ORIGINAL ARTICLE

Depression during multiple sclerosis relapse: relation to disability and relapse severity

Selma Šabanagić-Hajrić[1], Enra Suljić[1], Gorana Sulejmanpašić-Arslanagić[2]

[1]Department of Neurology, [2]Department of Psychiatry; University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To examine the presence of depressive symptoms in patients with multiple sclerosis relapse and its relation to disability and relapse severity.

Methods This study included 120 patients who were assessed during the acute relapse of multiple sclerosis according to Mc Donald criteria. Depression was assessed using Beck Depression Inventory II (BDI-II) calculating both affective and somatic symptom scores. The Expanded Disability Status Scale (EDSS) measured disability. Relapse severity was graded according to the difference between the EDSS score during relapse and EDSS score before the onset of the attack as mild, moderate or severe.

Results There was statistically significant difference between patients with different level of depression considering age ($p<0.001$), disability ($p<0.001$), relapse severity ($p=0.005$) and disease duration ($p=0.032$). Significant moderate positive correlation of depression with age (rho=0.43) and disability (rho=0.46) was confirmed. There was moderate correlation between disability and somatic symptoms of depression (rho=0.54, $p<0.001$) with only weak correlation between disability and affective symptoms of depression (rho=0.31, $p<0.01$). Multiple regression analysis showed that patient's age and relapse severity ($p<0.05$) were independently related to depression in these patients while disability did not.

Conclusion Correlation between disability and depression was mostly due to somatic symptoms of depression. Although highly correlated, depression during multiple sclerosis relapse was not independently predicted by disability. Depression should be recognized and treated independently from disability treatment, especially in the group of older patients with more severe relapse.

Key words: multiple sclerosis, disability, somatic symptoms, affective symptoms

Corresponding author:
Selma Šabanagić-Hajrić
Department of Neurology, Clinical Center,
University of Sarajevo
Bolnička 25, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 29 73 54;
Fax:+387 33 29 78 21;
E mail: selmahajric@gmail.com

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system and is regularly accompanied by psychiatric symptoms such as depression (1). Clinically significant depression can affect up to 50% of patients with MS over the course of their lifetime and it is associated with an increased morbidity and mortality (2). Lifetime prevalence of major depression in multiple sclerosis ranges from 19 to 54%, depending on the population sample and diagnostic criteria used (3,4). Annual prevalence is estimated at 16% (5), and point prevalence of clinically significant depressive symptoms is as high as 50% (6). Evidently, prevalence is considerably higher than in the general population or among patients with general medical conditions other than MS (4,7). Higher levels of depressive symptoms are also linked to poorer treatment compliance (8), and thus can affect long-term health outcomes. If left untreated, depressive symptoms in MS may worsen over time (9).

The factors responsible for mood disturbances in MS are still controversial. A psychological reaction to a progressively disabling and unpredictable disease may be a relevant contributor while reactive mechanisms alone are probably not sufficient to explain the high prevalence and wide spectrum of depression. (10). The etiological factors of depression in multiple sclerosis are considered to be both biological and psychosocial (11). Unfortunately, mental comorbidity and depression in particular are frequently underdiagnosed and undertreated, with reported rates of missed diagnosis around 23–30% (12) and rates of inadequate treatment around 20%–36% of those reporting depression (13).

In the McDonald criteria for the diagnosis of MS, a relapse is defined as an episode of neurological disturbance of the kind seen in MS, when the clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature (14). It is not known whether emotional states, including depression, can actually affect the neurobiological course of MS, but it is reported that emotionally stressful experiences commonly happen prior to clinical exacerbations in MS (4). A series of prospective studies has reported a relationship between stressful life events and increased exacerbation rates in MS populations (4). Confirmed exacerbations are associated with concurrent anxiety and depressive symptoms. Pathogenic factors underlying exacerbation may aggravate underlying pathogenic factors related to depression. For example, there may be a lower threshold for MS inflammatory processes to amplify preexisting depressive symptoms relative to new depressive symptoms (15). Added to this is the risk associated with MS that the somatic symptoms may lead to inflated estimates of depression (7).

The aim of this study is to examine the presence of depressive symptoms in a sample of patients with multiple sclerosis relapse and its relation to relapse severity and disability. Considering possible influence of increased somatic symptoms during MS relapse on depression, we also investigated correlations of disability with both somatic and affective symptoms of depression.

PATIENTS AND METHODS

Patients and study design

This observational, cross-sectional study included 120 patients who were assessed consecutively between 1st January 2011 and 31st December 2013 during the acute relapse of relapsing-remitting multiple sclerosis according to Mc Donald criteria (14). They were treated at the Department of Neurology, University Clinical Center Sarajevo. The study included patients aged between 18-60 years. Patients were excluded if having progressive type of the disease. The Ethics Committee of the University Clinical Center Sarajevo gave an ethical consent to perform the study. All patients signed a written informed consent for the use of the results obtained for publication before the enrollment. Instruments

Methods

The questionnaire for the collection of socio-demographic and clinical data was designed for the purposes of this study, and included information on age, gender, disease duration, level of disability, relapse severity and depression scores. All patients were examined at the time of recruitment, and underwent complete neurological examination. Physical disability was assessed using the Expanded Disability Status Scale (EDSS) (16). The EDSS is the standard measure of disease progression and the degree of neurological impairment in clinical practice and clinical trials scoring. It is divided in eight functional systems

(FS). Scores for the total scale can range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis). Patients with a score of ≤3.5 are fully ambulatory, while patients with higher scores have ambulatory limitations.

The relapse severity was graded according to the difference between the EDSS score during the relapse and the EDSS score before the onset of the attack, as: mild (EDSS increase by 0.5 point, or 1 point change in up to three FS scores), moderate (EDSS increase by 1 or 2 points, or 2 points change in one or two FS scores, or 1 point change in four or more FS scores), or severe (exceeding prior criteria) (17).

Depression was assessed by using the Beck Depression Inventory II (BDI-II) (18). The BDI is an objective self-report assessment tool comprising 21 items, and one of the most commonly used for patients with multiple sclerosis. When the test is scored a value of 0 to 3 is assigned to each answer and the total score is compared to a key to determine the severity of depression symptoms. The standard cut-offs are: 0-13 indicates no depression symptoms; 14–19: mild depression, 20–28: moderate depression, 29–63: severe depression. Evidence-based guidelines published in 2014 by the American Academy of Neurology (AAN) cautiously endorsed the BDI-II as the psychometric scale of choice for assessing people with MS (19).

Based on reviews of existing factor models and item content, scores on BDI-II items 1–14 (sadness, pessimism, past failure, loss of pleasure, guilt feelings, punishment feelings, self-dislike, self-criticalness, suicidal ideation, crying, agitation, loss of interest, indecisiveness, worthlessness) were summed to calculate cognitive/ affective symptom scores. Items 15–21 (loss of energy, sleep problems, irritability, appetite problems, concentration, fatigue, sexual disinterest) were summed to calculate somatic symptom scores (20).

Statistical analysis

Data are presented as mean ± standard deviation or as median with interquartile range (IQR, 25th to75th percentiles) dependent on normality of variables distribution. The Kolmogorov–Smirnov statistic with a Lilliefors significance level was used for testing normality of distribution. In the case of categorical variables, counts and percentages were reported. Differences between two groups were tested by non-parametric Mann Whitney U test. A Kruskal-Wallis H test was conducted to determine if there were differences in BDI-II scores between three or more groups. Subsequently, pairwise comparisons were performed using Mann Whitney U Test with a Bonferroni correction for multiple comparisons. Chi-square test was applied for comparison of the categorical variables. Correlation of BDI score with age, disease duration and EDSS scores was determined using Pearson's and Spearman Rank Correlation Test. Spearman's Rank Correlation test was performed to test correlation of EDSS scores with somatic and affective symptoms of depression. A multiple regression was run to predict BDI score from age, gender, disease duration, relapse severity and EDSS score. The assumptions of linearity, independence of errors, homoscedasticity, unusual points and normality of residuals were met. All statistical tests were two-sided, and P-value less than 0.05 was considered as significant.

RESULTS

A total of 82 (68.3%) of the patients included in the study were females. The mean age of the patients at enrollment was 40+/-11 years; range was 20-60 years. The median of the disease duration was 6 years (IQR= 4 to 11). Forty (33.3%) patients were classified as non-depressed, 47 (39.2%) patients as mildly depressed and 33 (27.5%) patients were classified as moderately or severely depressed. There was statistically significant difference between patients with different levels of depression considering age (p<0.001), disability (p<0.001), relapse severity (p=0.005), and disease duration (p=0.032) (Table 1). After performing the Spearman's Rank Correlation test, significant moderate positive correlation of

Table 1. Level of depression measured by Beck Depression Inventory-II (BDI-II) scale by different demographic and clinical characteristics

Characteristics	Level of depression			p
	*1 (n=40)	†2 (n=47)	‡3 (n=33)	
Patient age (years)	34.6 ± 9.9	39.8 ± 11.4	46.7 ± 8.1	< .001
Male	27.5%	34.0%	33.3%	0 .784
Relapse severity				
Mild	37.5%	50.0%	12.5%	
Moderate	39.5%	38.3%	22.2%	0 .005
Severe	8.7%	34.8%	56.5%	
Disease duration (years)	5.0 (3.1 to 9.8)	5.0 (4.0 to 14.0)	11.0 (4.5 to 13.0)	0 .032
EDSS score	2.8 (2.5 to 3.5)	4.0 (2.5 to 6.0)	5.5 (3.8 to 6.3)	<0.001

*1 – non depression, †2 – mild depression; ‡3 – moderate or severe depression; EDSS, Expanded Disability Status Scale

depression with age (r_s=0.43; p<0.001) and disability (r_s=0.46; p<0.001) was confirmed.

Patients with higher disability (EDSS≥4) had higher median BDI score (Me=17; IQR=14-21) than patients with lower disability (Me=9, IQR=6.5-13) (p<0.001).

There was moderate correlation between disability and somatic symptoms of depression (r_s=0.54, p<0.001) (Figure 1), while the correlation between disability and affective symptoms of depression was only weak (r_s=0.31, p<0.01) (Figure 2).

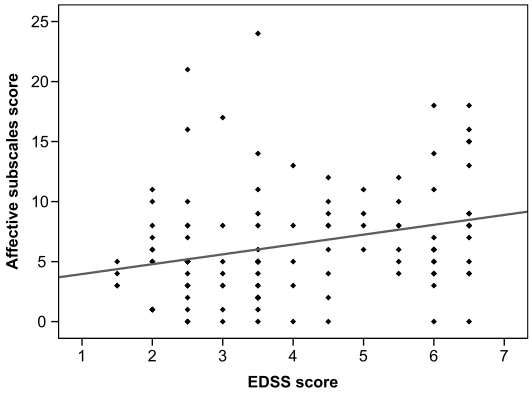

Figure 1. Correlation between disability and affective symptoms score; EDSS, Expanded disability status scale

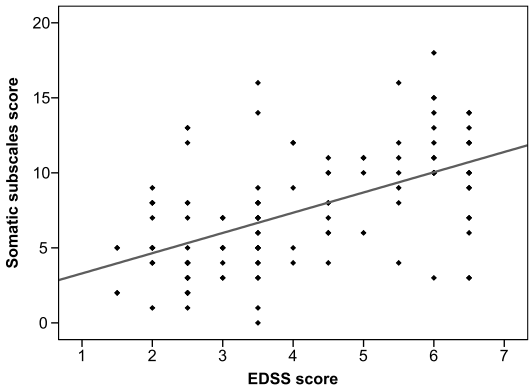

Figure 2. Correlation between disability and somatic symptoms score; EDSS, Expanded disability status scale

Median BDI scores were statistically significantly different between the different relapse severity status (p<0.01). Post hoc analysis revealed statistically significant differences in median BDI scores between the mild (Me=14.5, IQR=7.3-17.5) and severe relapse (Me=20.0; IQR=15-23) (p=0.004), and moderate (Me=12.0; IQR=7-16.5) and severe relapse (20.0, IQR=15-23) (p< 0.001), but not between mild and moderate relapse.

Multiple regression analysis showed that only patient's age (p<0.05) and relapse severity (p<0.05) were independently related to depression severity in these patients.

DISCUSSION

In this study the patient's age significantly correlated with depression, which is similar to the results from the study that investigated depression in MS patients (21). Still, other studies showed different results with no correlation between age and level of depression in MS patients (22-24). The correlation between age and depression level in this study may be explained by different psychological response of older patients during relapse than during stable course of the disease.

Relapse severity proved the positive correlation with depression severity in this study which is consistent with the fact that most individuals with MS who experience relapses suffer from multiple symptoms, which adversely impact daily activities (25). The reported symptoms had a substantial impact on daily function both with respect to employment and household tasks, implying far-reaching impact on the patient (25). Relapses are associated with increased emotional distress and depression (26,27).

Various studies have looked at physical disability in relation to depression among people with MS and these have produced mixed results (1). Although higher levels of disability have been associated with more severe depressive symptoms in several chronic illnesses, the relationship between depression and functional disability in multiple sclerosis remains controversial (6). Over four fifths (82.9%) of people with low physical disability scores were not experiencing depression, and just 0.4% reported severe depression. For those with a high physical disability score, just 28.3% fell into the normal category and 9.4% reported severe depression (28). A similar chart displaying the relationship between the physical and psychological impacts of multiple sclerosis was shown in other study (29). In addition to differences in the frequencies of people suffering from depression by physical disability level, differences were also found in the depression scores (21). Depression scores were highest in respondents in the high disability category with marked difference in the proportions experiencing depression in relation to their physical disability (28). This study also found positive correlation between disability level and depression scores, which is consistent with findings of increased prevalence of depression during times of MS exacerbations and increased physical impairment (30). Depression in multiple sclerosis is proved to

be highly correlated to both physical and mental composite scores of Multiple Sclerosis Quality of life-54 (MSQOL-54) questionnaire (31)

Pathogenic factors underlying exacerbation may aggravate underlying pathogenic factors related to depression. This makes a threshold for MS inflammatory processes lower, which may amplify preexisting depressive symptoms relative to new depressive symptoms (15).

Depression and anxiety are common in persons with somatic diseases in general and have significant association with physical health. This connection has considerable implications for somatic diseases management and clinical guidelines (32). The diagnosis of depression includes a number of somatic and vegetative symptoms that overlap with typical symptoms of MS (e.g., fatigue, sleep disturbance, impaired concentration), which can make difficulties in this patient's population (33). This raises the possibility that increased reporting of somatic symptoms potentially unrelated to depression may influence diagnosis of depression during MS relapse. The results of the present study showed that correlation between disability and depression is mostly due to somatic symptoms of depression, while the correlation between disability and affective symptoms of depression is rather weak. Although highly correlated, depression during multiple sclerosis relapse was not independently predicted by disability.

In conclusion, recognizing and treating depression during multiple sclerosis relapse is very important. Depression should be treated independently from disability treatment, especially in the group of older patients with more severe relapse. Other mechanisms related to the MS underlying inflammatory process could also be responsible for the development of depression during multiple sclerosis relapse. Future studies should investigate an influence of relapse treatment based on the application of anti-inflammatory and immunomodulatory drugs on depression during MS relapse.

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Competing interests: none to declare

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Depresija u toku relapsa multiple skleroze: povezanost sa fizičkim onesposobljenjem i težinom relapsa

Selma Šabanagić-Hajrić[1], Enra Suljić[1], Gorana Sulejmanpašić-Arslanagić[2]

[1]Neurološka klinika, [2]Psihijatrijska klinika; Univerzitetski klinički centar, Sarajevo, Bosna i Hercegovina

SAŽETAK

Cilj Evaluirati prisustvo depresivnih simptoma u toku relapsa multiple skleroze i njihovu povezanost s onesposobljenjem i težinom relapsa.

Metode U istraživanje je uključeno 120 pacijenata koji su ispitivani u toku relapsa multiple skleroze, dijagnosticiranog prema Mc Donaldovim kriterijima. Depresija je evaluirana primjenom Beckovog inventara depresivnosti II (BDI-II), a onesposobljenost je mjerena primjenom Proširene skale onesposobljenosti (EDSS). Težina relapsa je procijenjena na osnovu razlike EDSS-skora u toku i prije relapsa, te ocijenjena kao „blaga“, „umjerena“ ili „teška“.

Rezultati Uočena je statistički signifikantna razlika između pacijenata s različitim stupnjem depresije u odnosu na dob ($p<0,001$), onesposobljenost ($p<0,001$), težinu relapsa ($p=0,005$) i dužinu trajanja bolesti ($p=0.032$). Značajna umjerena pozitivna korelacija između depresije i dobi ($r_s=0,43$) te onesposobljenja ($r_s=0,46$) je potvrđena. Uočena je umjerena korelacija između onesposobljenja i somatskih simptoma depresije ($r_s=0.54$, $p<0,001$), uz samo slabu korelaciju između onesposobljenja i afektivnih simptoma depresije ($r_s=0,31$, $p<0,01$). Multipla regresiona analiza pokazala je da su dob pacijenta i težina relapsa ($p<0,05$) neovisno povezane s težinom depresije, ali ne i onesposobljenje.

Zaključak Korelacija onesposobljenja i depresije najvećim dijelom zasnovana je na povezanosti sa somatskim simptomima depresije. Iako su onesposobljenje i depresija značajno povezani, onesposobljenje nema ulogu neovisnog prediktivnog faktora depresije. Depresiju bi trebalo prepoznati i liječiti neovisno od tretmana onesposobljenja, posebno u grupi starijih pacijenata i pacijenata s težim relapsom.

Ključne riječi: multipla skleroza, onesposobljenost, somatski simptomi, afektivni simptomi