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Validation and cross-cultural adaptation of Columbia Cramp Scale in Serbian ALS patients

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Abstract

Background & Objectives: Muscle cramps are present in more than three quarter of amyotrophic lateral sclerosis (ALS) cases. The objective of the present study was to translate and validate Columbia Cramp Scale (CCS) for use in Serbian ALS patients, and to identify the potential epidemiological and clinical factors which could influence worse overall CCS score. *Methods:* This study involved 21 patients with muscle cramps and 17 patients with no previous cramps history. Patients with cramps were retested 3 months after first assessment. Main socio-demographic and clinical data were obtained from patients at time of testing. The revised ALS functional rating scale (ALS-FRS-R) was used to score activities of daily living. The study subjects were assessed with CCS, Hamilton scales for the assessment of anxiety (HAM-A) and depression (HAM-D) and 36-Item Short Form Survey (SF-36). *Results:* Mean CCS score was 17.2±6.7 (range 6-30). The Cronbach's alpha coefficient reflecting internal consistency was 0.76, which suggest acceptable internal consistency. Multiple linear regression analysis including all parameters associated with worse CCS scores, showed that lower ALSFRS-R scores (beta=0.55, $p<0.01$) and depression (beta=0.52, $p<0.01$), were independent predictors of the worse CCS score (adjusted $R2=0.35$, $p<0.01$ for overall model). Subjects with cramp history were retested after 3 months and no statistically significant difference between CCS scores in this two time points was noted. *Conclusion:* Selection of appropriate measure for assessing muscle cramps is important. In ALS patients we recommend CCS questionnaire. Results of our study also show that high CCS scores correlate with depression and anxiety, worse QoL and some epidemiological and clinical characteristics.

Keywords: Amyotrophic lateral sclerosis, muscle cramps, Columbia Cramp Scale

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by degeneration of booth upper and lower motor neurons.[1] The disease is fatal, associated with high mortality (average survival time is approximately 3-4 years).[2] Although progressive weakness dominates the clinical picture, ALS is a multisystem degeneration, and other symptoms (such as psychiatric, extrapyramidal, sensory, and autonomic symptoms) are increasingly recognized.

Muscle cramps (painful, involuntary muscle contractions) are present in more than three quarter of ALS cases, sometimes even earlier then motor weakness.[3] It is unknown if epidemiological or clinical factors (gender, age, sex, region of onset, genetically determined disease versus apparently sporadic disease) affect muscle cramps. Clinically cramps are important cause of pain in ALS.[4] A patient-reported outcome, such as cramp diary, is the most commonly used measure to assess muscle cramps in this disease.[5] The success of application in future therapies for muscle cramps in ALS depends on valid and relevant outcome measures. A newly developed scale for ALS patients, called Columbia Cramp Scale (CCS) is thought to be useful for everyday clinical practice and also for clinical trials that assess cramps in this disease.[6]

The objective of the present study was to translate and validate CCS for use in Serbian ALS patients. In addition we want to identify the potential epidemiological and clinical factors which is associated with worse overall CCS score.

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METHODS

This study included 21 patients (12 males and 9 females), with positive medical history of cramps (at least 5 cramps per week). We also assessed, sex and age matched, 17 ALS patients (10 males and 7 females) with no previous history of muscle cramps. All patients were diagnosed as either probable or definite ALS based on El Escorial diagnostic criteria.[7] Patients treated between July 2019 and April 2020 in tertiary healthcare institution (Clinic of neurology, Clinical Center of Nis) were assessed. Only patients aged >18 years were included in the study. All patients were on riluzole therapy. Patients with signs and symptoms of frontotemporal dementia were excluded. Patients with positive cramp history were retested 3 months after first assessment (2 patients were not retested due to lost in follow up). During this period of time they received various drugs for cramp treatment (baclofen, gabapentin, quindine).

The study was conducted in accordance with the Basics of Good Clinical Practice, the Helsinki Declaration and the Law on Health Care of the Republic of Serbia. Local review board gave their ethical approval for the conduction of this study. Verbal and written consent of all subjects prior to enrollment was obtained.

Main socio-demographic data (current age, gender, place of residence, current emotional status, number of children, professional and employment status, history of addiction, significant comorbid disorder) were obtained from all patients at time of first testing. Alcohol and tobacco smoking addiction was defined according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[8] Relevant clinical factors were collected from medical history (onset region of the body, disease duration, diagnostic delay, sporadic or familial ALS). The revised ALS functional rating scale (ALS-FRS-R) was used to score activities of daily living. The ALSFRS-R scale includes bulbar function (ALSFRS-R-B), motor function (ALSFRS-R-M) and respiratory function (ALSFRS-R-R) subscales. A lower score (range 0-48) means lower functional ability.[9]

The study subjects were assessed with CCS, Hamilton scales for the assessment of anxiety (HAM-A) and depression (HAM-D) and 36-Item Short Form Survey (SF-36). Questionnaires were assigned to patients only after carrying out a complete neurological examination, nerve conduction study, electromyography and collecting of epidemiological data (for establishing ALS diagnosis).

The CCS includes the following items: (1) factors that triggered muscle cramps, (2) cramp frequency, (3) location of cramps and (4) severity. Each item included in the measure was assigned a 5-point Likert-type scale, from none to most severe. A visual analog scale that assess the effects of muscle cramps on overall daily living (10-point subscale) was also included. The CCS score range from 0-30. Original scale in English is presented in Table 1.[6] Consent for using the CCS was obtained from the author of the original paper. CCS was translated and cross-culturally validated using accepted guidelines and standard methodology.[10] The translation process was done by two translators (native Serbian speakers who are bilingual in English) and two neurologists with special interest in field of neuromuscular disorders. As a result, the first Serbian version of the CCS was created. Two translators (native English

Table 1: Columbia Cramp Scale (CCS)

I. Triggering 1. No cramps 2. Rare with strenuous muscle activity 3. Frequently with strenuous muscle activity 4. Almost always with strenuous muscle activity 5. Almost always with any activity
II. Frequency 1. None a week 2. < 3 in a week 3. On average once a day 4. < 5 a day 5. > 5 a day
III. Location (involved part of the body - right or left arm, right or left leg, torso, neck) 1. One area 2. Two areas 3. Three areas 4. Four areas 5. Everywhere
IV. Severity 1. Trivial sensation of cramps 2. Minor discomfort 3. A special maneuver can be used to abort or stop cramps 4. A massage or special maneuver cannot easily abort or stop cramps that last less than a few minutes 5. Nearly continuous cramps, pains, or discomfort
V. Muscle Cramps Affecting Overall Daily Activity - Visual Analog Scale None 0 1 2 3 4 5 6 7 8 9 10 Severe

speakers who are bilingual in Serbian), translated this version back to English and compared it to the original CCS. This phase resulted in the second Serbian version which was also evaluated by two previously mentioned neurologist. Second version was applied in all ALS patients (native Serbian speakers) and after minor corrections the final Serbian CCS version was established.

HAM-D measures the severity of depression, and the values are interpreted as follows: 0-9 (without depression), 10-13 (mild depression), 14-17 (mild to moderate depression) and 18 or more (moderate to severe depression).[11] HAM-A measures severity of anxiety, where the values below 17 indicate absence or mild anxiety, values between 18-24 on mild to moderate anxiety, and values 25-30 on moderate to severe anxiety.[12] All patients completed the Serbian version of the SF-36 questionnaire as a measure of quality of life (QoL).[13] It is a generic measure which comprises eight general health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Total SF-36 score, physical composite score (PCS) and mental composite score (MCS) are the main scores which summarize these eight domains. All scores range from 0 to 100, where higher numbers represent better QoL.

Normality of data was tested by the Kolmogorov-Smirnov test. Mann-Whitney U test, Student's t-test and $\chi 2$ test were used, as appropriate. Internal consistency of CCS items was analyzed using Cronbach's alpha. Construct and criterion related validity was assessed as an impact of socio-demographic and clinical factors on CCS: through the Mann-Whitney U test and the linear regression analysis. In addition CCS was compared in terms of correlation with SF-36 (Spearman's rho). For multiple correlation Bonferroni correction was used (0.05/7=0.007). In all analyses, significant testing was two-sided, with α set at 0.05 for statistical significance and 0.01 for high statistical significance.

RESULTS

Mean age of patients was 64.4 ± 7.2 years (median 62 years). Gender ratio was M:F=1.35:1. Mean CCS score in the group with cramps was 17.2±6.7 (range 6-30). The Cronbach's alpha coefficient reflecting internal consistency was 0.76, which suggest acceptable internal consistency. Other socio-demographic and clinical characteristics, as well as scores obtained on used questionnaires are presented in Table 2. Between groups of patients with and without history of cramps we found significantly lower values in SF-36scores and higher values in HAM-A and HAM-D score ($p<0.05$).

Regarding clinical characteristics we found higher CCS scores in patients with spinal onset of the disease then in bulbar ALS onset ($p<0.05$). ALSFRS-R score correlate with total CCS score ($p<0.01$). There was no correlation of CCS score with diagnostic delay, disease duration or difference between sporadic and familial form and scores obtained on cramp questionnaire.

Current age, gender, place of residence, emotional status, number of children and employment status did not correlated with the total CCS score. Smokers and alcohol users had significantly higher scores on CCS ($p<0.05$). Presence of depression and anxiety (measured with HAM-D and HAM-A), as well as lower QoL (measured with SF-36) were in association with the CCS total score ($p<0.01$). All statistically significant correlation between CCS score and questioned parameters are presented in Table 3. We retested 19 subjects with cramp history 3 months after the first test and did not found and statistically significant difference between CCS scores in these two time points.

Multiple linear regression analysis including all parameters associated with worse CCS scores, showed that lower ALSFRS-R scores (beta=0.55, $p<0.01$) and depression (beta=0.52, $p<0.01$), were independent predictors of the worse CCS score (adjusted R2=0.35, $p<0.01$ for overall model).

DISCUSSION

Cramps are common and very disturbing symptom in patients with ALS.[14] The pathophysiology of muscle cramps in ALS is still not clear (a possible explanation is the generation of free radicals and spontaneous discharges of motor nerves).[15] There is no specific medication approved for muscle cramps in ALS population.[16] For that reason future clinical trials should focus on this need, and it is crucial to have reliable questionnaire which could asses cramps properties: such as severity, localization, frequency and triggers.[17] Cramp diaries is the common tool use to assess and monitor the muscle cramp, but it has several inherent weaknesses. New assessment scales developed will have to be accessible, simply and reliable. Recently CCS has been proposed to be used for assessing muscle cramps in ALS. CCS takes only a few minutes to complete and can be

Table 2: Demographic and clinical characteristics of patients with ALS

	Patients with positive cramp history (N=21)	Patients without positive cramp history (N=17)	P value
Onset region - spinal onset	14 (66.7%)	12 (70.6%)	
Diagnostic delay in months	6.5±4.9	5.9±4.5	
Disease duration in months	11.2±6.3	10.5±5.4	
Familial ALS	4 (19.1%)	2 (17.6%)	
Education			
Primary studies	6 (28.6%)	5 (29.4%)	
Secondary studies	9 (42.8%)	8 (47.0%)	
University degree	6 (28.6%)	4 (23.5%)	
Married or cohabitant	16 (76.2%)	12 (70.6%)	
Unemployed (including retired)	15 (71.4%)		
Number of children			
Zero	4 (19.1%)	2 (11.7%)	
One or two	13 (61.8%)	11 (64.7%)	
Three or more	4 (19.1%)	4 (23.5%)	
Smokers	14 (66.7%)	14 (82.3%)	
Alcohol users	6 (28.6%)	3 (17.6%)	
ALSFRS-R	35.31± 12.27	33.26±11.4	
HAM-A	18.10 ± 5.67	16.4±4.9	0.035
HAM-D	19.61 ± 5.53	16.8±5.3	0.021
SF-36 total score	44.37 ± 22.42	48.52±4.9	0.019
Physical composite score (PCS)	42.61 ± 24.12	45.34±5.6	0.017
Mental composite score (MCS)	49.22 ± 23.71	51.25±4.8	0.026

ALS - Amyotrophic lateral sclerosis; ALSFRS-R - ALS functional rating scale; SF-36 - 36-Item Short Form Survey; HAM-A - Hamilton scales for the assessment of anxiety; HAM-D- Hamilton scales for the assessment of depression

administered in person or by telephone. One major advantage is that it is administered by an evaluator, which can limit subjective assessments. Also, the CCS demonstrated high agreement with frequency of muscle cramps described via the cramp diary.[6] Based on our knowledge this is the first validation of this questionnaire in a non-English language. In the original study by Mitsumoto *et al.,* the internal consistency, measured with Cronbach alpha coefficient was 0.74. In our study internal consistency of CCS items is 0.76, which suggest acceptable internal consistency.

As there is a lack of studies to provide data about the influence of socio-demographic and clinical variables on cramps severity or frequency, we tried to find if any of epidemiological or clinical

Table 3: Statistically significant correlation between Columbia Cramp Scale scores and socio-demographic and clinical characteristics of the disease (N = 21)

	Columbia Cramp Scale score	
	Rp	p
Spinal onset	0.289	0.0059*
Smoking	0.323	0.0054*
Alcohol use	0.311	0.0061*
ALSFRS-R	-0.576	0.0018*
HAM-A	0.522	0.0024*
HAM-D	0.547	0.0019*
SF-36	-0.499	0.0023*

ALSFRS-R - ALS functional rating scale; SF-36 - 36-Item Short Form Survey; HAM-A - Hamilton mscales for the assessment of anxiety; HAM-D- Hamilton scales for the assessment of depression; *p<0.007 (level of significance after Bonferroni`s correction)

characteristics influence muscle cramps in ALS patients. Previous studies showed that there is high variability in the severity and frequency of cramps among different ALS patients. In those who experienced many cramps, there is variability in the severity from month to month. Cramps are more prevalent in the first year of ALS and lessen over time.[5] Caress *et al*. found that frequency of cramps is usually stable for a period of couple of years in single patient diagnosed with ALS. In our study we also did not find any significant increase or decrease in CCS scores obtained three months after the first test. Majority of subjects received various drugs for treatment of muscle cramps (baclofen, gabapentin, quindine) but with no significant response during this period. Cramps were more common in patients with spinal onset ALS then in group with bulbar onset, likely reflecting the greater degree of lower motor neuron involvement.[3] Our findings also support greater prevalence of muscle cramps in spinal onset ALS, then in bulbar onset. Other studies found that older patients reported more cramps.[18] In our study we have not found any significant correlation in age with the CCS scores. Because there is no similar data in the published literature we could not compare all our results with the others. Our studies also indicated a significantly higher CCS scores in patients with history of alcohol and smoking addiction. Also depression, anxiety and worse QoL have a statistically significant correlation with high CCS scores. Relationship of these items with muscle cramps could be bidirectional, where more severe depression, anxiety and worse QoL worsen muscle cramps and vice versa. We found significantly lower QoL and more pronounced depression and anxiety in group of patients with cramps than in ALS patients without cramps, which could suggest an impact of this underestimated symptom on overall quality of life in ALS patients.

There are some limitations of our study. We were unable to obtain information about long-term changes in CCS scores in order to investigate a causal relationship that may be associated with cramps in patients with ALS. The number of included participants was small, and the results of the present study may not be generalizable, as the demographic characteristics may differ from region to region. Our study has the advantage of all patients being examined by a clinician to confirm the diagnosis, and that this is one of the few studies in ALS patients, which examines the correlation of various socio-demographic factors and clinical characteristics of the disease with severity of muscle cramps. We believe that our study complement the existing knowledge and open up some new questions for further research in this topic. It can also be of importance in future treatment trials of ALS patients with cramps.

Selection of appropriate management measure is important in investigatory trials and in daily clinical practice. Due to the high prevalence of muscle cramps in ALS patients we suggest regular screening and monitoring of muscle cramps in these patients. We recommend the use of CCS for this purpose, because it is simple and provide useful data for everyday practice. Results of our study also show that high CCS scores correlate with depression and anxiety, worse QoL, high levels of neurological disability, spinal onset, as well as history of smoking and alcohol addiction.

DISCLOSURE

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Conflicts of interest: None

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