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The association of serum carnitine levels with severity of fatigue in patients with multiple sclerosis: A pilot study

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Fatigue; Multiple Sclerosis; Carnitine; Expanded Disability Status Scale

Abstract

Background: Fatigue is a common complaint of patients with multiple sclerosis (MS), adversely affecting their quality of life. There is a lot of evidence showing that carnitine deficiency is linked to fatigue development and severity in some conditions. This study aimed to evaluate the association between free L-carnitine serum levels and the severity of fatigue in patients with MS.

Methods: This case-control study included 30 patients with relapsing-remitting MS (RRMS) in two age-matched equal-number groups according to the presence or absence of fatigue. Fatigue was scored using the valid questionnaire of Fatigue Severity Scale (FSS) and serum level of free L-carnitine was measured simultaneously. Finally, the association between serum level of free L-carnitine and fatigue severity was evaluated in patients with MS.

Results: The mean value of FSS in patients with fatigue was 48.80 ± 8.55, which was nearly two-fold higher than the group without fatigue. We found a significant correlation between the serum level of free L-carnitine and FSS and showed that the patients with fatigue had a significantly lower serum level of free L-carnitine compared to patients without fatigue ($P < 0.001$).

Conclusion: Present study demonstrated that patients with lower serum levels of free L-carnitine were more likely to experience fatigue. We recommend that a higher dietary intake of carnitine might be a useful complementary treatment for MS-related fatigue.

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Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disorder characterized by demyelination and inflammation in the central nervous system (CNS).[1] Fatigue is one of the most common debilitating symptoms of MS, affecting approximately two-thirds of patients throughout the disease course.[2-5] Although the pathophysiology of fatigue in MS has not been understood well, it is hypothesized that the involvement of both CNS and musculoskeletal components is responsible for developing this symptom.[6-8] The multifactorial and unknown nature of the mechanisms has complicated fatigue management in MS and necessitated further studies to find the exact pathophysiology and treatment.

It has been shown that the impaired control of energy metabolism in muscle cells predisposes individuals to develop fatigue.[9] L-carnitine is an endogenous amino acid derivative having a crucial role in the proper control of energy metabolism in the muscle system via appropriate transporting of fatty acids into muscle cells and subsequent beta-oxidation of them in mitochondria. It also helps remove the excess waste products of acetyl coenzyme A (CoA) accumulated due to the reduced adenosine triphosphate (ATP) synthesis in mitochondria.[10] Thus, L-carnitine seems to be a key element for proper functions of mitochondria, thereby helping to provide necessary ATP used for energy production and inhibiting fatigue development. These advantages are supported by some studies that have shown the association of serum carnitine deficiency with developing fatigue in several neurological and inflammatory disorders.[9,11]

Serum carnitine deficiency in patients with MS might be caused by disease-modifying therapies (DMTs),[12] probably explaining one of the culprits of fatigue in these patients. Moreover, despite controversial results, evidence has shown the benefit of L-carnitine supplementation for treating MS-related fatigue.[13,14] However, there are still doubts in this regard, so that in one study no difference has been found in serum carnitine levels between MS patients with and without fatigue.[15] Because of insufficient data on this issue, further studies are needed to clarify the association between serum L-carnitine deficiency and MS-related fatigue. Hence, considering the deteriorating impact of fatigue on the quality of life of patients with MS and mentioned role of carnitine in modulating energy homeostasis, the present study aimed to evaluate the contribution of serum L-carnitine level and fatigue severity among patients with MS.

Materials and Methods

Study design and patients: This pilot case-control study was performed at the MS clinic between January 2019 to July 2021. We included 30 patients with MS matched according to age and type of MS [all patients had relapsing-remitting MS (RRMS)] in two equal-number groups using fatigue score according to the cut-off value of 35 for Fatigue Severity Scale (FSS) (FSS < 35 as "without fatigue" and FSS ≥ 35 as "with fatigue").[16] For all patients, diagnosis of RRMS was confirmed based on the McDonald criteria.[17] Patients with MS with known anemia, vitamin D deficiency, a history of inflammatory diseases, other autoimmune diseases, and severe depression, and those being on antidepressant medication did not enter the study. We included patients in two groups similarly producing three age groups: 20-30 years old, 31-40 years old, and 41-50 years old.

The study protocol was in accordance with the principles of the Declaration of Helsinki and confirmed by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran. All individuals signed written informed consent.

Clinical and laboratory measurements: Data regarding demographics and body mass index (BMI) were registered and calculated. The severity of fatigue was assessed using the validated Persian version of FSS.[18,19] Disability progression of patients with MS was measured using the Expanded Disability Status Scale (EDSS).[20] Then a total of 5 ml fasting blood samples were collected from patients simultaneously.

The blood sample was centrifuged, and serum fractions were stored at -70 ^{o}C until the assay. The serum levels of free L-carnitine were measured for all participants using an enzyme-linked immunosorbent assay (ELISA) kit (Crystal Day Biotech Co., China) according to the instructions described by suppliers. The level of dietary carnitine was estimated according to data on the consumption of high carnitine foods using a three-day 24-hour dietary recall questionnaire.

Data analyses were performed via SPSS software (version 22, IBM Corporation, Armonk, NY, USA). First, Kolmogorov-Smirnoff test was used to determine the normality of data distribution. Continuous data with or without normal distribution were indicated as mean ±

standard deviation (SD) and median [interquartile range (IQR)] and then compared between study groups using an independent t-test or Mann-Whitney U test, respectively. Categorical variables were presented as frequency (percentage) and then compared using the chi-square test between study groups. Spearman correlation test was performed to evaluate the association between serum levels of free L-carnitine and fatigue severity. $P < 0.05$ was considered as the significant value.

Results

Table 1 shows the comparison of demographic, clinical, and laboratory data between MS patients with and without fatigue. The mean value of FSS in patients with fatigue was 48.80 ± 8.55, which was nearly two-fold higher than those without fatigue. We found no significant differences in age groups, sex, BMI, EDSS, and dietary intake of carnitine between MS patients with and without fatigue ($P \geq 0.05$). There was a considerable correlation between the serum levels of free L-carnitine and FSS (Spearman rank correlation = 0.76, $P < 0.001$). Therefore, the patients with fatigue had significantly lower serum values of free L-carnitine compared to patients without fatigue (22.53 ± 15.84 vs. 75.36 ± 51.98, $P < 0.001$).

Discussion

We found a significant correlation between serum levels of free L-carnitine and the severity of MS-related fatigue, and demonstrated that MS patients with fatigue had lower serum levels of free L-carnitine compared to patients without fatigue.

As we stated, fatigue is the most common complaint of patients with MS, affecting different aspects of their quality of life. Although the underlying pathophysiological mechanisms have not been entirely cleared, some candidates, including immune dysregulation, CNS dysfunctions, endocrine factors, psychological factors, behavioral habits, and medications seem to be the main culprits of developing fatigue in these patients.[21] Evidence shows that carnitine deficiency, because of either reduced dietary intake or defective endogenous synthesis, makes healthy individuals or patients with some known diseases highly susceptible to experience of fatigue, probably due to the vital role of carnitine as a cofactor in mitochondrial energy metabolism.[9,11,14,22,23] To our knowledge, only one case-control study by Fukazawa et al.[15] has evaluated the link between serum carnitine levels and fatigue severity in patients with MS. They found no significant difference in serum carnitine levels between MS patients with and without fatigue. However, this study has not evaluated the confounding effects of dietary carnitine intake between groups. With this important limitation and lack of enough relevant studies, we decided to investigate this hypothesis more clearly. The different point in the present study was that there was no significant differences between groups in dietary intake of carnitine and adiposity, indicated by BMI. Therefore, contrary to the Fukazawa et al. study, we found a significant inverse correlation between the serum carnitine levels and fatigue severity.

Table 1. The comparison of demographic, clinical, and laboratory data between patients with multiple sclerosis (MS) with fatigue and without fatigue

Variables	RRMS patient groups		P
	Without fatigue (n = 15)	With fatigue (n = 15)	
Age* (year) (mean ± SD)	34.53 ± 8.33	33.73 ± 7.61	0.790
Age range (year) [n (%)]			0.690
20-30	4 (26.66)	6 (40.0)	
31-40	7 (46.66)	5 (33.33)	
41-50	4 (26.66)	4 (26.66)	
Sex [n (%)]			0.360
Men	6 (40.0)	8 (53.33)	
Women	9 (60.0)	7 (46.66)	
BMI* (kg/m^2) (mean ± SD)	25.07 ± 1.66	25.75 ± 2.55	0.400
Serum carnitine level# (mg/dl) (mean ± SD)	75.36 ± 51.98	22.53 ± 15.84	< 0.001
Dietary carnitine# (mean ± SD)	230.55 ± 88.38	213.48 ± 33.67	0.940
EDSS* [median (IQR)]	3 (1-5)	3 (1-6)	0.990

The Fatigue Severity Scale (FSS) ≥ 35 was considered as the considerable fatigue

*Normally distributed continuous variables compared using independent t-test; #Non-normally distributed continuous variables compared using the Mann-Whitney U test; categorical variables were compared using the chi-square test

RRMS: Relapsing-remitting multiple sclerosis; BMI: Body mass index; EDSS: Expanded Disability Status Scale; SD: Standard deviation; IQR: Interquartile range

Considering the similar amount of dietary carnitine intake between study groups, the carnitine deficiency might be caused by impaired endogenous production due to MS pathophysiology. Thus, the exact pathophysiology of that should be considered in future studies and the augmentation of carnitine may provide insight into the treatment of fatigue in patients with MS.

Some specific non-pharmacological and pharmacological treatments are used in MS cases with fatigue. Amantadine and modafinil are the mostly used medications for MS-related fatigue. Few studies have shown L-carnitine supplementation's beneficial effects for reducing fatigue among patients with MS. A double-blind crossover study showed the advantage of L-carnitine over amantadine for treating fatigue in patients with MS.[13] Another study of patients with MS found that L-carnitine was partially effective for fatigue compared to placebo, but the effect size was not more than that seen with amantadine treatment.[24] A recent meta-analysis has evaluated the existing evidence and clarified that the beneficial effect of L-carnitine supplementation for MS-related fatigue was similar to that seen with amantadine.[14] These results further support our finding, suggesting that carnitine deficiency might be responsible for developing fatigue in these patients.

Our study had some strengths and limitations. One of our research strengths is the case-control study design, which boosts the comparability of the findings. However, because of the nature of an observational study, we could not discover the causal role of serum carnitine deficiency in the development of MS-related fatigue. Another strength of our study is a partially novel perspective, in which we focused on the link between serum carnitine levels and fatigue severity in patients with MS. Our findings show that serum carnitine deficiency may play an important role in the physiopathology of MS-related fatigue. The main limitation of our study is that we did not investigate different etiologies of carnitine deficiency in the participants.

Conclusion

We showed that MS patients with fatigue had lower serum carnitine levels than those without fatigue. It suggests that MS patients with lower serum carnitine levels might experience more severe fatigue. This study also recommends that a higher dietary intake of carnitine might be an effective complementary treatment for fatigue in patients with MS.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

1. Weinshenker BG. The natural history of multiple sclerosis. Neurol Clin 1995; 13(1): 119-46.
2. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996; 9(6): 456-60.
3. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988; 45(4): 435-7.
4. Flachenecker P, Meissner H. Fatigue in multiple sclerosis presenting as acute relapse: Subjective and objective assessment. Mult Scler 2008; 14(2): 274-7.
5. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: Mechanisms, evaluation, and treatment. Sleep 2010; 33(8): 1061-7.
6. Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: The impact of fatigue and depression. J Neurol Sci 2002; 205(1): 51-8.
7. Kent-Braun JA, Sharma KR, Miller RG, Weiner MW. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. Muscle Nerve 1994; 17(8): 835-41.
8. Kent-Braun JA, Sharma KR, Weiner MW, Miller RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. Muscle Nerve 1994; 17(10): 1162-9.
9. Cruciani RA, Dvorkin E, Homel P, Malamud S, Culliney B, Lapin J, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: A phase I/II study. J Pain Symptom Manage 2006; 32(6): 551-9.
10. Reuter SE, Evans AM. Carnitine and acylcarnitines: pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 2012; 51(9): 553-72.
11. Anty R, Marjoux S, Bekri S, DeGalleani L, Dainese R, Gelsi E, et al. Plasma carnitine is associated with fatigue in chronic hepatitis C but not in the irritable bowel syndrome. Aliment Pharmacol Ther 2011; 33(8): 961-8.
12. Lebrun C, Alchaar H, Candito M, Bourg V, Chatel M. Levocarnitine administration in multiple sclerosis patients with immunosuppressive therapy-induced fatigue. Mult Scler 2006; 12(3): 321-4.
13. Tomassini V, Pozzilli C, Onesti E, Pasqualetti P, Marinelli F, Pisani A, et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci 2004; 218(1-2): 103-8.
14. Yang TT, Wang L, Deng XY, Yu G. Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. J Neurol Sci 2017; 380: 256-61.
15. Fukazawa T, Sasaki H, Kikuchi S, Hamada T, Tashiro K. Serum carnitine and disabling fatigue in multiple sclerosis. Psychiatry Clin Neurosci 1996; 50(6): 323-5.

16. Kos D, Nagels G, D'Hooghe MB, Duportail M, Kerckhofs E. A rapid screening tool for fatigue impact in multiple sclerosis. BMC Neurol 2006; 6: 27.
17. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17(2): 162-73.
18. Harirchian MH, Nasergivechi S, Maddah M, Meysamie A, Amini H, Shandiz EE, et al. Evaluation of the Persian version of modified fatigue impact scale in Iranian patients with multiple sclerosis. Iran J Neurol 2013; 12(1): 32-4.
19. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46(10): 1121-3.
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33(11): 1444-52.
21. MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. Phys Med Rehabil Clin N Am 2005; 16(2): 483-502.
22. Okubo H, Ando H, Ishizuka K, Kitagawa R, Okubo S, Saito H, et al. Carnitine insufficiency is associated with fatigue during lenvatinib treatment in patients with hepatocellular carcinoma. PLoS One 2020; 15(3): e0229772.
23. Hockenberry MJ, Hooke MC, Gregurich M, McCarthy K. Carnitine plasma levels and fatigue in children/adolescents receiving cisplatin, ifosfamide, or doxorubicin. J Pediatr Hematol Oncol 2009; 31(9): 664-9.
24. Ledinek AH, Sajko MC, Rot U. Evaluating the effects of amantadin, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis--result of a pilot randomized, blind study. Clin Neurol Neurosurg 2013; 115(Suppl 1)s: S86-S89.