



Comparison of Life Stressors before Diagnosis in Multiple Sclerosis Patients and Healthy Individuals: A Case-Control Study

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Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system that occurs when a genetically predisposed person is exposed to possible environmental factors. Stressful life events have been mentioned as effective factors in the incidence of MS, but the nature of this relationship remains to be adequately understood. This study aimed to determine the amount of exposure to stress before the onset of the disease.

Methods: This case-control study was performed on 34 recently diagnosed MS patients in Yazd, Iran, from 2019 to 2020. Their demographic information and scores on the Paykel questionnaire were collected, and the data were analyzed using the SPSS software version 26.

Results: In the study population, the number of women with MS was 26% higher than that of men. The case group's mean age of developing the disease was 31.70 ± 8.03 . In this study, no significant relationship was found between marital status and the incidence of MS ($P=0.15$). Those with education lower than a high school diploma obtained a higher stress score. In terms of life stressors in general ($P=0.001$), psychosocial stressors ($P=0.011$), grief-disappointment ($P=0.013$), and individual-family problems ($P=0.0001$), there were significant differences between the cases and the controls.

Conclusion: This study showed that stressful life events are more common in MS patients than healthy individuals. In addition to stress, other factors such as anxiety, coping mechanisms, attitudinal aspects (optimism and pessimism), and the amount of social support should be taken into consideration when dealing with MS.

Keywords: Multiple sclerosis, Anxiety, Stressful life events, Paykel questionnaire

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with a chronic relapsing/remitting or progressive course. In this disease, local inflammation causes demyelination and nerve cell damage in the brain and the spinal cord, leading to cognitive changes, depression, and anxiety in the affected individuals and the gradual disturbance of their lives (1-4). Studies have shown that genetic susceptibility and environmental and viral factors play a role in the occurrence of the disease (2,3). However, the etiology and pathogenesis of this multifactorial disease are still not clearly understood (1,5). According to some reports, the incidence of MS has increased significantly in Iran (5). MS causes serious and limiting attacks in people of young age. As a result, it can have highly adverse social and economic consequences (4).

Most people are exposed to stressful events in their lifetimes. Stress leads to various psychological reactions and changes in lymphocytes and cytokines, impairing the immune system and making the person susceptible to MS. Since the middle of the last century, psychosocial factors such as stressful life conditions have been considered effective in the occurrence and exacerbation of diseases caused by the weakened immune system (6,7).

The relationship between stressful situations and the increased risk of MS has been indicated in some studies (7,8). In contrast, a number of other studies (9,10) have found no association between exposure to stress and increased risk of developing MS. In the same research context, acute stress has been reported to be associated with MS relapse, while chronic stress is not correlated with an increased risk of MS (11). Considering the numerous unanswered questions in this regard and concerns about



the impact of stress on the risk of MS, this study was conducted with the aim of determining the amount of exposure to stress before the onset of MS.

Methods

Study design and participants

This case-control study was conducted to investigate the level of exposure to stress before the onset of MS in the patients of the MS Association of Yazd province in 2018–2019. Examining various environmental risk factors for MS can be helpful. A neurologist confirmed newly diagnosed MS cases based on their symptoms and the McDonald 2017 criteria. The participants in this study were people suffering from MS (16 years and older) who lived in Yazd Province and had been diagnosed in the previous six months. The exclusion criteria were drug addiction, psychosis, bipolar disorder, dementia, aphasia, and delirium. Also, the control group was selected from the patients' companions referring to Shahid Sadoughi Hospital in Yazd. The control subjects had no MS or other chronic diseases. Sampling was done using the census method, and the case and control groups were matched based on age and gender.

After the subjects were selected in the two groups, they were asked to answer the questions on the Paykel questionnaire in the presence of the interviewer. For those who could not complete the questionnaire due to movement, balance, or vision disorders, the questions were asked orally by a trained person.

The experimental protocol was approved by the Ethics Committee of Yazd Shahid Sadougi University of Medical Sciences (IR.SSU.MEDICINE.REC.1398.137). The study's main objectives were fully explained to both groups, and written informed consent was obtained from all the study participants or their legal representatives.

Paykel questionnaire

The Paykel questionnaire is a tool for comprehensively evaluating stressful events and the rate and intensity of the experienced stress. Khoosfi et al used the questionnaire to assess the stress level in patients with coronary heart disease. They reported a reliability of 0.72 for the number of events and 0.73 for the stress level (12). Paykel includes 65 crucial life events and evaluates psychosocial stressors (21 questions), personal-family stressors (21 questions), occupational-educational stressors (14 questions), bereavement and despair stressors (4 questions), and psycho-physical stressors (5 questions). The score on this questionnaire is suggestive of the frequency of stressors and the effect of stress on the person.

The Paykel questionnaire and the demographic forms to elicit information on age, gender, marriage, and education were completed in a quiet, almost private environment. The questionnaire asked for a wide range of information, such as whether or not an accident had happened to the

person in the past two years. In this case, a yes answer was scored as 1, and a no answer was scored as 0. If the answer was affirmative, the participant was asked about the event's severity. The answer to each Paykel question was scored on a five-point Likert scale ranging from very severe to none (none = 0 and very severe = 4).

Statistical analysis

Statistical analysis was performed using the SPSS software version 26.0 (SPSS Inc., Chicago, USA). The data were obtained from the stress scores in percentages or mean \pm SD values. *P* values less than 0.05 were regarded as statistically significant. Chi-square tests, independent samples *t* tests, analysis of variance (ANOVA), and Pearson correlation coefficients were used to compare variables between the two groups.

Results

Characteristics of the participants

From March 21, 2019, to March 20, 2020, 68 participants were included in the study based on the inclusion criteria. Of the participants, 34 patients were selected as the case group and 34 as the control group. The demographic characteristics of the study subjects at admission are reported in Table 1. The baseline characteristics were similar in the case and control groups. The average age of the patients in the MS group was 31.70 ± 8.03 years. This was 30.17 ± 7.86 years in the control group. In terms of gender distribution, there were 14 (41.2%) males and 20 (58.8%) females in the control group versus 15 (44.1%) males and 19 (55.9%) females in the case group (Table 1). There was no significant difference between the groups in terms of marital status and level of education (Table 1).

Paykel questionnaire results

As presented in Table 2, the overall scores on stressful

Table 1. Sociodemographic characteristics of the MS cases and the controls

Variable	MS cases (n = 34)	Controls (n = 34)	<i>P</i> value
Gender			
Female, n (%)	19 (55.9)	20 (58.8)	0.806*
Male, n (%)	15 (44.1)	14 (41.2)	
Age	31.70 ± 8.03	30.17 ± 7.86	0.43**
Marital status			
Single	13 (38.23)	9 (26.47)	0.3*
Married	21 (61.76)	25 (73.52)	
Education			
High school	7 (20.58)	5 (14.70)	0.71*
High school diploma	13 (38.23)	21 (61.76)	
Bachelor	8 (23.52)	7 (20.58)	
Master	5 (14.70)	1 (2.94)	
Doctorate	1 (2.94)	0 (0.0)	

The values are reported as mean (\pm SD) or number (percent). The *P* values were obtained from *chi-square and **independent samples *t* test (2-tailed).

life events were 0.78 ± 1.65 for the MS group and 0.47 ± 1.10 ($P=0.001$) for the control group. The scores of the subgroups, including grief-despair (1.08 ± 1.17 vs. 0.50 ± 0.56 ; $P=0.013$), individual-family problems (1.86 ± 0.97 vs. 0.57 ± 1.01 ; $P=0.0001$) and psychosocial problems (1.68 ± 0.95 vs. 1.12 ± 0.77 ; $P=0.011$), were significantly different for the case and control groups. The MS group had experienced more negative life events, such as bereavement and disappointment, as well as individual-family and psychosocial problems. The scores of the stressors in the other subgroups are given in Table 2. As can be seen, no significant difference was found between the two studied groups.

The findings of this study show that the scores of stressful life events in the MS group were significantly related to the age ($P=0.002$), gender ($P=0.021$), and education level ($P=0.002$) of the patients. These relationships were not significant in the control group. The post hoc Bonferroni test results showed that the patients with education below a high school diploma scored higher than the other patients ($P=0.0001$, [0.51, 2.19]).

The score of stressful life events in the MS group was not significantly related to marital status, while this relationship was significant in the control group ($P=0.03$, see Table 3).

Discussion

This case-control study aimed to evaluate the level of exposure to stress before the onset of MS in patients from Yazd province. So far, different factors such as viral and bacterial infections, physical damage, and stressful life events have been mentioned as the initiating factors in the onset of MS (13). In the meantime, there has been some disagreement about the role of stressful events in life (13). In most studies, stress has been defined as a problem and a limitation. In the Paykel questionnaire, stress is classified into five subgroups: psychosocial, individual-family, bereavement-disappointment, occupational-education, and psychological-physical (14). The results of this study showed that, compared to healthy individuals, patients with MS experience significantly more stressful life events, particularly bereavement, disappointment, individual-family-induced stress, and psychological-social stress.

Table 2. Total scores and subgroups of the Paykel questionnaire in the two studied groups

Stressful life events	MS cases	Controls	P value
Mental-physical	0.76 ± 0.74	0.90 ± 0.68	0.79
Bereavement-disappointment	1.17 ± 1.08	0.56 ± 0.50	0.013
Job-educational	1.78 ± 1.73	1.58 ± 1.52	0.52
Individual-family	1.86 ± 0.97	1.01 ± 0.57	0.0001
Psychological	1.68 ± 0.95	1.12 ± 0.77	0.011
Total stressors	1.65 ± 0.78	1.10 ± 0.47	0.001

The values are reported as mean (\pm SD), and the P -values are obtained from independent samples t -tests (2-tailed).

A growing body of experimental research demonstrates that stress can affect the release of cytokines, inflammatory factors such as Interleukin (IL)-6 and IL-10, and the activity of T-cells. It can also disrupt cellular immunity and cause irregularity in the hypothalamus-pituitary-adrenal axis, thus affecting MS disease.

According to the results of this study, the score of stressful life events had a significant positive relationship with the age of the patients. In the studied society, the average age of disease diagnosis in the case group was 31.70 ± 8.03 years. Some other studies have reported it to be from 20 to 40 years (15). Naeeni et al (16) also reported the average age of MS diagnosis to be 30.9 ± 7.1 years, consistent with the results obtained in the present study. Hamarat et al (17) demonstrated that older patients have weaker coping mechanisms, less enjoyment of life, and more mental concerns, as shown by their higher stress scores. Similar results were reported by Marchant et al (18).

In the present study, women with MS outnumbered the male patients (by a factor of 1.26). This finding is consistent with other studies conducted in this field (19). However, the ratio has sometimes varied from 1.3 to 3 times (19). As shown in this study, the average stress score of the females was higher than that of the males.

The results obtained from the studies about the relationship between marital status and the incidence of MS are contradictory. In a study by Abdollahpour et al (5), the possible relationship between stressful events and the risk of MS was investigated. It was concluded that a potential divorce and the associated stress can trigger MS. Jiang et al (1) also reported that both marriage and

Table 3. Scores of the relationship between stressful life events and age, gender, education and marital status in the two groups

Variables		Stressful life events	
MS cases	Age	P	0.002*
		R	0.50
	Gender	P	0.021**
		R	[-1.12, -0.10]
	Education	P	0.002***
		R	5.37
Controls	Marital status	P	0.15**
		R	[-0.94, 0.16]
	Age	P	0.073*
		R	0.31
	Gender	P	0.140**
		R	[-0.57, 0.08]
	Education	P	0.648***
		R	0.556
	Marital status	P	0.03**
		R	[-0.73, -0.02]

The P values were obtained from *Pearson correlation, **independent samples t -test (2-tailed), and ***ANOVA.

divorce can contribute to the occurrence of this disease.

In this study, the MS patients and the control group were significantly different in terms of their level of education. Also, those with an education lower than a high school diploma had a higher stress score. These findings align with many other studies conducted in this field (20). Feizi et al (21) announced that higher education improves coping mechanisms, and people with poor coping skills should see a psychiatrist. According to those researchers, people with good coping abilities are in a better position to earn money and gain life satisfaction.

Many studies have indicated that the psychosocial stress in MS patients is significantly higher than in control groups, and psychosocial factors have a significant relationship with the pathogenesis and clinical symptoms of MS. In this regard, the present study agrees with numerous reports in the literature.

The results obtained from a case-control study (1) on 2930 patients with MS showed that stressful events such as arguments with a spouse, marriage, and divorce may have adverse effects on the risk of developing MS. Liu et al (3) also showed that family problems can have a significant impact on a person's risk of developing MS. In another study (8), family conflicts and marriage and pregnancy problems were mentioned as factors affecting MS. These studies' findings align with the effects of individual and family stressors and the corresponding significant difference between the case and control groups in the present study.

In the current study, the case and control groups were significantly different in terms of bereavement-disappointment stressors. In another study (1), it was shown that the death of a spouse or child increases the risk of MS significantly. In addition, a number of studies (2,16) have provided evidence that the death of a first-degree relative increases the risk of developing MS.

In our study, mental-physical and occupational-educational stressors were not significantly different in the MS patients compared to the control group. Several controversial findings have been reported in this regard. The 2020 study conducted by Jiang et al (1) on patients with MS aimed at determining which stressful life events were associated with the risk of developing MS. It was concluded that conflict with co-workers can significantly increase the risk of developing MS. In a number of other studies (5,8), unemployment and job problems were considered influential factors in increasing the risk of MS. Therefore, to confirm the results of the present study, it is necessary to conduct more studies with larger sample sizes and also to consider the genetic background of people.

This research is not without limitations. First, there was a recall bias, but this factor was present not only in the patient group but also in the control group. Therefore, its effect on the obtained results is reduced. Also, anxiety and depression may play a role in people's reactions to stress;

however, these variables could not be evaluated due to the type of study. As for the strengths of the study, one was the selection of the case group members up to six months after the diagnosis of their disease so that the potential post-disease stress would have less impact on the study results.

Conclusion

In summary, this study showed that stressful life events were more common in the newly diagnosed MS patients than in the controls. However, there was a causal relationship between stressful events and the incidence of MS. Perhaps stress is one of the several factors involved in the occurrence of MS. In addition to stress, other factors such as anxiety, coping mechanisms, optimism, and the amount of social support should be considered. Considering that stress can be managed and mitigated, specific measures are recommended, such as training in problem-solving skills and relaxation techniques, increasing positive activities, and strengthening the support of family and friends. These measures ultimately help the patients and their families manage stressful factors.

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Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The principles of the Declaration of Helsinki were observed, and informed consent was obtained from all the patients. This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences and Health Services of Yazd (IR.SSU.MEDICINE.REC.1398.137).

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