

Prevalence of Nocturnal Leg Cramps in Patients with Liver Disease is Higher than with Other Chronic Disease

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1. Abstract

1.1. Objective: A nocturnal leg cramps (NLC) is caused by a continuous, involuntary, painful, and localized contraction of a muscle or simply some muscle bundles. NLC is associated with a reduced quality of sleep and a subsequent lower health related quality of life. The purpose of our study is to clarify both prevalence and characteristics of NLC in patients with chronic diseases.

1.2. Methods: Three hundred and ninety-five patients with chronic disease were enrolled in our study. We simply asked "Did you experience the Nocturnal leg cramps in past a month?" to the patients. We examined the relation between the presence of NLC and the demographics and other baseline characteristics.

1.3. Results: One hundred and twenty-three patients (31.1%) experienced NLC in a past month. The multivariate analysis revealed that presence of \geq age50 (HR, 3.78; $P < 0.001$), Type 2 diabetes mellitus (HR, 2.19; $P < 0.001$), Hyper lipidemia (HR, 2.62; $P < 0.001$), Liver Cirrhosis (HR, 14.6; $P < 0.001$), and Chronic liver disease (HR, 2.70; $P < 0.001$) were independently associated with the prevalence of NLC.

1.4. Conclusion: Prevalence of NLC in patients with chronic disease was not low in primary care. Especially, prevalence of NLC in patients with liver disease was higher than with other chronic disease. When treating chronic diseases, we should consider NLC, and treat it.

2. Keywords: Chronic disease; Chronic pain; Cramps; Liver disease; Cirrhosis

3. Objective

A Nocturnal Leg Cramps (NLC) is caused by a continuous, involuntary, painful, and localized contraction of a muscle or simply some muscle bundles. NLC last a few seconds to a few minutes and ease spontaneously [1]. NLC is associated with a reduced quality of sleep and a subsequent lower health related quality of life. Stretching or contraction of the antagonist muscle usually speeds relief [2]. Most NLC occur during periods of rest, mainly during the night [3].

NLC are an overlooked but clinically meaningful event. Reports from a United States veteran outpatient clinic and a United Kingdom primary care setting indicate 37 to 56 % of patients are affected [4, 5]. Most studies to date were conducted more than 20 years ago, in hospital and/or specialized settings and were limited by small sample sizes. To our knowledge, no previous study has examined both prevalence and the main features of NLC in patients among the chronic diseases attending primary care units.

The purpose of our study is to clarify both prevalence and characteristics of NLC in patients with chronic diseases.

4. Methods

A single center, observational cross-sectional study was conducted in the Department of Internal medicine, Kainan municipal Medical Center between May 1st 2018 and July 31 2018. Sample size calculation was undertaken by methods [6]. The confidence level was set to 95% and confi-

dence interval was set to 5%. The population was set to 126,520,000 of Japan population. The sample size was calculated to be 385. Three hundred and ninety-five patients with chronic disease were enrolled in our study. We simply asked “Did you experience the Nocturnal leg cramps in past a month?” to the patients.

We examined the relation between the presence of NLC and the demographics and other baseline characteristics of 395 patients.

Our study was performed according to the Declaration of Helsinki and the clinical research guidelines in Japan. The study protocol was approved by the institutional review board of Kainan Municipal Medical Center. All patients agreed to cooperate in the chronic disease therapy. Written informed consent to participate in this study was not obtained from the patients because this study did not report on a clinical trial and the data were retrospective in nature and analyzed anonymously.

The analyses carried out in the 395 patients. The results shown are mean \pm standard deviation (SD) or number (%). Comparisons between groups were performed using Kruskal–Wallis test for categorical variables. To assess the relation factors with NLC, both univariate and multivariable analysis were performed. We used Fisher's Exact Test in the univariate analysis specifically, variables with $P < 0.05$ in univariate analysis were included in the multivariable models. We used a stepwise variable selection method logistic regression analysis method. The threshold for significance was $P < 0.05$. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [7].

5. Results

The demographics and other baseline characteristics of 395 patients are shown in (Table 1). The mean patient age was 67.3 years (SD, 15.6). One hundred and eighty-two patients (46.1%) were male. Chronic diseases that patients had were as follows; Type 2 diabetes mellitus (T2DM) (107, 27.1%), Hypertension (HT) (180, 45.6%), Hyperlipidemia (HL) (120, 30.4%), Malignancy (28, 7.1%), Liver Cirrhosis (LC) (25, 6.3%), Chronic Liver Disease (CLD) (156, 39.4%), Cerebral Vascular Disease (CVD) (23, 5.8%), Atrial Fibrillation (AF) (19, 4.8%), Chronic Heart Disease (CHD) (10, 2.5%), Thyroid Disease (15, 3.8%), Hyperuricemia (17, 4.3%), Inflammatory Bowel Disease (IBD) (12, 3.0%), Chronic pancreatitis (11, 2.8%), Collagen disease (21, 5.3%), Gastro-esophageal reflux disease (23, 5.8%) and Chronic Obstructive Pulmonary Disease (COPD) (21, 5.3%).

One hundred and twenty-three patients (31.1%) experienced NLC in a past month. No relation between prevalence of NLC and the distribution according to age were statistically significant ($P = 0.08$) (Figure 1). The NLC prevalence in demographics and individual chronic disease was as follows; male (55/182 30.0%), female (68/213, 31.9%), T2DM (51/107, 47.7%), HT (59/180, 32.8%), HL (56/120, 30.4%),

Malignancy (8/28, 28.6%), LC (19/25, 76.0%), CLD (60/156, 38.5%), CVD (7/23, 30.4%), AF (6/19, 31.6%), CHD (2/10, 20.0%), Thyroid disease (8/15, 53.3%), Hyperuricemia (4/17, 23.5%), IBD (2/12, 16.7%), Chronic pancreatitis (6/11, 54.5%), Collagen disease (9/21, 42.8%), Gastro-esophageal reflux disease (6/23, 26.1%) and COPD (5/21, 23.8%) (Table 2).

The multivariate analysis revealed that presence of \geq age50 (HR, 3.78; $P < 0.001$), T2DM (HR, 2.19; $P < 0.001$), HL (HR, 2.62; $P < 0.001$), LC (HR, 14.6; $P < 0.001$), and CLD (HR, 2.70; $P < 0.001$) were independently associated with the prevalence of NLC (Table 3).

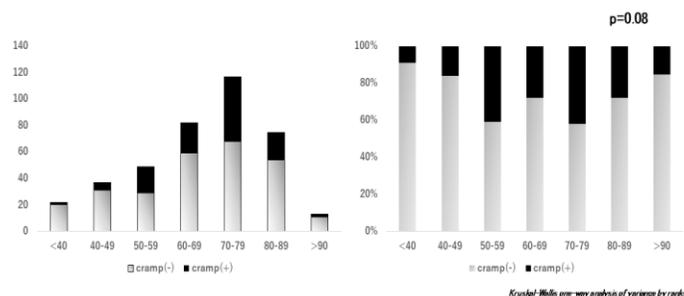


Figure 1: Total cramp prevalence and distribution according to age. No relation between prevalence of NLC and the distribution according to age were statistically significant.

Table 1: The demographics and other baseline characteristics of 395 patients

Number	395
Age, mean(SD)	67.3(15.6)
Male, n(%)	182(46.1)
Cramps, n(%)	123(31.1)
Type 2 diabetes mellitus, n	107(27.1)
Hypertension, n(%)	180(45.6)
Hyperlipidemia, n(%)	120(30.4)
Malignancy, n (%)	28(7.1)
Liver disease, n(%)	181(45.8)
Liver Cirrhosis, n(%)	25(6.3)
Chronic liver disease, n(%)	156(39.4)
Cerebral vascular disease, n(%)	23(5.8)
Atrial fibrillation n,(%)	19(4.8)
Chronic heart disease, n(%)	10(2.5)
Thyroid disease, n(%)	15(3.8)
Hyperuricemia, n(%)	17(4.3)
Inflammatory bowel disease, n(%)	12(3.0)
Chronic pancreatitis, n(%)	11(2.8)
Collagen disease, n(%)	21(5.3)
Gastro esophageal reflux disease, n(%)	23(5.8)
Chronic obstructive pulmonary disease, n(%)	21(5.3)

Table 2: Prevalence of nocturnal leg cramps in patients with chronic disease

Male, n (%)	55(30.0)
Female, n (%)	68(31.9)
Type 2 diabetes mellitus, n (%)	51(47.7)
Hypertension, n (%)	59(32.8)
Hyperlipidemia, n (%)	56(46.7)
Malignancy, n (%)	8(28.6)
Liver Cirrhosis, n (%)	19(76.0)
Chronic liver disease, n (%)	60(38.5)
Cerebral vascular disease, n (%)	7(30.4)
Atrial fibrillation, n(%)	6(31.6)
Chronic heart disease, n (%)	2(20.0)
Thyroid disease, n (%)	8(53.3)
Hyperuricemia, n (%)	4(23.5)
Inflammatory bowel disease, n (%)	2(16.7)
Chronic pancreatitis, n (%)	6(54.5)
Collagen disease, n (%)	9(42.8)
Gastro-esophageal reflux disease, n (%)	6(26.1)
Chronic obstructive pulmonary disease, n (%)	5(23.8)

Table 3: Multivariable analysis for prevalence of nocturnal leg cramps in patients with chronic disease (Cox proportional hazard model).

	Univariate analysis	Multivariate analysis	
	p-value	Odds Ratio(95%CI)	P-value
Age>=50	0.001	3.78(1.62-8.84)	p<0.001
Age>=60	0.182		
Age>=70	0.083		
Age>=75	1.00		
Age>=80	0.297		
male	0.744		
Type 2 diabetes mellitus	p<0.001	2.19(1.28-3.74)	p<0.001
Hypertension	0.586		
Hyperlipidemia	p<0.001	2.62(1.56-4.41)	p<0.001
Malignancy	0.835		
Liver Cirrhosis	p<0.001	14.6(5.29-40.5)	p<0.001
Chronic liver disease	0.0148	2.70(1.64-4.45)	p<0.001
Cerebral vascular disease	1.00		
Atrial fibrillation	1.00		
Chronic heart disease	0.731		
Thyroid disease	0.0845		
Hyperuricemia	0.6		
Inflammatory bowel disease	0.356		
Chronic pancreatitis	0.104		
Collagen disease	0.235		
Gastro-esophageal reflux disease	0.651		
Chronic obstructive pulmonary disease	0.629		

6. Discussion

In this study, we have shown that the prevalence of NLC in patients with various chronic diseases was not low, and presence of \geq age50, T2DM, HL, LC, and CLD were independently associated with the prevalence of NLC. Especially, prevalence of NLC in patients with liver disease was higher than with other chronic disease. To our

knowledge, this is the first study to demonstrate direct comparison of the prevalence of NLC in the population among various chronic disease.

Muscle cramps included NLC are involuntary, painful, sudden contractions of the skeletal muscles. They are present not only in normal subjects under certain conditions (during a strong voluntary contraction, sleep, sports, pregnancy) but also in several pathologies such as myopathies, neuropathies, motoneuron diseases, metabolic disorders, hydro electrolyte imbalances or endocrine pathologies. Reported a simple classification of muscle cramps as follows; Idiopathic cramps with nocturnal leg cramps, Para physiological cramps with pregnancy related cramps and exercise induced cramps, and Symptomatic cramps related to etiological factors such as medication or medical conditions [8]. In this study, our subjects included the group of “Symptomatic cramps related to etiological factors such as medication or medical conditions”.

Several reports showed although nocturnal cramps are idiopathic in most people, a large number of potential etiological factors. Medications that have been reported to cause leg cramps include diuretics, nifedipine, β -agonists, steroids, morphine, cimetidine, penicillamine, statins, and lithium [9-11]. In our study, HL was independently factor associated with the prevalence of NLC. On the other hand, all patients with HL took statins. Therefore, we might have shown the possibility that statins administration lead to this result.

There were some reports about the prevalence of nocturnal leg cramps in patients with individual chronic disease. Some medical conditions associated with muscle cramps include T2DM, thyroid disease, Cancer treatment, Cardiovascular disease, LC, End-stage renal disease and hemodialysis, Lumbar canal stenosis, Neurologic deficit, Osteoarthritis, Peripheral neuropathy, Peripheral vascular disease, Pregnancy, Venous insufficiency, hypocalcemia, and hypokalemia (4,12-17). Our finding showed the prevalence of NLC in T2DM, Thyroid disease, and LC. Our results met previous reports.

Aging might be the factor of the high prevalence factor of NLC. Reported prevalence of cramps in patients over the age of 60 in primary care. They showed that the adjusted prevalence was 46%, logistic regression revealed a slightly higher prevalence in the age group 65–69 years compared to 60–64 years, and no significant association was observed between other age groups and prevalence, or between gender and prevalence [18]. In our study, no relation between prevalence of NLC and the distribution according to age were statistically significant. Our results met previous reports.

Our study revealed that liver disease was the high prevalence factor of NLC in patients with various chronic diseases. Generally, the incidence of cramps in patients with cirrhosis is 22-88%. NLC of LC occurred during periods of rest, mainly during the night [19, 20]. I was reported muscle cramps in Japanese patients with CLD. They reported that 51.8% of patients with LC have experienced muscle

cramps, and patients who experienced muscle cramps were more likely to have reduced QOL and sleep disturbance. They revealed that Age, female sex, positive results for hepatitis C virus, low serum albumin concentration, and cirrhosis were independent factors related to the severity of muscle cramps in patients with CLD [21]. Our results met previous reports. However, we could not reveal independent factors related to the NLC, because number of LC patients was very small in our study, our study is associated with some limitation. First our study was a single center, observational cross-sectional study. Because data on each participant are recorded only once it would be difficult to infer the temporal association between a risk factor and an outcome. Therefore, only an association can be inferred, and not causation cannot be inferred from our study. Second, there was the possibility of sampling bias in a single center study. In future, we should perform a multi-center study.

7. Conclusion

Prevalence of NLC in patients with chronic disease was not low in primary care. Especially, prevalence of NLC in patients with liver disease was high these preliminary findings warrant validation and further exploration. When treating chronic diseases, we should consider NLC, and treat it.

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