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National Study of Muscle Cramps in ALS in the USA

Helen E. Stephens, MS,
Principle Consultant, Patient Centered Research, Gillette WY

Nanette C. Joyce, DO, MAS, and
Associate Professor of Clinical Physical Medicine and Rehabilitation, University of California, Davis

Björn Oskarsson, MD, FAAN
Associate Professor of Clinical Neurology and Pathology, University of California, Davis and the Mayo Clinic Jacksonville

Abstract

Objective—The objective of this study was to describe muscle cramps in an US sample of amyotrophic lateral sclerosis (ALS) patients.

Methods—Utilizing an anonymous web based questionnaire we queried ALS patients regarding the severity, frequency, time course, treatment of muscle cramps and their relationship to pain.

Results—The survey had 282 respondents with 92% reporting having cramps. For 20% of the sample, cramps were stated to be the presenting ALS symptom. Cramp severity was rated at a mean of 5.2/10 and the mean cramp frequency was 5.3 cramps per day. Cramp intensity and frequency did not correlate to duration or severity of ALS. Pain as measured with the Patient Reported Outcome Measurement Information System (PROMIS) pain scales was not statistically different from the US general population. Cramp severity and frequency significantly and positively correlated with the PROMIS pain scales. Patients with more severe cramps were more likely to use prescription medications for their cramps compared to patients with milder symptoms. Treatments directed at cramps were tried by 57%.

Conclusion—Cramps are a common symptom in ALS and it does not correlate with disease duration or severity. The severity of cramps is on average moderate and many patients try treatments.

Keywords

Cramp; questionnaire; patient reported outcome

Corresponding and senior author: Björn Oskarsson, MD, Associate Professor of Clinical Neurology and Pathology, University of California, Davis and the Mayo Clinic Jacksonville. boskarsson@ucdavis.edu, Address: 4860 Y st. Suite 3700, Sacramento CA 95817, USA, Phone: +1 916 871 9494.

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Introduction

Muscle cramps are common in ALS(1), however, many aspects of cramps remain unknown. It is unknown; gender, age, sex, muscle bulk, relative upper and lower motor neuron involvement, region of onset, genetically determined disease versus apparently sporadic disease influence muscle cramps. The relationship between the pathophysiology of ALS and cramps is unknown, but neuronal hyperexcitability has emerged as a possible central feature. (2, 3) Muscle cramps can be indirectly measured using electrophysiological methods, or recorded directly by the person experiencing the symptom. The direct patient reported measure can be collected using a web-based questionnaire as done here.

Clinically cramps are an important cause of pain in ALS.(4) Cramps have been reported by 67 to 95 percent of ALS patients.(1, 5) A recent study focused on understanding pain in ALS showed that of those patients who report pain, 67% attribute their pain to cramps alone. (4) Despite this common occurrence of cramps in ALS only a single center natural history study by Caress et al has been published.(5) This study which captured two or more time points of 33 patients is the most comprehensive study to date and it has the highest reported cramp frequency of 95 percent. The study did not show a general change of cramps frequency over time, a finding that was contrary to what many researchers and clinicians in the field had assumed.

Our objective with this study was to describe the frequency and severity of cramps in a large cross sectional United States (US) ALS sample. We attempted to capture the relationship between cramps and disease duration and severity. Additionally we applied the National Institute of Health (NIH) Patient Reported Outcome Measurement Information System (PROMIS) outcomes of pain intensity, pain behavior and pain interference to relate cramps to overall perceptions of pain.

Participants and Methods

The study was a cross-sectional observational design using a public online and anonymous survey. Patients were recruited from the Agency for Toxic Substances and Disease Registry (ATSDR), National ALS Registry. The Registry is the largest dataset of ALS patients in the US with 12000 registrants.(6) ATSDR sent 4880 solicitation emails to registered ALS participants in December 2014 and enrolment was closed in April 2015. The survey website provided participants with information regarding research objectives, risks, benefits, directions for how to complete the survey and contact information for the study team. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The study was reviewed by the University of California, Davis Institutional Review Board (IRB) ID 31166-1.

Instruments

Basic demographic information and data on ALS disease characteristics was collected. One page of information defining muscle cramps, spasticity and fasciculations was provided in order to clarify the symptoms to participants (see appendix 1). This was followed by

questions regarding the severity and frequency of cramps and also of fasciculations. Free text fields were utilized in order to query participants about pharmacological and non-pharmacological treatments used. The following measures were collected:

ALS Functional Rating Scale-Revised (ALSFRS-R).(7) This is a 12-item questionnaire measuring speech, swallowing, fine and gross motor skills and respiratory status. Total scores vary from 0 (worst possible function) to 48 (normal function). The self-administered version of the tool was used for this study.(8, 9)

Patient Reported Outcome Measurement Information System (PROMIS).(10) The PROMIS measures were developed using item response theory and provide accurate information about numerous health constructs.(11) The PROMIS measures are generic patient reported outcome measures developed with high methodological rigor and proven validity.(12) Most PROMIS items employ five response options (e.g., 1=Not at all, 2=A little bit, 3=Somewhat, 4=Quite a bit, 5=Very much) with the exception of the Pain Behavior instrument which uses six response options to allow for respondents to endorse “no pain.” PROMIS pain intensity, pain behavior, and pain interference instruments were used in this study. The pain intensity measure is a simple 3 item battery exploring perceptions of severity of pain. The pain behavior domain is a 39 item measure collecting behavioral expressions of pain, and the pain interference domain is a 44 item battery capturing pain interference in daily activities. The pain behavior and interference PRO measures can provide very accurate information without exhaustive item presentation by utilizing CAT. This method allows simultaneous adaptive item selection depending on the proceeding answer. CAT provides the accuracy of a longer item list with only four to five items being presented to the participant. The questionnaire was administered though the NIH Assessment Center Web portal; http://www.assessmentcenter.net. This site is capable of administering computer adaptive testing (CAT) and is hosted by Northwestern University. Scores for each of the three measures are generated by the PROMIS system and provided as a T score. Score distributions are standardized such that a score of 50 represents the general US population and the standard deviation around the mean is 10.

Statistics

All variables were summarized initially with frequencies and percentages or means, medians, and standard deviations. Several variables were calculated for analysis: the ALSFRS-R score by summing the individual components, and PROMIS pain intensity, pain behavior, and pain interference scores as T scores. Correlations between variables were determined using Spearman correlation. Analysis of Variance was used to compare several groupings of participants on pain outcome measures. A P value of <0.05 was considered significant. No adjustments were done for multiple comparisons. All analyses were performed using the Statistical Package for the Social Sciences, Version 22.0. Armonk, NY: IBM.

Results

Participant Demographics

The study had 287 respondents, which corresponds to a response rate of 5.9% of the emails sent by ATSDR. Participant demographics and disease characteristics are presented in Table 1. Also represented in Table 1 are the demographics of patients enrolled in the Registry.(6)

Cramp Presentation

Ninety two percent of respondents indicated that they suffered from muscle cramps. The aggregate self-estimated severity of muscle cramps was 5.2/10 with a range from 0 to 10/10, consistent with a moderate average severity of cramps. The average reported frequency was 5.3 cramps per day. Twenty percent of patients recalled that muscle cramps were their first symptom of ALS, preceding any weakness or fasciculations. In regards to the experienced severity of cramps, 48% felt that the cramp symptom had worsened as compared to at disease onset, 23% felt that it was unchanged and 29% appreciated that the cramps were reduced. Sixty seven percent of participants stated that muscle cramps were their sole source of pain. There was no correlation between cramp severity and frequency to either disease duration or ALS severity as measured by the ALSFRS-R.

PROMIS Pain Outcomes

Table 2 presents the PROMIS pain scores for the sample. The PROMIS pain intensity, pain interference, and pain behavior scores all correlated significantly with cramp frequency, $r=0.32$, $r=0.31$, and $r=0.30$, all, $P<0.001$. The strongest correlations were observed with cramp severity and the three pain outcomes, $r=0.67$, $r=0.54$, and $r=0.55$, all, $P<0.001$.

Cramp Treatment and Management

In regards to treatments for cramps, 47% reported that they had not tried any treatments, 17% percent reported trying over the counter remedies and 36% reported trying prescription medications. Table 3 presents the cramp frequency, cramp severity, and PROMIS pain scores by treatments tried. Those who used prescription medications reported the highest cramp frequency, cramp severity, and PROMIS pain scores compared to the other two groups. The frequencies of reported medication use are provided in Table 4, along with corresponding mean cramp frequency and severity ratings.

Discussion

This is the first US large-scale investigation of cramps in ALS and it is a useful extension of previous studies of cramps and pain. The greatest limitation of the study is the low response rate of 5.6% which may result in a sampling error. We believe that the reason for the low response rate lies in the email blast methodology used to solicit potential participants through the Registry. Not all participants in the Registry may be able to actively participate, due to disease progression, or yet unrecorded death. Furthermore the responders are a self-selected cohort and a truly random sample is unlikely to have been achieved. Our study's demographic characteristics closely mimic the characteristics of the web portal participants, (6) and no overt discrepancy between our sample and the whole population is apparent.

Another potential bias leading to an overestimation of the pain and cramp could be that the title of the study was “Questionnaire of cramps and pain in ALS”. However, the reported pain severity is low compared to most series and the cramp frequency is on par with the current best estimates. This study demonstrates a 92 percent prevalence of cramps which is consistent with what has recently been reported in a longitudinal single center study.(5) Cramps are also notably common in the general population (13) making the relative increase in the ALS population less than a doubling.

For the majority of patients in this study, cramps are their sole source of pain, similar to a recent study of pain in ALS.(4) The moderate severity of cramps in this series (5.2/10) is comparable to the prior single center study where most rated their pain as “moderate” and two ALS cramp treatment trials; 4.0/10(14) and 63.5/100(15). The average cramp frequency the patients in our study reported was 5.3 per day, which is higher than the 46 per month reported in the natural history study, being more comparable to the frequencies reported in treatment trials; 5.9(14) and 4.0(15). The Registry is a prevalent cohort presumably enriched with long survivors creating yet another potential bias. The mean number of cramps did not decrease or increase as a function of disease duration as reported in this study, but 77 % of responders reported a change from disease onset. Thus there seems to be an individual variation of cramps but no overall correlation between duration of disease and muscle cramp frequency.

The generic PROMIS PRO measures are powerful tools which have yet to be widely applied in the ALS field. The carefully crafted test characteristics and CAT methodology provide a comparison to the US general population. While a specific cramp instrument is lacking amongst the PROMIS instruments the pain instruments presumably are measuring pain only from muscle cramps in the patients who indicated that muscle cramps were their only source of pain. In this group we see less total pain as compared to patients with pain from both cramps and other sources.

Given the pervasiveness of cramps in ALS, both early in the disease and at later stages, future research into the origins and treatments of muscle cramps is warranted. In clinical practice ALS clinicians may consider the use of cramp diaries to identify those who could benefit from treatments. Quinine sulfate has traditionally been the main cramp treatment. Meta-analysis of trials in multiple conditions supports its use,(16) but the US Food and Drug Administration recommends against its use due to rare fatalities.(17) Recently mexiletine has been shown to reduce muscle cramps in ALS.(18) This study does not provide data that allows for a formal comparison of the effect of drugs on cramps. It is however intriguing that the two medications reported with the lowest cramp frequencies are these two medications. These two treatments can be offered backed not only by expert opinion but also at least limited evidence. The management of cramps may be appropriate for inclusion in the next iteration of the US ALS practice guideline as it is in the European.(19)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ringel SP, Murphy JR, Alderson MK, Bryan W, England JD, Miller RG, et al. The natural history of amyotrophic lateral sclerosis. Neurology. 1993; 43(7):1316–22. [PubMed: 8327132]
2. Wainger BJ, Kiskinis E, Mellin C, Wiskow O, Han SS, Sandoe J, et al. Intrinsic membrane hyperexcitability of amyotrophic lateral sclerosis patient-derived motor neurons. Cell reports. 2014; 7(1):1–11. [PubMed: 24703839]
3. Fritz E, Izaurieta P, Weiss A, Mir FR, Rojas P, Gonzalez D, et al. Mutant SOD1-expressing astrocytes release toxic factors that trigger motoneuron death by inducing hyperexcitability. Journal of neurophysiology. 2013; 109(11):2803–14. [PubMed: 23486205]
4. Stephens HE, Lehman E, Raheja D, Yang C, Walsh S, Simmons Z. The role of mental health and self-efficacy in the pain experience of patients with amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2016:1–7.
5. Caress JB, Ciarlone SL, Sullivan EA, Griffin LP, Cartwright MS. Natural history of muscle cramps in amyotrophic lateral sclerosis. Muscle Nerve. 2016; 53(4):513–7. [PubMed: 26332705]
6. Mehta P, Antao V, Kaye W, Sanchez M, Williamson D, Bryan L, et al. Prevalence of amyotrophic lateral sclerosis - United States, 2010–2011. Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002). 2014; 63(Suppl 7):1–14.
7. Cedarbaum JM, 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. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169(1–2):13–21. [PubMed: 10540002]
8. Montes J, Levy G, Albert S, Kaufmann P, Buchsbaum R, Gordon PH, et al. Development and evaluation of a self-administered version of the ALSFRS-R. Neurology. 2006; 67(7):1294–6. [PubMed: 17030772]
9. Maier A, Holm T, Wicks P, Steinfurth L, Linke P, Munch C, et al. Online assessment of ALS functional rating scale compares well to in-clinic evaluation: a prospective trial. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2012; 13(2):210–6.
10. Fries JF, Bruce B, Cella D. The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes. Clinical and experimental rheumatology. 2005; 23(5 Suppl 39):S53–7.
11. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. Journal of clinical epidemiology. 63(11):1179–94.
12. Stone AA, Broderick JE, Junghaenel DU, Schneider S, Schwartz JE. PROMIS Fatigue, Pain Intensity, Pain Interference, Pain Behavior, Physical Function, Depression, Anxiety, and Anger Scales Demonstrate Ecological Validity. Journal of clinical epidemiology. 2015
13. Oboler SK, Prochazka AV, Meyer TJ. Leg symptoms in outpatient veterans. The Western journal of medicine. 1991; 155(3):256–9. [PubMed: 1659038]
14. Weber M, Goldman B, Truniger S. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial. Journal of Neurology, Neurosurgery and Psychiatry. 2010; 81(10):1135–40.

15. Bedlack RS, Pastula DM, Hawes J, Heydt D. Open-label pilot trial of levetiracetam for cramps and spasticity in patients with motor neuron disease. Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2009; 10(4): 210–5.

16. El-Tawil S, Al Musa T, Valli H, Lunn MP, Brassington R, El-Tawil T, et al. Quinine for muscle cramps. Cochrane Database Syst Rev. 2015; 4:Cd005044.

17. Administration FaD. FDA orders unapproved quinine drugs from the market and cautions consumers about 'off-label' use of quinine to treat leg cramps. FDA. 2006

18. Weiss MD, Macklin EA, Simmons Z, Knox AS, Greenblatt DJ, Atassi N, et al. A randomized trial of mexiletine in ALS: Safety and effects on muscle cramps and progression. Neurology. 2016; 86(16):1474–81. [PubMed: 26911633]

19. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)–revised report of an EFNS task force. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2012; 19(3):360–75.

Table 1

Characteristics of study sample

Characteristic	Current Study Sample Percent or Mean (SD)	National ALS Registry(6)
Men	64%	62%
Age (years)	58 ± 10	56.5% in age group 50–69
Caucasian	92%	92.8
ALSFRS-R Total Score	30.3 ± 9.3	Not reported
Disease Duration (months)	52 ± 48 months	Not reported
First reported symptom of ALS		Not reported
Weakness	49%	
Cramps	20%	
Fasciculations	15%	
Slurred speech	14%	
Breathing problems	1.5%.	
Changes in your thinking	0.5%	

Table 2

PROMIS pain scores

	Min	Max	Mean	SD
Pain Intensity	30.7	71.8	45.8	8.7
Pain Interference	38.6	77.8	54.5	10.0
Pain Behavior	35.3	71.1	54.3	9.3

Table 3

Comparison of treatment groups on cramp and pain outcomes

	Cramp Frequency Mean ± SD	Cramp Severity Mean ± SD	Pain Intensity Mean ± SD	Pain Interference Mean ± SD	Pain Behavior Mean ± SD
No Treatment	3.3 ± 4.5	4.5 ± 2.6	43.1 ± 8.6	51.4 ± 9.9	51.1 ± 10.1
Only Over the Counter	3.8 ± 7.6	5.1 ± 2.8	46.0 ± 8.0	55.5 ± 8.0	56.3 ± 7.2
Prescription Medication	10.6 ± 18.6	6.2 ± 2.4	48.7 ± 8.1	57.2 ± 9.7	56.7 ± 7.9

Table 4

Medication usage and cramp frequency and severity ratings

Medication	**Frequency (N) *80 respondents reported treatments**	**Cramp Frequency Mean (SD)**	**Cramp Severity Mean (SD)**
Baclofen	12.2% (35)	17.3 (27.2)	6.3 (2.22)
Gabapentin	2% (7)	7.5 (8.4)	6.75 (2.5)
Mexiletine	2% (5)	3.0 (2.0)	6.7 (2.9)
Flexeril	1% (2)	12.5 (10.6)	6.0 (2.8)
Tizanidine	2% (5)	5.0 (7.0)	4.5 (5.0)
Opiates	1% (2)	12.5 (10.6)	8.0 (2.8)
Potassium and Magnesium	4% (11)	13.0 (33.0)	6.3 (2.5)
Quinine	4% (11)	4.6 (5.3)	5.4 (2.1)
Stretching	5% (13)	6.2 (7.7)	6.8 (1.6)
Multiple Medication using RX combinations of the list above	8% (24)	12.2 (17.9)	6.1 (2.2)