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Fatigue Syndrome, Depression and the Quality of Life in Patients with Multiple Sclerosis

Zespół zmęczenia, depresja oraz jakość życia u pacjentów ze stwardnieniem rozsianym

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Abstract

Introduction. Multiple sclerosis is a chronic disease of central nervous system of autoimmune origin, in which next to an increased physical disability, neuropsychological disorders exist, that lead to significant decrease in patients' quality of life.

Aim. The aim of the study was the assessment of prevalence of fatigue syndrome and depression in patients with multiple sclerosis and their influence on functioning in physical, cognitive and psychosocial dimension as well as on the quality of life.

Materials and Methods. 62 patients (37 females and 25 males) with relapsing-remitting subtype of multiple sclerosis and 15 patients with sciatica (9 females and 6 males) as the reference group were included in the study. Prevalence of fatigue syndrome and depression, as well as patients' quality of life were assessed with use of Modified Fatigue Impact Scale (MFIS), Beck Depression Inventory (BDI) and a standardized instrument for use as a measure of health outcome EQ-5D.

Results. Fatigue of moderate intensity was noticed in 45.16% (n=28) of patients with relapsing-remitting subtype of MS, when depression was apparent in 51.61% of patients (n=32), including mild depressive disorders in 33.8% of patients (n=21), moderate in 11.29% of patients and severe in 6.45% (n=4). The obtained results did not reach statistical significance when compared to results obtained in the reference group. Statistically significant dependence between the intensity of depression and influence of fatigue on functioning in psychosocial dimension was mainly observed in the group of patients with multiple sclerosis.

Conclusions. Fatigue syndrome and depression occur in significant part of patients with relapsing-remitting subtype of multiple sclerosis, disturbing their functioning in psychosocial dimension and considerably decreasing their quality of life. Increase in fatigue in general dimension has a significantly positive correlation with exacerbation of depression in the group of patients with relapsing-remitting subtype of multiple sclerosis. (JNPN 2017;6(2):81–87)

Key Words: multiple sclerosis, depression, fatigue syndrome, quality of life

Streszczenie

Wstęp. Stwardnienie rozsiane jest przewlekłą chorobą ośrodkowego układu nerwowego o podłożu autoimmunologicznym, w której obok narastającej niesprawności fizycznej występują zaburzenia neuropsychologiczne, prowadzące do znacznego obniżenia jakości życia pacjentów.

Cel. Celem badania była ocena częstości występowania zespołu zmęczenia i depresji u pacjentów ze stwardnieniem rozsianym oraz ich wpływ na funkcjonowanie w obszarze fizycznym, poznawczym i psychospołecznym oraz na jakość życia.

Materiał i metody. W badaniu wzięło udział 62 pacjentów (37 kobiet i 25 mężczyzn) z remitująco-rzutową postacią stwardnienia rozsianego oraz 15 pacjentów (9 kobiet i 6 mężczyzn) z rwą kulszową, którzy stanowili grupę referencyjną. Częstość występowania zespołu zmęczenia, depresji i jakość życia pacjentów oceniano za pomocą zmodyfikowanej Skali Wpływu Zmęczenia, Skali Depresji Becka oraz Kwestionariusza Dotyczącego Zdrowia EQ-5D.

Wyniki. U pacjentów z remitująco-rzutową postacią stwardnienia rozsianego zmęczenie o średnim nasileniu wykazano u 45,16% (n=28), natomiast depresję u 51,61% chorych (n=32), w tym łagodne zaburzenia depresyjne u 33,87%

chorych (n=21), umiarkowane u 11,29% pacjentów (n=7), a nasilone u 6,45% (n=4). Uzyskane wyniki nie różniły się istotnie statystycznie od wyników uzyskanych w grupie referencyjnej. W grupie chorych na stwardnienie rozsiane stwierdzono istotną statystycznie zależność nasilenia depresji od wpływu zmęczenia na funkcjonowanie, głównie w wymiarze psychospołecznym.

Wnioski. Zespół zmęczenia i depresja występują u znaczącej części chorych na postać remitująco-rzutową stwardnienia rozsianego, zaburzając funkcjonowanie chorych w wymiarze psychospołecznym i istotnie obniżając ich jakość życia. Nasilenie zmęczenia w wymiarze ogólnym w grupie chorych na postać remitująco-rzutową SM istotnie dodatnio koreluje z nasileniem depresji. (PNN 2017;6(2):81–87)

Słowa kluczowe: stwardnienie rozsiane, depresja, zespół zmęczenia, jakość życia

Introduction

Multiple sclerosis (MS) is a chronic disease of central nervous system (CNS), for which an underlying reason is the autoimmune response, in which apart from increasing physical disability there often occur neuropsychological disorders, such as fatigue syndrome and depression, which significantly decrease patients' quality of life [1].

Chronic fatigue syndrome, which is characterized by feeling tiredness inadequate to performed activities, also being intensified by heat, stress and physical activity is found in 70 to 95% patients with MS [2,3]. In MS we distinguish central fatigue that is a feeling of weariness due to demyelination in central nervous system and peripheral fatigue that is muscle fatigue caused by neuromuscular transmission disorder [4]. Fatigue can also be categorized as primary, resulting from pathophysiology of the disease and secondary, as an effect of sleep disorder, pain, stress, depression or other concomitant diseases [5,6]. Fatigue affects three areas of functioning: physical, psychosocial and cognitive [7].

Depression was diagnosed in 25.7 to 54% patients with MS [8]. It can be caused by primary pathology as well as be the result of patient's reaction to the disease related factors, such as pain, progressing disability, difficult life situation, tiredness and cognitive dysfunctions [5,9].

A significant decrease in the quality of life is observed in MS patients, especially directly after the diagnosis has been made, in patients with progressive forms of the disease, the elderly, in patients with concomitant

cognitive or emotional disorders, fatigue syndrome, and in those with higher degree of disability measured in EDSS [10,11]. Also, such factors as the patient's age, personality traits, applied strategies of coping with stress, sleep disorders, socioeconomic status and current treatment influence patient's quality of life as well [10].

There are numerous reports concerning the occurrence of fatigue and emotional disorders in MS. So far as there has been a general agreement in the literature on the influence of fatigue and depression on the welfare of patients with MS, there has been however some ambiguity in the data concerning mutual affiliation of fatigue and depression in this group of patients.

The prevalence of fatigue syndrome and depression in the group of patients with relapsing-remitting subtype of MS was analyzed in our study, as well as their influence on patient's functioning in physical, cognitive, psychosocial area and on the quality of life.

Material and Methods

62 patients (37 females and 25 males) hospitalized in Department of Neurology of The Medical University of Białystok with relapsing-remitting subtype of multiple sclerosis and 15 patients with sciatica (9 females and 6 males) as reference group were included in the study (Table 1). The study was approved by The Medical University of Białystok Ethics Committee for Research

Table 1. Characteristics of examined group

	Females			Males			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age									
Multiple sclerosis	37	37.81	11.163	25	35.16	9.534	62	36.74	10.536
Age									
Reference group	9	44.89	9.493	6	45	7.563	15	44.93	8.481
Duration of the disease									
Multiple sclerosis	37	7.16	5.346	25	7.16	4.776	62	7.16	5.084
EDSS									
Multiple sclerosis	37	2.31	1.506	25	2.06	1.557	62	2.21	1.519

n — number of patients; EDSS — Expanded Disability Status Scale

on Humans and Animals (R-I-002/325/2012) and written consent was obtained from all subjects.

Assessment of Occurrence of Fatigue and its Influence on Functioning

Patients from the examined and reference groups were assessed towards occurrence of fatigue and its influence on functioning in physical, cognitive and psychosocial area with the use of Modified Fatigue Impact Scale (MFIS). On the foregoing scale the patient could obtain a number of points ranging from 0 to 84. The growing number of points indicated greater influence of fatigue on the patient's functioning and the quality of life [12].

Assessment of the Occurrence and Intensity of Depression

The occurrence and intensity of depressive disorders were assessed with the use of Beck Depression Inventory (BDI). The maximum score possible to obtain is 63 points. Scores from 0 to 9 points mean lack of depression, scores from 10 to 19 — mild form of depression, scores 20–25 — moderate depression, 26–63 — severe depression [13].

The Assessment of Quality of Life

The quality of life of the examined patients was assessed with the use of Health Questionnaire EQ-5D, which consisted of two parts: descriptive system EQ-5D and visual analogue scale EQ-VAS. EQ-5D system scores five dimensions of everyday life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression discerning 3 levels of severity: absence of problem (1), moderate problem (2), extreme problem (3). Descriptive index EQ-5D can range from 0.0523 (standing for the lowest quality of life) to 1.0 (standing for the highest quality of life). EQ-VAS is a visual scale of the quality of life, which is pictured as 20-cm long, vertical line, dissected with numerical values ranging from 0 to 100. Respondents evaluated their health condition by marking corresponding value on the line. 0 meaning the poorest health condition, whereas 100 meaning the best health condition possible [10].

Statistical Analysis

The results were analyzed statistically using the Shapiro–Wilk, the Mann–Whitney, the Fisher, the Fisher–Freeman–Halton, IBM® SPSS® Statistics 20.0 tests and the Spearman correlation. A p-value <0.05 was considered statistically significant.

Results

Assessment of the Occurrence of Fatigue and its Intensity in the Group of Patients with Relapsing-remitting Subtype of Multiple Sclerosis

We noted slightly higher level of influence of fatigue on general functioning in the group of patients with relapsing-remitting MS in comparison with the reference group, however the differences were not statistically significant (Figure 1). 28 patients (45.16%) with relapsing-remitting subtype of MS showed moderate influence of fatigue on functioning in physical dimension, 9.1% of the examined patients admitted the influence was strong. The results did not reach the statistical significance level, when compared to the results obtained in the reference group. The increased influence of fatigue on cognitive functioning was higher in the group of patients with RRMS comparing to the reference group,

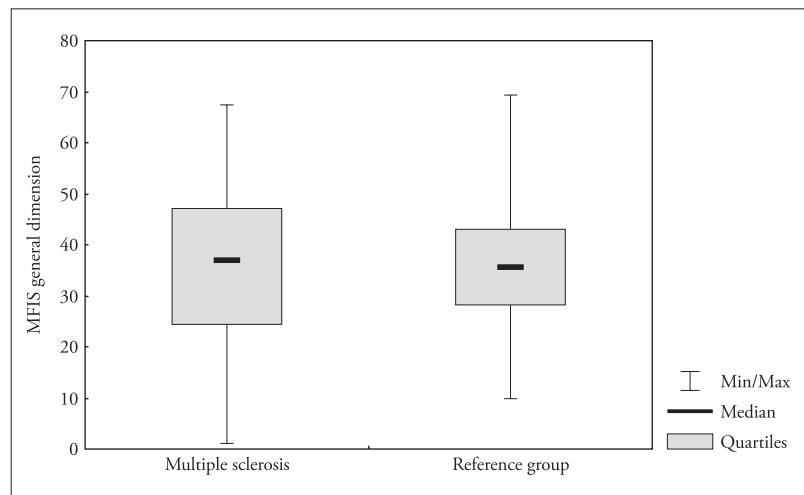


Figure 1. Comparison of dispersion of the Modified Fatigue Impact Scale in reference to general dimension in the group of patients with relapsing-remitting subtype of multiple sclerosis and in the reference group

however the differences were not statistically significant. The influence of fatigue on functioning in psychosocial dimension in both groups was very similar, although the values scored in the reference group were slightly higher.

The Assessment of the Occurrence of Depression and its Intensity in the Group of Patients with Relapsing-remitting Subtype of Multiple Sclerosis

The occurrence of depression was shown in 51.61% of patients (n=32) with relapsing-remitting subtype of MS, including mild disorders in 33.87% of patients (n=21), moderate in 11.29% (n=7) and severe in 6.45% (n=4) respectively. No statistically significant differences were noted in comparison with the reference group, in which mild depression appeared in 40% of patients (n=6) (Figure 2).

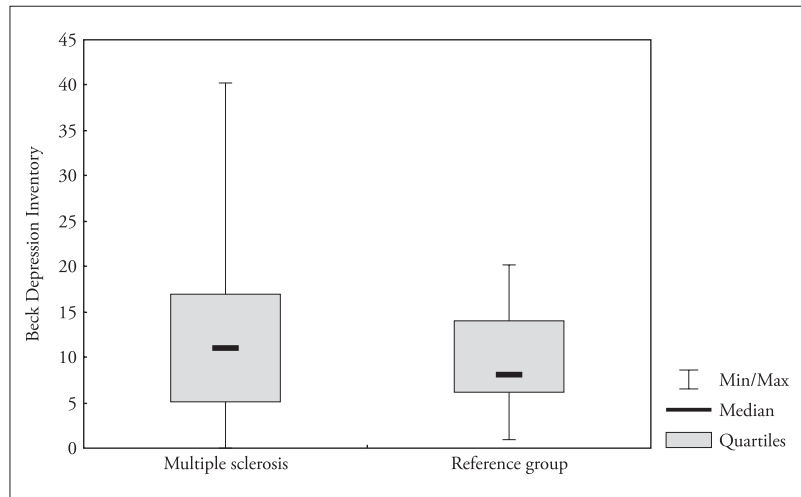


Figure 2. Comparison of dispersion of depression index measured by Beck Depression Inventory in the group of patients with relapsing-remitting subtype of multiple sclerosis and in the reference group

The Assessment of the Quality of Life in the Group of Patients with Relapsing-remitting Multiple Sclerosis

No statistically significant differences were shown between the surveyed group and the reference group in the self-assessment of quality of life with the use of visual, analogue scale EQ-VAS (Figure 3). Statistically significant percentage of patients with RRMS reported difficulties in self-care compared to the reference group ($p=0.003$). Higher proportion of patients with RRMS reported problems concerning anxiety and mood disorders, but differences between groups did not show statistical significance ($p=0.129$). Patients from the reference group reported more problems, than the examined group in the following areas: mobility, everyday activity and pain/discomfort, nevertheless differences between those two groups did not achieve the assumed level of significance ($p=0.249$; $p=0.216$; $p=0.180$).

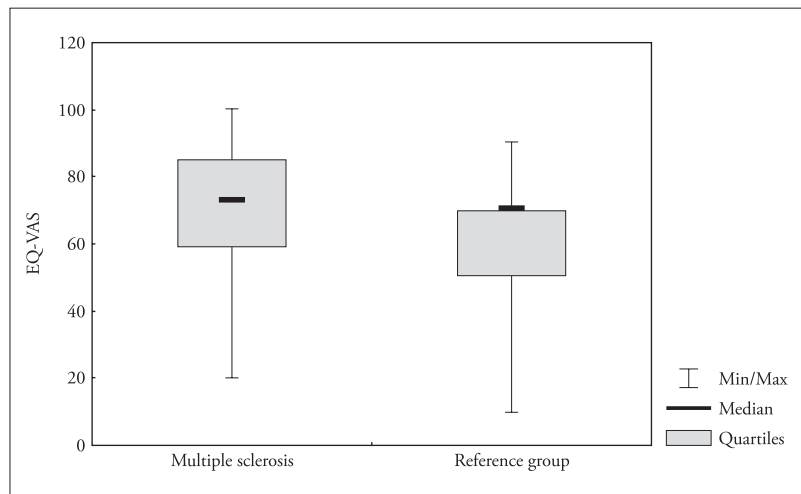


Figure 3. Comparison of dispersion of the quality of life index on visual, analogue scale EQ-VAS in the group of patients with relapsing-remitting subtype of multiple sclerosis and in the reference group

Correlation Between the Intensity of Influence of Fatigue and the Level of Disability in the Group of Patients with Relapsing-remitting Subtype of Multiple Sclerosis

A significant positive correlation between the level of influence of fatigue on functioning in general dimension and the level of disability measured in EDSS was obtained in patients with RRMS ($p=0.050$). Such a correlation was proven to exist also in the case of functioning in physical dimension ($p=0.024$), but no such correlation was found between functioning in cognitive dimension and the level of physical disability

measured in EDSS ($p=0.299$). A significant positive correlation between the level of influence of fatigue on functioning in psychosocial dimension and the level of disability measured in EDSS was observed in patients with RRMS ($p=0.014$).

Correlation Between the Intensity of the Influence of Fatigue and Duration of the Disease in the Group of Patients with Relapsing-remitting Subtype of Multiple Sclerosis

No significant correlation between the duration of the disease and intensity of influence of fatigue on functioning in physical ($p=0.807$), cognitive ($p=0.832$), psychosocial ($p=0.288$) and general ($p=0.970$) dimension was found in the group of patients with relapsing-remitting multiple sclerosis.

Correlation Between the Intensity of Depression and Influence of Fatigue on Functioning in the Group of Patients with Relapsing-remitting Subtype of Multiple Sclerosis

A strong positive correlation between the intensity of fatigue and the intensity of depression was found in the group of patients with RRMS ($p=0.000$). Statistically significant dependence of the intensity of depression upon the influence of fatigue in physical ($p=0.000$), cognitive ($p=0.000$) and psychosocial ($p=0.000$) dimension was shown in the group of patients with RRMS (Table 2).

Table 2. Correlation between depression and the intensity of influence of fatigue on functioning in the group of patients with relapsing-remitting subtype of multiple sclerosis

	R	p
MFIS physical dimension	0.48	0.000
MFIS cognitive dimension	0.59	0.000
MFIS psychosocial dimension	0.44	0.000
MFIS general dimension	0.56	0.000

MFIS — Modified Fatigue Impact Scale; R — Spearman's Correlation Coefficient; p — results of Correlation Coefficient test

Correlation Between the Intensity of the Influence of Fatigue on Functioning and the Quality of Life Measured in EQ-5D and EQ-VAS in the group of patients with relapsing-remitting multiple sclerosis

The increase of the influence of fatigue on functioning in general dimension, physical, cognitive and psychosocial dimension has negative correlation with the quality of life measured in EQ-5D ($p=0.000$) and EQ-VAS.

Discussion

In the study 45.16% of patients with relapsing-remitting MS obtained results in MFIS indicating moderate level of influence of fatigue on general functioning, and 9.1% of the examined patients reported considerable influence of fatigue on general functioning. The obtained results could suggest lower index of occurrence of fatigue in patients with multiple sclerosis than stated in literature [2]. However, it needs to be emphasised, that solely moderate and higher levels of the intensity of fatigue were taken into account in the conducted study, and only when the influence of fatigue on functioning existed in at least one dimension.

As the conducted research showed, the differences between the group of patients with RRMS and the patients with sciatica in relation to the occurrence and

intensity of influence of fatigue on functioning in physical, cognitive and psychosocial dimension were not relevant, as well as it comes to the occurrence and intensity of depression. The presence of fatigue in other neurological diseases, particularly those of chronic character was also indicated by Bol et al. [14]. Biological factors involvement e.g. temperature, as well as psychological, including personality traits, the ways of coping with everyday activities and the presence of depression are emphasized in the development of fatigue syndrome [15]. Currently the existence of fatigue syndrome in MS is connected with the effect of pro inflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 12 (IL-12) and interleukin 17 (IL-17) on the central nervous system. It has been proved that administration of IL-6, which is capable of crossing blood-brain barrier, elicits the fatigue in healthy volunteers [16]. Patients with autoimmune diseases, such as lupus erythematosus and rheumatoid arthritis, who were treated with IL-6-blocking substances, reported significant decrease in fatigue [15]. A positive effect of immunomodulatory treatment on decreasing the symptoms of fatigue syndrome in patients with MS was shown as well [17].

Statistically significant correlation between fatigue and depression was noted in the group of patients with relapsing-remitting MS, as opposed to the patients with sciatica. Therefore, it seems that different pathomechanisms are responsible for fatigue and depression in both analyzed groups. Concomitance of fatigue and depression in the group of patients with RRMS can be an effect of primary pathology of the central nervous system, as well as the result of patient's reaction to the disease related factors, such as chronic course, pain, progressing disability, difficult life situation, weariness and cognitive dysfunction [5]. In the case of patients with sciatica, fatigue and depression should be mainly considered secondary to several factors e.g. pain, stress, use of medication, ways of coping with the disease and personality traits [14]. Fatigue and depression in these patients could be perceived as a failure of strategy of coping with the situation of long-term disease, which is accompanied by pain that degrades functioning in family, as well as social and professional life. This view is supported by statistically significant influence of fatigue on functioning in physical and psychosocial dimension noted in the reference group, with its absence on functioning in cognitive dimension at the same time.

A significant correlation between the occurrence of fatigue syndrome and depression was shown in the group of patients with RRMS in the conducted research. The concomitance of the above was also noted by Pittion-Vouyovitch et al. in patients with RRMS, which can suggest their mutual pathomechanism [18]. It is

concluded from the literature that the etiopathogenesis of fatigue as well as the depression in multiple sclerosis is not fully recognized. Multifactorial view, that takes into consideration biological, disease-related, behavioral and psychosocial factors is postulated in pathophysiology of both of the aforementioned factors [18]. This approach can explain the concomitance of fatigue and depression in the course of MS observed in research studies, which was also shown in the conducted study in relation to patients with relapsing-remitting subtype of MS. The lack of significant mutual dependence between fatigue and depression in the reference group seems to indicate the necessity of searching for separate mechanisms leading to its occurrence in patients with chronic sciatica.

Works of numerous authors indicate univocally the fact, that MS significantly lowers patients' quality of life [10]. Significant influence of fatigue on diminishing the quality of life and well-being of patients with RRMS, in physical, cognitive and psychosocial dimension was shown in the conducted research, which is also confirmed by literature data [19]. Among factors that affect the assessment of the quality of life by patients with MS are accentuated by the following: depressive disorders, cognitive ability, subtype of the disease (relapsing-remitting MS, primary progressive MS and secondary progressive MS), age, employment or the lack of it, functional mobility, receiving or not immunomodulatory or immunosuppressive treatment [20].

Despite the progress in medicine and implementation of immunomodulatory treatment, multiple sclerosis is still the disease of unfavorable prognosis. Fatigue syndrome and depression as well as physical disability influence the decrease in patients' quality of life. Searching for main components of potential lowering of the quality of life and correlations between them seems to be of considerable importance. Appropriate diagnostics and early detection of difficulties in the aforementioned areas of functioning, might provide good background for the implementation of pharmacological treatment, psychotherapy and cognitive therapy.

Conclusions

1. Fatigue syndrome and depression coexist in significant part of patients with relapsing-remitting multiple sclerosis.
2. Increase in fatigue in general dimension has significant positive correlation with exacerbation of depression in the group of patients with relapsing-remitting subtype of multiple sclerosis.
3. Fatigue syndrome significantly disturbs functioning of patients with relapsing-remitting multiple sclerosis in psychosocial dimension and is a relevant factor decreasing patients' quality of life.

Implications for Nursing Practice

Depression and fatigue are neuropsychological symptoms, most commonly reported by patients with multiple sclerosis, and their presence significantly influences the decrease in patient's quality of life. Comprehensive approach in care over patient is recommended for nursery staff, including education of patients and their families on fatigue-increasing factors, teaching methods of coping with fatigue, stress and depression, introduction of relaxation techniques and physical exercises.

References

- [1] Alajbegovic A., Loga N., Tiro N., Alajbegovic S., Todorovic L., Jasminika-Djelilovic. Depression in multiple sclerosis patients. *Med Arh.* 2011;65(2):115–118.
- [2] Béthoux F. Fatigue and multiple sclerosis. *Ann Readapt Med Phys.* 2006;49(6):265–271, 355–360.
- [3] Dworzańska E., Mitosek-Szewczyk K., Stelmasiak Z. [Fatigue in multiple sclerosis]. *Neurol Neurochir Pol.* 2009;43(1):71–76.
- [4] Kasatkin D.S., Spirin N.N. Possible mechanisms of the formation of chronic fatigue syndrome in the clinical picture of multiple sclerosis. *Neurosci Behav Physiol.* 2007;37(3):215–219.
- [5] Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler.* 2003; 9(3):219–227.
- [6] Braley T.J., Chervin R.D. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep.* 2010; 33(8):1061–1067.
- [7] Berard J.A., Bowman M., Atkins H.L., Freedman M.S., Walker L.A. Cognitive fatigue in individuals with multiple sclerosis undergoing immunoablative therapy and hematopoietic stem cell transplantation. *J Neurol Sci.* 2014;336(1–2):132–137.
- [8] Ferreira M.L. Cognitive deficits in multiple sclerosis: a systematic review. *Arq Neuropsiquiatr.* 2010;68(4): 632–641.
- [9] Arnett P.A., Higginson C.I., Voss W.D., Randolph J.J., Grandey A.A. Relationship between coping, cognitive dysfunction and depression in multiple sclerosis. *Clin Neuropsychol.* 2002;16(3):341–355.
- [10] Mitosek-Szewczyk K., Kułakowska A., Bartosik-Psujek H., Hożejowski R., Drozdowski W., Stelmasiak Z. Quality of life in Polish patients with multiple sclerosis. *Adv Med Sci.* 2014;59(1):34–38.
- [11] Wynia K., van Wijlen A.T., Middel B., Reijneveld S.A., Meilof J.F. Change in disability profile and quality of life in multiple sclerosis patients: a five-year longitudinal study using the Multiple Sclerosis Impact Profile (MSIP). *Mult Scler.* 2012;18(5):654–661.
- [12] Fisk J.D., Ritvo P.G., Ross L., Haase D.A., Marrie T.J., Schleich W.F. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis.* 1994;18(Suppl. 1):S79–83.

- [13] Steer R.A., Cavalieri T.A., Leonard D.M., Beck A.T. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiatry*. 1999;21(2):106–111.
- [14] Bol Y., Duits A.A., Hupperts R.M., Vlaeyen J.W., Verhey F.R. The psychology of fatigue in patients with multiple sclerosis: a review. *J Psychosom Res*. 2009;66(1):3–11.
- [15] Norheim K.B., Jonsson G., Omdal R. Biological mechanisms of chronic fatigue. *Rheumatology (Oxford)*. 2011;50(6):1009–1018.
- [16] Späth-Schwalbe E., Hansen K., Schmidt F. et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab*. 1998;83(5):1573–1579.
- [17] Ziemssen T. Multiple sclerosis beyond EDSS: depression and fatigue. *J Neurol Sci*. 2009;277(Suppl. 1):S37–41.
- [18] Pittion-Vouyovitch S., Debouverie M., Guillemin F., Vandenberghe N., Anxionnat R., Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *J Neurol Sci*. 2006;243(1–2):39–45.
- [19] Salehpoor G., Rezaei S., Hosseini-zhad M. Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran. *Iran J Nurs Midwifery Res*. 2014;19(6):593–599.
- [20] Van Schependom J., D’hooghe M.B., De Schepper M. et al. Relative contribution of cognitive and physical disability components to quality of life in MS. *J Neurol Sci*. 2014;336(1–2):116–121.

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(A — Concept and design of research, B — Collection and/or compilation of data, C — Analysis and interpretation of data, D — Statistical analysis, E — Writing an article, F — Search of the literature, G — Critical article analysis, H — Approval of the final version of the article)

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