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Original article

Psychological status of patients with relapsing-remitting multiple sclerosis during coronavirus disease-2019 outbreak



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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) is a global health emergency. The aim was to investigate the impact of COVID-19 pandemic on the psychological status of patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: Data on the socio-demographic and clinical characteristics of 95 RRMS patients were collected. We used a self-designed questionnaire, the Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54), Hamilton scales for the assessment of anxiety (HAM-A), and depression (HAM-D). Patients who were tested one year ago were reassessed using the same questionnaires during the COVID-19 outbreak. Group of 99 healthy individuals (HC) were tested, using the same questionnaires.

Results: The main concerns in RRMS patients were that someone that they know could be infected with COVID-19 (78.5%), or could die due to the infection (33.8%), and the lack of specific treatment options (25.8%). The main concerns about the RRMS status were that their disease would be worse if they get infected with COVID-19 (36.4%), that they would experience some difficulties in drug availability (43.6%), that they could not go to the hospital as usual (72.4%). Results on all questionnaires were worse in RRMS patients than in HC ($p < 0.01$). We noticed a statistically significant difference between the results obtained a year ago and the results from April 2020 in HAM-A ($p < 0.05$).

Conclusions: There is an impact of the COVID-19 pandemic on the psychological status of RRMS patients. Healthcare organizations need to provide professional therapeutic advice and psychosocial support for this population of patients during the pandemic.

1. Introduction

The coronavirus disease 2019 (COVID-19) was first reported in the city of Wuhan, China (Zhu et al., 2020). At the beginning of March 2020, after becoming a global health emergency, the disease was first seen in Serbia. Several restrictive measures have been adopted by Serbian government officials, as the number of cases increased during the time. As a consequence of the pandemic and the measures taken to combat the pandemic, anxiety and depression emerged in the global population (Torales et al., 2020). COVID-19 pandemic was also associated with impaired quality of life (QoL) (Zhang and Ma, 2020). Patients with co-morbidities are at higher risk of developing a severe or fatal phenotype of the disease, and immunosuppressed patients might be more susceptible to COVID-19 complications (Wu et al., al.,2020).

This could be an aggravating factor for patients with chronic diseases. There is very little information regarding patients with chronic autoimmune diseases and the impact of the pandemic on their psychological status and is there some specificity in this group of patients.

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory and neurodegenerative disease of the central nervous system, that predominantly affects females and individuals between the ages of 20 to 50 years old (Howard et al., al.,2016). Up to 85% of MS patients are characterized by the relapsing-remitting phenotype of multiple sclerosis (RRMS), which implies the emergence of new or worsening recurrent neurological problems that have a complete or partial recovery, lasting from several days to several weeks (Inojosa et al., al.,2019).

During 2019 we tested RRMS patients using questionnaires for QoL, level of depression, and anxiety symptoms (Stojanov and

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Stojanov, 2020). In April 2020, we reassessed these patients to investigate the possible impact of the COVID-19 pandemic and the state of emergency and the police lockdown in Serbia on psychological status and QoL of RRMS patients.

2. Methods

We performed a cross-sectional study over a period of one month (April 2020), during Serbia's state of emergency and police lockdown because of the COVID-19 pandemic. RRMS patients according to McDonald criteria, aged >18 who were assessed during 2019, were invited to do the reassessment. Enrollment of patients and both assessments were conducted by the same researcher. Exclusion criteria on both assessment time points were: the presence of other chronic illness (diabetes, asthma, hypertension, heart failure, renal and hepatic insufficiency), active infection, known history of addiction, relapses of the disease in previous 3 months and intravenous methylprednisolone treatment within the previous 3 months. Known psychiatric comorbidity before the time of the establishment of MS diagnosis was also an exclusion criteria (these patients were not included in the first assessment), because we wanted to exclude the impact of previous psychiatric disease on psychological status of RRMS patients. All patients had an MMSE score >24, and have been receiving immunomodulatory therapy (beta-interferons or glatiramer acetate) at the time of both assessments. Sex and age-matched healthy controls (HC) were included in this study. The HC group consists of volunteers, recruited via emails that were sent on addresses of volunteers who were included in previous trials implemented in our Clinic.

The study procedures were conducted with approval from the local clinical research ethics committee. All procedures were conducted per accordance with the committee's guidelines and regulations, including the Basics of Good Clinical Practice, the Declaration of Helsinki, and the Law on Health Care of the Republic of Serbia. All participants provided written informed consent.

Data on the epidemiological and clinical characteristics of the disease were collected (current age, gender, place of residence, current partner status, number of children, employment status, presence of psychiatric disease in the family, history of addiction, disease duration, and number of relapses). Expanded Disability Status Scale (EDSS) was used for the assessment of current disability status. EDSS is the standard measure of physical disability in addition to disease progression and the degree of neurological impairment (Kurtzke, 1983).

For the investigation of the psychological status and emotional response, we used a self-designed questionnaire, consisting of 8 questions. RRMS related problems during the COVID-19 pandemic were assessed with 4 additional questions. Quality of life (QoL) was measured using the Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54), which is a valid and reliable multidimensional health-related QoL measure that combines both general and MS-specific items into a single instrument (Vickrey et al., 1995). Hamilton scales for the assessment of anxiety (HAM-A) and depression (HAMD) were also used (Hamilton, 1959, 1960).

All data were statistically processed by IBM SPSS statistical software (version 21) for Windows Operative System. Numerical data are presented as medians and interquartile range (IQR) for nonparametric data and as mean \pm standard deviation (SD) for parametric data. The Mann-Whitney test was used to compare continuous variables between two groups, and the Kruskal-Wallis test was used to compare more than two groups. Correlations were assessed using Pearson's correlation coefficients or Spearman's correlation coefficients. For multiple correlations Bonferroni correction was used. Factors that significantly correlated with higher scores on used questionnaires were included in the multiple linear regression analysis (stepwise method). Stepwise criteria were as follows: the probability of F to enter variable was ≤ 0.05 , and the probability to remove variable ≥ 0.10 .

Table 1

Socio-demographic characteristics of patients with relapsing-remitting multiple sclerosis ($N = 95$) and healthy controls ($N = 99$).

	RRMS	Control group
Age in years (mean \pm SD)	43.4 \pm 9.7	44.3 \pm 9.3
Female gender (%)	67.6	66.3
Disease duration in years (median (min, max))	8.2 (2–17)	/
EDSS (mean \pm SD)	3.6 \pm 1.3	/
Number of relapses (mean \pm SD)	4.5 \pm 1.9	/
Education (%)		
Primary studies	25.3	33.3
Secondary studies	47.3	43.0
University degree	27.4	23.7
Partner status (married or cohabitant) (%)	58.6	61.3
Occupational status (unemployed) (%)	59.4	48.2
Number of children (%)		
Zero	38.4	32.5
One	35.5	35.3
Two or more	26.1	32.2
Smokers (Yes) (%)	60.5	63.7
Area of living (urban) (%)	67.5	63.4
Psychiatric disease in family (Yes) (%)	18.3	16.6

SD = standard deviation; RRMS = relapsing-remitting multiple sclerosis; EDSS = Expanded Disability Status Scale;

3. Results

The study included 95 adult RRMS patients (≥ 18 years), and 99 HC whose socio-demographic characteristics are listed in Table 1.

In the self-designed part of the questionnaire, the first two questions were regarding knowledge of infection routes and the main source of information. In the RRMS group, only 2.7% of patients did not have any knowledge about the infection routes, and 48.4% believed that they know everything about the ways for COVID-19 transmission. Television was the main source of information for RRMS patients (54.4%), followed by social media (35.5%). Regarding the information that they received from media, we found that 12.5% of patients were very concerned, 33.5% somewhat generally concerned, 44.6% not very concerned, and 8.4% were not concerned at all. Furthermore, regarding the concerns about the impact of the COVID-19 pandemic on their health or the health of their relatives and friends, 14.5% of patients were very concerned, 38.5% somewhat generally concerned, 40.6% not very concerned, and 6.4% were not concerned at all. The main reason for concern was that some patient's relatives or friends could be infected with COVID-19 (78.5%), that someone they know could die due to the infection (33.8%), and the lack of specific treatment options for COVID-19 (25.8%). Other causes were noted in less than 15% of our patients (high mortality rates in the world, high contagiousness, changes in the lifestyle after the pandemic, changes in incomes, etc.). We asked patients how they were sleeping compared to the time before the pandemic outbreak, and 43.1% of patients answered that they were sleeping worse. Daily activities of 16.7% of patients were very influenced by the pandemic and the police lockdown and the state of emergency, whereas 45.7% of the patients did not experience any changes in their daily activities. Results obtained from HC were similar regarding all questions, with the following exceptions - HC were more concerned about changes in lifestyle (25.5% vs 11.2%) and lower incomes during and after pandemic (22.4% vs 9.2%) ($p < 0.01$).

Regarding the status of RRMS, during the COVID-19 outbreak, 2.2% of patients thought they had an improvement, 70.8% of patients reported feeling no change, and 27.0% of patients reported their condition got worse. The main concern about the MS status was that their disease would be worse if they got an upper respiratory infection (36.4%), that they would experience some difficulties in drug availability (43.6%), that they could not go to the hospital as usual (72.4%). All other causes were noted in less than 10%. On the question where they will try to find help if their condition gets worse, 83.4% of patients

Table 2
Scores on used questionnaires in patients with RRMS ($N = 95$) and HC ($N = 99$).

Variables	RRMS (2019)	RRMS (april 2020)	HC (april 2020)
MSQOL-54 mental health (mean \pm SD)** ^B	51.2 \pm 19.1	47.1 \pm 18.4	77.2 \pm 19.7
MSQOL-54 physical health (mean \pm SD)** ^B	45.5 \pm 18.2	44.2 \pm 19.3	91.2 \pm 21.2
HAM-D (Mean \pm SD) ** ^B	16.7 \pm 4.5	17.3 \pm 4.5	8.7 \pm 3.7
HAM-A (Mean \pm SD) ** ^A , ** ^B	15.8 \pm 4.7	18.9 \pm 5.1	10.2 \pm 4.3

$p < 0.05^*$; $p < 0.01^{**}$; A – difference between RRMS in 2019 and April 2020; B – difference between RRMS in April 2020 and HC; SD = standard deviation; RRMS = relapsing-remitting multiple sclerosis; HC = healthy controls; MSQOL-54 = Multiple Sclerosis Quality of Life-54 Instrument; HAM-D = Hamilton depression scale; HAM-A = Hamilton anxiety scale;

would try to get in contact with their medical doctor, 10.3% would try to get in contact with a nearby hospital or any physician by phone, 6.3% would try to find information on the internet. Patients who would not go to the hospital and try to find their doctor stated the fear of getting infected as the main reason (85.5%).

The results obtained on used questionnaires are presented in Table 2. Results on all questionnaires were worse in RRMS patients than in HC ($p < 0.01$). We noticed a statistically significant difference between the results obtained a year ago and the results from April 2020 in HAM-A ($p < 0.05$). Nevertheless, the scores on MSQOL-54 and HAM-D were worse than a year ago but without any statistically significant difference.

Statistically significant correlations between the scores on HAM-A, HAM-D, MSQOL-54, and other variables in patients with RRMS are presented in Table 3. Other epidemiological or clinical factors did not significantly correlate with the scores from the obtained questionnaires. Scores on obtained questionnaires significantly correlated with each other ($p < 0.01$). Patients who were more concerned about the impact of the COVID-19 pandemic on their health or the health of their relatives, and who feared that they would be infected with COVID-19 which would negatively affect their RRMS status had lower scores on MSQOL-54, and higher scores on HAM-D and HAM-A ($p < 0.05$). Multiple linear regression analysis showed that higher scores on HAM-D (beta = -0.68 , $p < 0.01$) was an independent predictor of the lower MSQOL-54 mental score (adjusted $R^2 = 0.47$, $p < 0.01$ for the overall model). Higher EDSS (beta = -0.58 ; $p < 0.01$) was independent predictor of the lower MSQOL-54 physical score (adjusted $R^2 = 0.52$, $p < 0.01$ for the overall model).

4. Discussion

The impact of COVID-19 pandemic on the psychological status of RRMS patients is presented in this study. RRMS patients had different degrees of fear of COVID-19 disease. COVID-19 is a global health crisis with the potential to kill hundreds of thousands of people, particularly people with comorbidities. Also, this pandemic could last for months which could jeopardize the use of medical services to patients with chronic diseases. We do not know if people with MS are at increased

Table 3
Clinical and socio-demographic variables of RRMS patients which correlate with the obtained scores on used questionnaires.

Variables	HAM-A	HAM-D	MSQOL-54 Physical health	MSQOL-54 Mental health
EDSS	0.61**	0.64**	-0.67**	-0.58**
Number of relapses	0.49**	0.55**	-0.62**	-0.56**
Female gender	0.27*	0.23*	-0.28*	-0.35*
Employment	-0.24*	-0.29*	0.25*	0.33*
Partner status	-0.28*	-0.32*	0.26*	0.32*

* $p < 0.05$; ** $p < 0.01$ (level of significance after Bonferroni's correction); RRMS = relapsing remitting multiple sclerosis; EDSS = Expanded Disability Status Scale; HAM-D = Hamilton depression scale; HAM-A = Hamilton anxiety scale; MSQOL-54 = Multiple Sclerosis Quality of Life-54 Instrument;

risk of developing severe COVID-19, but they are a unique group because they receive immunomodulatory therapy. Another aspect to consider in MS patients is that less mobility increases the risk of severe infection, especially if the patient is in a wheelchair.

In the study of psychological distress in the Chinese population during the COVID-19 outbreak, it was found that 35% of the general population experienced psychological distress (Qiu et al., 2020). Among people most affected psychologically by the COVID-19 are those with an accompanying chronic disease (Ozamiz-Etxebarria et al., 2020; Özdin S and Bayrak Özdin, 2020). For that reason, it was expected that RRMS patients have pronounced psychological distress than the general population during the COVID-19 outbreak. RRMS patients had different degrees of fear of COVID-19 disease. The main concerns were that some patient's relatives or friends could be infected with COVID-19 or could die due to infection. Also, lack of specific treatment options for COVID-19 was noted as one of the reasons for fear among RRMS patients. The main concern about RRMS status was that the patients could not go to the hospital as usual. The majority of patients would try to get to the hospital and to find medical doctors who treat them. The patients, who would not go to the hospital, stated the fear of getting infected as the main reason. Visits for RRMS care should preferably be done by telemedicine or phone, but it is of note that in Serbia telemedicine is not widely available. Also some hospitals in Serbia during the COVID-19 outbreak are converted in hospitals only for COVID-19 patients due to the large number of patients with this infectious disease.

Regarding depression levels we did not find a statistically significant difference between scores obtained before and during the COVID-19 outbreak in RRMS patients. On the other hand HAM-D scores were significantly higher in the RRMS group than in HC during the COVID-19 pandemic. Higher levels of depression and alcohol use were noted in the general population during the COVID-19 outbreak in the epicenter of the COVID-19 epidemic in China compared to other regions (Ahmed et al., 2020). Data of a large number of patients indicate an increased prevalence of depression and anxiety in MS independently of pandemic (Biernacki et al., 2019; Boeschoten et al., 2017).

Our results showed elevated levels of anxiety among RRMS patients compared to HC during the COVID-19 outbreak and also results in the same RRMS patients one year ago. Anxiety is common among MS patients and can exacerbate the severity of the disease (Artemiadis et al., 2011). The level of anxiety in Iranian MS patients during the COVID 19 pandemic was within the range of moderate to severe (Moghadashi, 2020). Our results also showed a mean level of anxiety in the range of moderate to severe according to the HAM-A scale. Results obtained a year ago showed mean levels below cut off point for mild anxiety. This implies a significant influence of global health emergencies on anxiety levels in RRMS patients.

In our study scores obtained on questionnaires for QoL were lower during the pandemic compared to scores from 2019 in the same cohort of patients, but with no statistical significance. Public health emergencies, such as a pandemic, have a significant impact on QoL of the general population (Chan and Huak, 2004; Kwek et al., 2006). QoL is impaired in RRMS patients for many reasons and pandemic could just aggravate this. We found a statistically significant correlation between female gender, employment and partner status, severe disease

according to EDSS and more relapses with worse QoL, and more pronounced anxiety and depression. Depression and higher disability are independent risk factors for lower QoL. Depression and psychological distress symptoms are among the factors with the most essential impact on subjective well-being in MS patients (Yalachkov et al., 2019). Lower household income, higher EDSS score and more progressive disease course have been all linked to a lower QoL, (Ruet et al., 2013; Lanzillo et al., 2016; Solaro et al., 2018). These findings are in line with our results.

There are some limitations of our study, such as a relatively small sample. Prolonged monitoring of RRMS patients after the COVID-19 pandemic is necessary for a better understanding of the influence of the COVID-19 pandemic on QoL and the overall psychological status. Also, it would be interesting to see whether patients treated with immunosuppressive therapies known to increase the risk for respiratory tract infections, exhibit higher degrees of psychological distress in the context of COVID-19 pandemic, compared to RRMS patients receiving beta-interferons or glatimer acetate. On the other hand, this study is done only on RRMS patients and for that reason could give a better insight into the psychological status of this subgroup of MS patients.

The COVID-19 epidemic has a significant impact on psychological status in RRMS patients. The results from the present study should inform the physicians who work in other fields about that the pandemic and restrictive measures which are taken, may have various concealed aspects, and can indirectly harm the patients. Professional advice for people with chronic autoimmune diseases is needed as soon as the pandemic occurs. Psychological support could alleviate the stress caused by the pandemic. It would help these patients in managing emotional distress, reducing anxiety and depression and improving their QoL and QoS.

CRedit authorship contribution statement

Aleksandar Stojanov: Investigation, Conceptualization, Writing - original draft. **Marina Malobabic:** Investigation, Formal analysis, Software. **Vuk Milosevic:** Data curation, Validation, Writing - review & editing. **Jelena Stojanov:** Conceptualization, Methodology, Writing - review & editing. **Slobodan Vojinovic:** Conceptualization, Supervision, Writing - review & editing. **Goran Stanojevic:** Supervision, Writing - review & editing. **Milos Stevic:** Supervision, Writing - review & editing.

Declaration of Competing Interest

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