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Contributing Factors to the Quality of Life in Multiple Sclerosis

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS). Quality of life (QoL) refers to the perception of an individual's life in the context of the system of culture and values in which they live. **Aim:** The aim of the study was to determine the distribution of cognitive disorders in people with MS. **Methods:** The prospective study included 135 participants with MS and 50 healthy participants. Participants were divided into three groups: the first group consisted of 85 participants where the disease lasted longer than one year, the second group consisted of 50 participants with newly diagnosed MS, the third group consisted of 50 healthy participants. The instruments of clinical assessment were: Extended Disability Score in Multiple Sclerosis Patients, Mini Mental Status, Beck Depression Scale, and Quality of Life Scale (SF-36, Contemporary Health Survey). **Results:** The quality of life related to health is impaired in the physical, mental dimension and overall quality of life. In the first group of participants, 62% had mild depression, and in the second group 38% of participants, while more severe forms were recorded in 16% of participants in both groups. As depression increases, the quality of life decreases in all measured dimensions, which would mean that depression negatively affects the quality of life. The results of all dimensions as well as the overall quality of life score are worse with the increase in the degree of clinical disability, for both groups of study patients. **Conclusion:** Quality of life is impaired in MS patients, and a higher degree of clinical disability and an increase in depressive disorder are predictors of deteriorating quality of life in MS patients.

Keywords: Multiple sclerosis, quality of life, Depression.

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, (auto) immune disease of the central nervous system (CNS) whose etiological background is not completely clear (1). Etiologically, it represents the association of genetic predisposition and dysregulation in the immune system, with the influence of various risk factors from the environment (2). MS, the most common chronic disabling disease of the CNS in young adults, affects 2.3 million people worldwide, is twice as common in women as in men, and usually occurs at a young age, or about 30 years. The course of MS is variable and unpredictable. According to the National Multiple Sclerosis Society, there are four types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). CIS is the first episode of neurological symptoms caused by inflammation and demyelination in the CNS, lasting at least 24 hours, and which does not meet the criteria for MS. RRMS is characterized by the appearance of defined seizures (relapse or worsening) of new or increasing neurological symptoms, followed by periods of partial or complete recovery (remission). At the time of diagnosis, about 85% of patients had this type of MS. Eighty percent of patients with RRMS will eventually transition to a secondary progressive course (SPMS), with a gradual and progressive deterioration of neurological function (accumulation of disability) over time. If this progressive course occurs from the onset of the disease, without early recurrence or remission, the patient develops PPMS, which accounts for 10% of patients (3). Symptoms most often (85-90%) occur in attacks (exacerbation or remission) or slowly progressively over time (4). Multiple sclerosis is characterized by a variety of symptoms that have a major impact on quality of life even in the early stages (5). In addition to individual motor, sensory, visual disturbances, brain stem and sphincter disturbances (6), which are expressed through the most widely used Kurtzke extended disability scale (EDSS score), there are other manifes-

tations of MS that have a detrimental effect on overall functioning and quality of life, such as cognitive impairment, depression, anxiety (7), fatigue, and pain (8).

WHO defines quality of life (QL) as the perception of an individual's life in the context of the culture and value system in which he or she lives, as well as in relation to their goals, expectations, standards and concerns. Some definitions of quality of life focus on the subjective perspective of the patient's health status (9, 10) while other constructions are broader and include objective indicators of health, housing and other material circumstances (11). Most researchers believe that both subjective and objective information are necessary to determine construction (12). Most QC models reflect a multidimensional conceptual approach, which often includes physical, mental, social, and functional aspects of health. Beyond these basic dimensions, many measures include disease- or treatment-specific variables (13). The combination of relapse, physical disability activity, and magnetic resonance imaging (MRI) activity reflects only part of the impact that MS has on a patient's daily life. In recent decades, QoL measurements have also been considered increasingly important for assessing disease progression, response to treatment, and the level of care required by patients with MS (14). In fact, in recent years, re-searchers have recommended that the assessment of QoL be included in the definition of "No evidence of disease activity" (15).

2. AIM

The aim of the study was to determine the distribution of cognitive disorders in people with Multiple Sclerosis.

3. PATIENTS AND METHODS

The research was prospectively conducted at the University Clinical Center Tuzla, in the Clinic of Neurology for a period of 2.5 years. The sample included 135 participants with MS and 50 healthy participants. Participants were divided into three groups: the first a) group consisted of 85 patients with MS disease lasting more than one year, the second, b) group consisted of 50 patients diagnosed with newly diagnosed MS (disease lasting no longer than one year), the third, c) the group consisted of 50 healthy participants adapted to the experimental groups according to age, gender and education. The selection of participants was done consecutively. Including the criteria for the first and second group of participants, the diagnosis of MS was made according to the valid McDonald criteria from 2011 (16). Including the criterion for the third group are participants who have no symptoms and signs of neurological diseases, nor cognitive disorders previously medically documented. Excluding criteria for the first and second groups are associated diseases and injuries of the brain and spinal cord. Demographic data (age, gender, level of education) were analyzed for each respondent who met the criteria for inclusion in the study.

The instruments of clinical assessment were: Extended Disability Status Scale (EDSS) (17); Mini Mental Status (MMSE) (18); Beck Depression Scale (19); SF 36 Contemporary Health Survey (20). EDSS quantifies disorders of certain functional systems (pyramidal system, cerebellum, brain stem, sensibility, intestines and bladder, visual system, cerebral functions and other functions). Based on the state of the functional systems, the degree of disability is derived (0.0-normal neurological finding up to 10-death).

MMSE is used to assess the following cognitive functions: orientation, repetition, computation, short-term memory, naming, reading, writing, executing complex commands, and copying. The total score is 30. Cognitive functioning according to MMSE will be graded as normal if the score is 25-30. Beck's scale for assessing depression is sensitive and specific that it can be used in making a diagnosis. The scale has 21 questions with four answer options graded from 0-3. An increase of almost above 10 speaks in favor of the presence of depressive disorder. SF 36 is a short guide to health assessment, consisting of 36 questions divided into eight areas (physical function, limitations of physical function, physical pain, social functioning, general mental health, emotional limitations, vitality and fatigue, general sense of health). It provides two general measures of function: physical component summary (PCS) and mental component summary (MCS). Each question is scored from 1 to 100, and results close to 100 indicate a better quality of life.

Participants from all three groups underwent basic testing and control testing for all groups of participants was performed one year after the primary testing. Statistical processing was performed in SPSS ver. 13 or SPSS 17.0 (Chicago, IL, USA).

4. RESULTS

Demographic and clinical characteristics of the participants are shown in Table 1.

Participants of the first and second groups showed impaired quality of life in the physical, mental dimension and overall SF 36 score Table 2.

Table 2 shows the distribution of all eight dimensions of quality of life for the first and second groups of participants. It is noticed that in the second group of participants the physical limitations were the least damaged. Participants of the first group show greater physical limitations, vitality is worse and overall health. Both groups of participants have mental disorders, which are possibly a consequence of coping with a serious illness and partly a consequence of the topographic distribution of demyelinating brain lesions.

Depression is an important predictor of the quality of life of people with MS. The degree of depression was measured using the Beck Depression Scale (BDS). Table 3 shows the prevalence of depression in the first and second groups of participants at initial testing and one year later. Chi square test revealed a statistically significant difference in the distribution of depression between the first and second group of participants due to the increased number of patients with mild / moderate depression at initial testing and after one year ($p < 0.0001$). We found that there is no statistically signif-

	Testing I			Testing II		
	Control	Group I	Group II	Control	Group I	Group II
Number of responders	50	85	50	50	80	45
RRMS	0	71	50	0	66	45
SPMS	0	14	0	0	14	0
Age in years	38 ± 5.8	42 ± 9.3	37.5 ±10.8	39 ± 5.8	43 ± 9.3	38.5 ±10.8
Gender (♀/♂)	35 / 15	60 / 25	41 / 9	35 / 15	59 / 21	39 / 6
Education in years	16 ± 1.8	12 ± 2.5	12 ± 2.4	16 ± 1.8	12 ± 2.5	12 ± 2.4
EDSS	0	2.5 ± 2.3	1.9 ± 1.8	0	3 ± 2.6	1.6 ± 1.5
Duration of disease in years	0	6 ± 4.0	< 1	0	7 ± 4.0	1

Table 1. Demographic and clinical characteristics of the participants. Testing I - initial testing; Testing II - testing after one year; Control - participants without multiple sclerosis; Group I - participants with multiple sclerosis which lasted more than one year; Group II - participants with newly diagnosed multiple sclerosis; RRMS - relapsing remitting form of multiple sclerosis; SPMS - secondary progressive form of multiple sclerosis; EDSS - extended scale of disability status in multiple sclerosis. A brief assessment of cognitive status via the minimum scale (MMSE) found that participants in the first and second groups had average scores that were in the reference values (the first group of subjects had an average value of MMSE 27, and the second group 26.

		Group I (> 1 yar)		Gropu II (< 1 yar)	
		Testing I	Testing II	Testing I	Testing II
		n = 85	n = 80	n = 50	n = 45
SF 36	Physical function	56.9	54.9	70.1	74.2
	Role-physical	47.9	50.3	50	57.2
	Body pain	80	78.5	85	86.2
	General health	54.6	52.9	57	58.0
	Vitality	48.9	46.2	53	55.7
	Social functioing	69.8	65.9	63	68.1
	Role emotional	63.5	65.4	61	64.4
	Mental health	68	68.5	65	68.8
	Physical health	57.7	56.6	63	66.2
	Mental health	60.9	59.8	60	62.9
	Total score	61.2	60.3	63	66.5

Table 2. Distribution of all eight dimensions of quality of life for the first and second group of participants.

		Group I (> 1 yar)		Gropu II (< 1 yar)	
		Testing I	Testing II	Testing I	Testing II
		n = 85	n = 80	n = 50	n = 45
Depression	Without depression	32 (37,6%)	25 (31,0%)	23 (46,0%)	24 (53,0%)
	Mild / Borderline	39 (46,0%)	35 (44,0%)	19 (38,0%)	13 (29,0%)
	Moderate / Severe	14 (16,4%)	20 (25,0%)	8 (16,0%)	8 (18,0%)

Table 3. Distribution of depression in participants of the first and second groups in the first and second tests examined using the Beck depression scale

icant difference in the degree of depression of the first group of participants at initial testing and after one year (Chi square test, p = 0.12). We obtained the same results in the group of participants with newly diagnosed disease (second group), and there is no statistically significant difference in the degree of depression after one year (Hi square test, p = 0.24).

Table 4 shows the significance of the differences in the correlation of the results of the SF-36 questionnaire with the BDS of the participants of the first, second and third groups of participants. All results have a negative correlation coefficient, which means that with the increase in the degree of depression, the quality of life of the participants decreases. The results of the physical and mental dimensions of quality of life as in the total SF-36 score are statistically significantly correlated with depression. As the degree of depression increases, the quality of life decreases in all measured dimensions (Spearman's rank correlation coefficient), which would mean that depression negatively affects the quality of life.

Table 5 shows the significance of differences in the correlation of SF 36 questionnaire results with EDSS participants with multiple sclerosis in the first group (with subgroups RRMS and SPMS) and the second group of participants.

All results have a negative correlation coefficient. The results of all dimensions as well as the overall quality of life score are statistically significantly correlated with the results of EDSS, for the group of newly discovered MS (second group) and for the group of old MS (first group). In the subgroup of the first group of participants, i.e. the RRMS group, we also found a statistically significant correlation of all dimensions of quality of life and EDSS, while in the subgroup SPMS there is no statistically significant correlation between the results of individual dimensions and the overall quality of life score with EDSS

		Depression					
		Group I				Group II	
		RRMS		SPMS			
		Rho	p...	Rho	p...	Rho	p...
SF 36	Physical health	-0,7073	<0.0001	-0,7396	0,0035	-0,7856	0,0001
	Mental health	-0,8317	<0,0001	-0,6780	0,0095	-0,8259	0,0001
	Total score	-0,8142	<0,0001	-0,7473	0,0030	-0,8213	0,0001

Table 4. Correlation of SF-36 questionnaire results with Beck Depression Scale SF 36 - General generic questionnaire for measuring quality of life (short form 36); BDS - Beck Depression Scale; Rho - Spearman rank correlation coefficient; p- the possibility of a random difference of the bidirectionally tested hypothesis. Control group-healthy participants, First group of participants with disease duration longer than one year; Another group of participants with newly diagnosed MS. RRMS-relapsing-remitting form of the first group of participants; SPMS-secondary-progressive from of the first group of participants.

		EDSS					
		Group I				Group II	
		RRMS		SPMS			
		Rho	p...	Rho	p...	Rho	p...
SF 36	Physical health	-0,7064	<0.0001	0,1099	0,7043	-0,6724	<0,0001
	Mental health	-0,4113	0,0005	-0,2198	0,4448	0,4953	0,0003
	Total score	-0,6146	<0,0001	-0,1736	0,5526	-0,5783	<0,0001

Table 5. Correlation of SF-36 questionnaire results with EDSS respondents of the first and second groups. SF 36 - General generic questionnaire for measuring quality of life (short form 36); EDSS - Expanded Disability Status Scale; Rho - Spearman rank correlation coefficient; p.- the possibility of a random difference of the bidirectionally tested hypothesis. The first group of participants with a disease duration of more than one year; The second group of participants with newly diagnosed MS; RRMS-relapsing-remitting form of the first group of participants; SPMS-secondary-progressive froma of the first group of par-ticipants.

results. This could be explained by the fact that the progression of the disease to one degree leads to adaptation to the disease and acceptance of disability.

5. DISCUSSION

Multiple sclerosis is a neurodegenerative progressive disorder that affects younger adults at the most productive age, women getting sick more often. In this study, women were more represented than men in both groups of participants (70.5% in the first group and 82% in the second group). The average age of the participants in the first group was 42.0 +/- 9.3 years, and in the second group 37.5 +/- 10.8 years. This result correlates with the results in other studies (2, 21, 22). The control group (gender and age distribution) was adjusted to the demographic parameters of the first and second groups. In this study, we had 82% of subjects with relapsing-remitting type and 18% of participants with secondary-progressive type of disease, in correlation with other studies (23).

Quality of life is a multidimensional concept that connects physical, social, psychological and emotional functioning. Quality of life in relation to health is defined by aspects that affect the patient's health status and is a measure of clinical assessment of quality of life, disease progression and the effects of therapy (6). Health assessment based on patient responses through a 36-question questionnaire from the health profile (SF-36) was most used in medical studies. The SF-36 questionnaire simply highlights the areas of health affected by the disease, and can reveal how patients cope with the disease.

Depression can occur during MS, even in mild forms of the disease (24), and a higher risk of depression has been reported in the first years after diagnosis (25). Disease activity, but not its duration, has been associated with depression and anxiety (26). Studies suggest that there are neurobiological risk factors associated with MS that determine the increased incidence of depressive disorders in these patients, such as increased lesion load in the left funiculus arcuatus (27), as well as in the prefrontal cortex, anterior temporal lobe, and parietal lobe (28). Cortical atrophy in regions located in bilateral frontal lobes, as well as parietal and occipital lobes, has been associated with depression in patients with MS (29). The hippocampus plays a key role in mood regulation. The study found true variations in hippocampal shape in women with MS with depression and that these changes were associated with an impact on symptoms but not with vegetative symptoms of depression (30). Another study showed changes in the cortico-striatal-pallidothalamic loop in patients with MS with depression, namely progressive loss of gray matter in the limbic basal ganglion structures, such as the globus pallidus, and thalamus, which can lead to typical deficits in hedonic motivations; on the other hand, atrophy of the prefrontal cortex may contribute to maladaptive coping strategies, promoting the development of depressive symptoms (31).

Participants in our study show a depressive disorder. In the first group, 62% of participants had mild depression, and in the second group 38% of participants, while more severe forms were recorded in 16% of participants in both groups. We found that the results of the physical and mental components of quality of life as well as the overall SF-36 scores were statistically significantly correlated with the results of the Beck Depression Scale. As the degree of depression increases, the quality of life decreases in all measured dimensions. Depression has been shown to be an important predictor of deteriorating quality of life in people with MS. This result is correlated with the results of Fuvesi et al. who find that depression as the statistically most significant factor is the weakened mental component of health and SF-36. Moreover, he also found that in depressed MS patients, QOL worsened to a significant extent (32). Similar results were found in the study by Salehpoor et al. (33) that depression alone is a significant predictor of mental health disorders. Also, this finding is consistent with previous reports of MS patients (34, 35). Based on the interpretation of this finding, depression impairs the motivation, interest and cooperation of the patient; this in turn can affect vitality, social function, mental health, and the mental health dimension in general. Another interpretation is that depression can distort people's views of the world and their health and change it in a way that worsens their self-esteem (36).

The results of all dimensions as well as the overall quality of life score are statistically significantly correlated with the degree of clinical disability (EDSS) for both groups of study participants. A nonlinear relationship between the degree of disability and quality of life was found in a study by Twork et al. (37). With the worsening of the state of disability, poorer physical and mental health, worse score of all subscales, as well as poorer cognitive functions were recorded. However, while patients with EDSS between 4.5 and 6.5 differed significantly compared to patients with a lower score (EDSS 0-4.0), a smaller difference was observed between the two groups of patients with a higher EDSS score (the

group with EDSS 4.5-6.5 and the group with EDSS 7.0 to 10). These results were similar for all dimensions of quality of life (physical, mental, and overall quality of life). In this study, a significant and negative association between disability and quality of life was found. Thus, the results suggest that when mobility is impaired (without the use of a wheelchair) there is a more pronounced impairment of quality of life, and the longer wheelchair-bound patients show no additional impairment in most health-related domains of quality of life. Pfaffenberger illustrated that increased impairment intensity and limited mobility are directly related to reduced quality of life in patients with MS (38). A study by Ghaem and Haghighi (39) also showed that MS patients have moderate to poor mental and physical health. The degree of clinical disability expressed by the EDSS result, as well as the severity of fatigue and the quality of sleep were significant indicators that correlated with the quality of physical and mental health. This study also showed that demographic data (age, gender, marital status, age of education) and disease duration had no impact on quality of life after conducting statistical modeling. As the quality of mental and physical health is in a high relationship with each other, patients with MS need special attention from health professionals and the assessment of those patients who may need additional psychological support (39).

6. CONCLUSION

The presence of depression worsens the quality of life of people with MS, impairs the mental and physical components of quality of life. A higher degree of disability leads to a poorer quality of life of MS patients for the physical and mental component of health as the overall quality of life of the participants.

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REFERENCES

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2008; 372(9648):1502-1517.
2. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007; 61(4): 288-299.
3. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of Multiple Sclerosis 2013: a growing global problem with widespread in-equity. Neurology. 2014; 83: 1022-1024.
4. Bergamaschi R. Prognostic factors in multiple sclerosis. Int Rev Neurobiol. 2007; 79: 423-447.
5. Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Eur J Neurol. 2016; 23: 1482-1486.
6. BenitoLeon J, Morales JM, Rivera-Navarro J. Healthrelated quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis pa-tients. Eur J Neurol. 2002; 9: 497-502.
7. Marrie RA, Patten SB, Berrigan LI, Tremlett H, Wolfson C, Warren S, Leung S, Fiest KM, McKay KA, Fisk JD. CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS). Diagnoses of Depression and Anxiety Versus Current Symptoms and Quality of Life in Multiple Sclerosis. Int J MS Care. 2018; 20: 76-84.
8. Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H & Paty D: Recent developments in the assessment of quality of life in multiple sclerosis (MS). Mult Scler J. 1999; 5: 251-259.
9. WHOQOL Group. Study protocol for the World Health Organization project to develop a quality of life assessment instrument (WHOQOL). Qual Life Res. 1993; 2: 153-159.
10. Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: definitions and conceptual issues. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. Philadelphia: Lippincott-Raven; 1996: 11-24.
11. Gotay CC, Moore TD. Assessing quality of life in head and neck cancer. Qual Life Res. 1992; 1(1): 5-17.
12. Lauer G. Concepts of quality of life in mental health care. In: Priebe S, Oliver JPJ, Kaiser W, editors. Quality of Life and Mental Health Care. Philadelphia, PA: Wrightson Biomedical; 1999; 19-34.
13. Post MW. Definitions of quality of life: what has happened and how to move on. Top Spinal Cord Inj Rehabil. 2014; 20(3): 167-180.
14. Lysandropoulos AP, Havrdova E, Paradig MSG. 'Hidden' factors influencing quality of life in patients with multiple sclerosis. Eur J Neurol. 2015; 22(Suppl 2): 28-33.
15. Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC. Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model. Ther Adv Neurol Disord. 2015; 8(1): 3-13.
16. Polman C, Reingold S, Banwell B, Clanet M, Cohen J, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin F, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson A, Waubant E, Weinshenker B, Wolinsky J. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria. Ann Neurol. 2011; 69: 292-302.
17. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983; 33(11): 1444-1452.
18. Folstein M, Folstein SE, McHugh PR. «Mini-Mental State» a practical method for granding the cognitive state of patients for the clinician. J Psychiat. 1975; 12(3): 189-198.
19. Beck AT, Beamsdorfer A. Assessment of Depression: The Depression Inventory. In Pichot P(ed). Psychological Measurments in Psychopharmacology, Modern Problems in Pharmacopsychiatry. Basel: Karger. 1974; 7: 151-169.
20. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey manual and in-terpretation guide. The Health Institute. Boston, MA:Nimrod Press. 1993.
21. ucchinetti C, Noseworthy JH, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000; 343: 938-952.
22. Kristen R, Slusher B, Kaplin A. Cognitive Impairment in Multiple Sclerosis: A Forgotten Disability remembered. Cerebrum. 2012; 14: 45-60.

23. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol. 2008; 7: 1139-1151.
24. Sullivan MFI, Weinshenker B, Mikai S, Edgley K. Depression before and after diagnosis of multiple sclerosis. Mult Scler .1995; 1: 104-108.
25. Possa MF, Minacapelli E, Canale S, Comi G, Martinelli V, Falautano M. The first year after diagnosis: psychological impact on people with multiple sclerosis. Psychol Health Med. 2017; 22: 1063-1071.
26. Noy S, Achiron A, Gabbay U, Barak Y, Rotstein Z, Laor N, SarovaPinhas I. A new approach to affective symptoms in relapsing-remitting multiple sclerosis. Compr Psychiatry. 1995; 36: 390-395.
27. Pujol J, Bello J, Deus J, Martí-Vilalta JL, Capdevila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. Neurology. 1997; 49: 1105-1110.
28. Bakshi R, Czarnecki D, Shaikh ZA, Priore RL, Janardhan V, Kaliszky Z, et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. Neuroreport. 2000; 11: 1153-1158.
29. Gobbi C, Rocca MA, Riccitelli G, Pagani E, Messina R, Preziosa P, et al. Influ-ence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis. Mult Scler. 2014; 20: 192-201.
30. Gold SM, O'Connor MF, Gill R, Kern KC, Shi Y, Henry RG, et al. Detection of altered hippocampal morphology in multiple sclerosis-associated depression using automated surface mesh modeling. Hum Brain Mapp. 2014; 35: 30-37.
31. Stuke H, Hanken K, Hirsch J, Klein J, Wittig F, Kastrup A, et al. Cross-sectional and longitudinal relationships between depressive symptoms and brain atrophy in MS patients. Front Hum Neurosci. 2016; 10: 622.
32. Fuvesi J, Bencsik K, Losonczi E, Fricska-Nagy ZS, Matyas K, Meszaros E, et al. Factors influencing the health-related quality of life in Hungarian multiple scle-rosis patients. J Neurol Sci. 2010; 293: 59-64.
33. Salehpoor G, Rezei S, Hosseinniezhad 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.
34. Merkelbach S, Sittinger H, Koenig J. Is there a differential impact of fatigue and physical disability on quality of life in multiple sclerosis? J Nerv Ment Dis. 2002; 190: 388-393.
35. Brola W, Fudala M, Czernicki J. Effect of depression on quality of life of patients with multiple sclerosis. Med Rehabil. 2007; 11: 1-5.
36. Mitchell AJ, Benito-Leon J, Gonzalez JM, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: Integrating physical and psychological com-ponents of wellbeing. Lancet Neurol. 2005; 4: 556-566.
37. Twork S, Wiesmeth S, Aspindler M, Wirtz M, Schipper S, Pohlau D, Klewer Jkugler J. Disability status and quality of life in multiple sclerosis: non-linearity of the Expanded Disability Status Scale (EDSS). Health and Qualiti of life Outcomes. 2010; 8: 55-60.
38. Pfaffenberger N, Pfeiffer KP, Deibl M, Höfer S, Günther V, Ulmer H. Association of factors influencing health-related quality of life in MS. Acta Neurol S. 2006; 114(2): 102-108.
39. Ghaem H and Haghighi. The impact of disability, fatigue and sleep quality on the quality of life in multiple sclerosis. Ann Indian Acad Neurol. 2008; 11(4): 236-241.