. Proc Staff Meet Mayo Clin 1957; 32(17): 441–6.
4. *Miller RG, Mitchell JD, Lyon M, Moore DH*. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2007; (1): CD001447.
5. *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. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1(5): 293–9.
6. *Makki AA, Benatar M*. The electromyographic diagnosis of amyotrophic lateral sclerosis: Does the evidence support the El Escorial criteria. Muscle Nerve 2007; 35(5): 614–9.
7. *Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J*, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008; 119(3): 497–503.
8. The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. The ALS CNTF treatment study (ACTS) phase I-II Study Group. Arch Neurol 1996; 53(2): 141–7.
9. *Okita T, Nodera H, Shibuta Y, Nodera A, Asanuma K, Shimatani Y*, et al. Can Awaji ALS criteria provide earlier diagnosis than the revised El Escorial criteria. J Neurol Sci 2011; 302(1–2): 29–32.
10. *Douglass CP, Kandler RH, Shaw PJ, McDermott CJ*. An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease. J Neurol Neurosurg Psychiatr 2010; 81(6): 646–9.
11. *Carvalho MD, Swash M*. Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. Amyotroph Lateral Scler 2009; 10(1): 53–7.
12. *Noto Y, Misawa S, Kanai K, Shibuya K, Isose S, Nasu S*, et al. Awaji ALS criteria increase the diagnostic sensitivity in patients with bulbar onset. Clin Neurophysiol 2012; 123(2): 382–5.
13. *Boekestein WA, Kleine BU, Hageman G, Schelhaas HJ, Zwarts MJ*. Sensitivity and specificity of the 'Awaji' electrodiagnostic criteria for amyotrophic lateral sclerosis: Retrospective comparison of the Awaji and revised El Escorial criteria for ALS. Amyotroph Lat Scler 2010; 11(6): 497–501.
14. *Mills KR*. Characteristics of fasciculations in amyotrophic lateral sclerosis and the benign fasciculation syndrome. Brain 2010; 133(11): 3458–69.
15. *Kimura J*. Types of electromyographic abnormalities. In: *Kimura J*, editor. Electrodiagnosis in Diseases of Nerve and Muscle. Principles and Practices. 4th ed. Oxford: Oxford University Press; 2001. p. 339–69.
16. *de Carvalho M, Swash M*. Fasciculation potentials: A study of amyotrophic lateral sclerosis and other neurogenic disorders. Muscle Nerve 1998; 21(3): 336–44.
17. *de Carvalho M, Swash M*. Fasciculation potentials and earliest changes in motor unit physiology in ALS. J Neurol Neurosurg Psychiatr 2013; 84(9): 963–8.
18. *Schrooten M, Smetcoren C, Robberecht W, van Damme P*. Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: A prospective study. Ann Neurol 2011; 70(1): 79–83.

Received on January 15, 2016.
Revised on June 02, 2016.
Accepted on August 03, 2016.
Online First November, 2016.